



BMJ Open Randomised, pragmatic, waitlist controlled trial of cannabis added to prescription opioid support on opioid dose reduction and pain in adults with chronic non-cancer pain: study protocol

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ABSTRACT

Introduction Chronic, non-cancer pain impacts approximately 50 million adults in the USA (20%), approximately 25% of whom receive chronic prescription opioids for pain despite limited empirical efficacy data and strong dose-related risk for opioid use disorder and opioid overdose. Also despite lack of efficacy data, there are many reports of people using cannabis products to manage chronic pain and replace or reduce chronic opioids. Here we describe the protocol for a randomised trial of the effect of cannabis, when added to a behavioural pain management and prescription opioid taper support programme, on opioid utilisation, pain intensity and pain interference.

Methods This is a pragmatic, single-blind, randomised, wait-list controlled trial that aims to enrol 250 adults taking prescription opioids at stable doses of ≥ 25 morphine milligram equivalents per day for chronic non-cancer pain who express interest in using cannabis to reduce their pain, their opioid dose or both. All participants will be offered a weekly, 24-session Prescription Opioid Taper Support group behavioural pain management intervention. Participants will be randomly assigned in 1:1 ratio to use cannabis products, primarily from commercial cannabis dispensaries or to abstain from cannabis use for 6 months. Coprimary outcomes are change in prescription monitoring programme-verified opioid dose and change in Pain, Enjoyment, General Activity scale scores. Secondary outcomes include quality of life, depression, anxiety, self-reported opioid dose and opioid and cannabis use disorder symptoms. All other outcomes will be exploratory. We will record adverse events.

Ethics and dissemination This study has ethical approval by the Massachusetts General Brigham Institutional Review Board (#2021P000871). Results will be published in peer-reviewed journals and presented at national conferences.

Trial registration number NCT04827992.

INTRODUCTION

Approximately 50 million adults in the USA suffer from chronic, non-cancer pain (CNCP),¹ a debilitating medical condition

STRENGTHS AND LIMITATIONS OF THE STUDY

- ⇒ This randomised, pragmatic trial in adults on chronic opioids for non-cancer pain will test whether cannabis use is associated with reduced opioid dose and reduced pain ratings when added to a behavioural pain management intervention.
- ⇒ We aim to enrol 250 participants across three sites, which will provide sufficient power to analyse the two primary outcomes, change in prescription monitoring programme-verified opioid dose and Pain, Enjoyment and General Activity score.
- ⇒ This pragmatic trial makes use of the cannabis distribution system being put into place in many US states and, as such, a limitation of this study is that it cannot include a placebo or control for the type or amount of cannabis used by participants.

that is challenging to manage. Though nearly 25% of those with CNCP are treated with chronic opioid therapy (COT),² the evidence to support the long-term effectiveness of opioid analgesics for pain and functional status is limited.³ In addition, high dose COT increases the risk for opioid use disorder (OUD) and subsequent opioid overdose death.^{4–9} The proposed CDC Clinical Practice Guidelines for Prescribing Opioids-2022¹⁰ recommends several strategies to mitigate risks of opioid use for chronic pain. These include the following: (1) initiating opioid therapy only if expected benefits to pain management and functioning outweigh risks, (2) utilising non-opioid and non-pharmacologic approaches for pain management, (3) prescribing the lowest dosage to achieve expected effects and (4) working collaboratively with patients to taper to lower dosages if risks outweigh benefits of continued use.¹⁰ Available evidence indicates that COT dose reduction generally improves



pain, function and quality of life for individuals with CNCP.¹¹ However, since optimal strategies for helping individuals reduce their opioid dose in real-world settings are largely unknown,¹² there are concerns that the risk for overdose increases during tapering due to rapid discontinuation and variability in dosing.^{13–15}

Cannabis and cannabinoids have been explored as potential treatments for chronic pain, and chronic pain is the most common reason individuals give for seeking state-issued medical cannabis cards.¹⁶ However, there is inconclusive evidence regarding the effectiveness of cannabis in facilitating analgesia.¹⁷ A Cochrane review of randomised controlled trials (RCTs) of cannabinoids for pain included studies of nabilone (FDA approved synthetic THC, two studies), dronabinol (plant-derived THC, two studies), sativex (nabiximols in the USA, an oromucosal spray with a 1:1 ratio of plant-derived THC and cannabidiol (CBD), 10 studies) and combusted herbal cannabis (two studies) and concluded that there was a lack of evidence that any cannabis-derived product was effective for any form of chronic pain.¹⁸ A review by the Department of Veterans Affairs¹⁹ similarly concluded that there was insufficient evidence to support efficacy of cannabis products for chronic pain. Though, it is worth noting they reported that low-quality evidence suggested cannabis may alleviate neuropathic pain for some patients. A recent RCT found no effect of commercial cannabis products obtained with medical marijuana cards on self-rated pain scores.²⁰ Yet, a 2017 report from the National Academies of Sciences, Engineering and Medicine²¹ reported “conclusive or substantial evidence” that cannabis is effective in treating chronic pain. Thus, there are contradictions in the literature surrounding the effectiveness of cannabis products for managing pain.

Despite the lack of sufficient evidence, cannabis began to be promoted as a substitute for opioids following a widely publicised study reporting that states with legal medical cannabis had lower-than-expected opioid overdose mortality rates from 1999 to 2010.²² Despite a reanalysis of state-level data through 2017 that showed the opposite trend²³ and no studies demonstrating efficacy, cannabis has been approved by many states as a ‘treatment’ for OUD.²⁴ Although a recent systematic review suggests that cannabis used in combination with opioids to treat CNCP may reduce opioid dose,²⁵ to date, there are no published reports of RCTs investigating the effectiveness of cannabis for reducing opioid utilisation. Still, many patients self report using cannabis as an alternative to pharmaceutical prescriptions, including opioids and adjuvant therapies.²⁶

Behavioural interventions are associated with sustained improvements in functioning for those with chronic pain,²⁷ particularly among those with co-occurring mental health diagnoses.²⁸ Patients with CNCP and comorbid mental health diagnoses are more likely to be prescribed opioids, be prescribed a higher dose and to report chronic opioid use, compared with those with CNCP without mental health conditions.^{29–33} The current study

utilises a behavioural intervention, based on the Prescription Opioid Taper Support (POTS) programme,³⁴ to help participants develop pain self-management skills and promote an individualised, voluntary opioid taper with a goal of a 10% reduction from the baseline dose every 4 weeks. Drawing on several therapeutic modalities, including cognitive behavioural therapy and motivational interviewing, this intervention promotes a strong therapeutic relationship and encourages participant autonomy in problem-solving challenges associated with chronic pain.^{35 36}

Objectives

The goal of this study is to provide controlled trial data about the potential benefits and unintended consequences of using cannabis, primarily from commercial cannabis dispensaries, to treat CNCP; we hope that these findings can help patients and providers make more informed treatment decisions. The primary objective of this study is to evaluate whether cannabis (CB), when added to the 24-week POTS programme, reduces opioid dose and/or improves pain intensity and interference in adults on COT for CNCP from baseline to 24 weeks, more so than those assigned to a waitlist (WL) condition in which they agree to wait 6 months to use cannabis, but receive the POTS intervention (WL+POTS). Prescription Monitoring Programme (PMP)-verified opioid dose and Pain, Enjoyment and General Activity (PEG)³⁷ score are our coprimary outcomes.

The secondary objectives are to evaluate whether participants assigned to CB+POTS, compared with those assigned to WL+POTS, have improved quality of life, depression, anxiety and reduced self-report opioid dose from baseline to 24 weeks. This study will evaluate changes in the number of OUD symptoms, as well as whether those assigned to CB+POTS develop symptoms of cannabis use disorder (CUD) over the 24-week intervention and at 12 months.

METHODS AND ANALYSIS

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

Study design

A randomised, pragmatic, single-blind controlled trial.

Study population

Adults ages 18–75 years old at three academic hospitals in the Northeastern USA (Massachusetts General Hospital, Cambridge Health Alliance, Maine Medical Centre) with CNCP on stable prescription opioid doses of ≥ 25 morphine milligram equivalents (MME)/day for at least 90 days who plan to use cannabis to control pain and/or reduce opioid dose will be invited to participate. Participants will be recruited through physician referrals, clinical programmes associated with the healthcare systems and community advertising. Importantly, to be

Box 1 Inclusion criteria

1. Men and women aged 18–75, inclusive.
2. Endorsing >6 months of chronic, non-cancer pain.
3. On stable prescription opioid doses of ≥ 25 morphine milligram equivalents/day for >90 days, verified by the prescription monitoring programme.
4. Either no prior use or current light cannabis use (weekly or less in the past 12 months, less than 10 times in the past 90 days).
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 have a negative urine pregnancy test at enrolment and agree to use effective contraception: abstinence; hormonal contraception; intrauterine device, sterilisation or double barrier contraception, during the study.

eligible, participants must be willing to abstain from any cannabis use during the intervention and to wait 24 weeks before using cannabis if they are randomised to the WL+POTS group. A full list of inclusion criteria can be found in [box 1](#). Exclusion criteria include current regular cannabis use (>weekly) in the past 12 months, use of non-prescribed opioids and uncontrolled major medical illness. Current moderate to severe substance use disorders, with the exception of tobacco and OUDs, are also exclusionary. A full list of exclusion criteria can be found in [box 2](#).

Participant enrollment

Interested participants will complete a telephone screen for eligibility. All individuals who are potentially eligible based on the phone screen will be scheduled for an enrolment visit where written informed consent will be obtained by a trained member of study staff. The consent form is available as supplemental information (online supplemental file 2). Study physicians or their delegates will use the PMP to document prescriptions for opioids and other medications monitored by the PMP. Additionally, they will use the electronic health record to document concomitant medications to improve the accuracy of self-reported of current medications.

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

Randomisation and allocation concealment

After the baseline visit, participants will be randomly assigned 1:1 to CB+POTS: WL+POTS in blocks of 3–6 (depending on speed of recruitment). If more patients drop out in the WL+POTS group, participants will

Box 2 Exclusion criteria

1. Current cannabis use (including ingested/inhaled cannabidiol products) of greater than weekly on average in the past 12 months, assessed via self-report (no more than 10 times in the past 90 days).
2. Current cannabis use disorder; moderate to severe substance use disorder for any substance (eg, alcohol, cocaine, stimulant) by structured interview, EXCEPT nicotine and opioids (opioid use disorder).
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 or urine toxicology screen.
5. Dose change or initiation of medications with significant analgesic effects (eg, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), gabapentin, non-steroidal anti-inflammatory drugs) in the past 4 weeks, verified by electronic health record.
6. Concomitant medications will be discussed at each study visit, and any medications that may interact with cannabinoids (eg, warfarin) will be discussed with a study clinician prior to enrolment or continued participation.
7. Actively suicidal and/or suicide attempt or psychiatric hospitalisation in past year, or current suicidal ideation with specific plan or intent.
8. History of intellectual disability (eg, Down's syndrome) or other severe developmental disorder or IQ < 70.
9. Current diagnosis of delirium, dementia, amnesic or other cognitive disorder; current diagnosis of bipolar II disorder; lifetime diagnosis of a clinically significant personality disorder (eg, borderline, antisocial, paranoid, schizoid, schizotypal, histrionic personality disorders); lifetime diagnosis of bipolar I, 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 safely participate in this study.

be randomised in blocks, 1:2 CB+POTS:WL+POTS to achieve the goal of 100 patients completed in each arm by the end of the trial.²⁰ Block randomisation will be done so that groups will be comprised only of participants in the same randomisation group; thus, those assigned to CB+POTS would not be in the same behavioural pain management groups as those assigned to WL+POTS.

Randomisation will be computer generated. Assessments will be conducted by study staff blind to the study intervention. Blinding of participants after group assignment is not possible due to the study design.

Interventions

Participants will be assigned to either begin cannabis use without delay (CB+POTS), or to a waitlist control (WL+POTS), in which they are incentivised through payments, to wait 24 weeks before beginning to use cannabis. After the 24-week period, those in the WL+POTS group will have the option to begin cannabis use. This is a pragmatic trial in which participants choose their cannabis products, dose and frequency of use, which mimics the certification process for cannabis in

many states (where patients have a broad range of choice in products and dosing) and mimics the use of recreational cannabis outside of any healthcare interactions. All participants will continue other medical care as usual.

All study participants, regardless of randomisation group, will participate in the POTS programme. POTS is a 24-week intervention that teaches behavioural pain self-management strategies and supports a voluntary taper of COT dose. POTS was developed by Turner and Sullivan,³⁴ and will be modified in this study to (1) allow for implementation in a group format, (2) reorder skill training based on the perceived difficulty of the skills being taught and (3) increase length of the programme from 18 to

24 weeks. There will be two additional sessions in weeks 25–26 to facilitate return of care to the primary care physician. During the five POTS sessions in study weeks 4–20 that coincide with monthly study visits, study clinicians will work with participants to reduce opioid dose in increments of approximately 10% of the baseline opioid dose. POTS sessions will be conducted virtually via teleconference with groups of 3–6 study participants and will last 1 hour. Sessions will be led by a trained clinician and use components of cognitive behavioural therapy, mindfulness and motivational interviewing to help individuals better manage their chronic pain and achieve an opioid

Table 1 POTS session content

Session	Content
Session 1 (individual)	Individual session to discuss pain and opioid use history, goals for taper
Session 2	Group introductions, relationship building, set expectations for participation, introduce tapering schedules, discuss overdose prevention strategies
Session 3	Psychoeducation: chronic opioid therapy
Session 4*	Diaphragmatic breathing
Session 5	Psychoeducation: pain neurobiology and pain gate theory
Session 6	Psychoeducation: pain neurobiology and pain gate theory
Session 7	Relaxation techniques and introduction to seven muscle group progressive muscle relaxation
Session 8*	Guided practice of seven-muscle group progressive muscle relaxation
Session 9	Diaphragmatic breathing-guided practice; psychoeducation on importance of sleep
Session 10	Distraction for pain relief
Session 11	Pacing and activity scheduling
Session 12*	Counterstimulation
Session 13 (individual)	Individual session to discuss opioid taper, experience with behavioural pain self-management techniques, individual challenges
Session 14	Coping with pain flare-ups
Session 15	Brief diaphragmatic breathing; introduction and practice of four-muscle group progressive muscle relaxation with tension
Session 16*	Introduction and practice of four-muscle group progressive muscle relaxation without tension and guided practice
Session 17	Developing positive coping thoughts and coping self-statements
Session 18	Psychoeducation: self-compassion
Session 19	Brief body scan
Session 20*	Mini-relaxation and incorporation into daily routine
Session 21	Pain beliefs and activity avoidance
Session 22	Setting pleasurable activity goals
Session 23	Psychoeducation: social and emotional factors that influence pain
Session 24	Maintaining gains and dealing with setbacks
Session 25	Group termination, skills review, facilitation of return of care to Primary Care Provider
Session 26 (individual)	Individual termination session, facilitate return of care to Primary Care Provider

*Taper Point.
POTS, Prescription Opioid Taper Support.

dose reduction. POTS session content can be found in [table 1](#).

Data collection

Participants will complete a daily online survey with questions regarding pain intensity and interference (PEG scale; range, 0–30), cannabis use, opioid use (MME/day) and ratings of sleep quality, mood and general health. Daily survey data will be assessed from 2 weeks pre-baseline to 24 weeks.

Study visits will take place approximately at weeks 0 (baseline), 4, 8, 12, 16, 20 and 24. Data collection at these visits will include self-administered and clinician-administered assessments. Assessments will use standard, validated measures, selected for consistency with the PhenX Toolkit,³⁸ the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations for chronic pain trials³⁹ and the National Institutes of Health (NIH) Research Standards for Chronic Low Back Pain.⁴⁰ A follow-up assessment will also be conducted at 12 months by telephone.

At all study visits, participants will provide a urine sample which will be qualitatively screened for substances, including opioids and cannabinoids, and used to verify that those assigned to WL+POTS are not using cannabis prior to week 24. Urine samples from the CB+POTS group will be sent to the Pharmacy and Therapeutics Committee at the University of Colorado School of Medicine for a quantitative metabolite assay to measure cannabis metabolites.

Outcomes

The primary outcome is to evaluate whether adults with CNCP on COT assigned to CB+POTS, compared with those assigned to WL+POTS, have (1) greater reduction in PMP-verified opioid dose (MME/day) at 24 weeks compared with baseline, and/or (2) greater improvement in pain intensity and interference (PEG scores) from postbaseline to 24 weeks as assessed by daily diaries (coprimary outcomes).

The secondary outcomes of this study are to evaluate whether participants assigned to CB+POTS, compared with those assigned to WL+POTS, have improved quality of life, depression and anxiety and reduced self-reported opioid dose.

We also plan to evaluate whether those assigned to CB+POTS have a reduced number of OUD symptoms at 24 weeks compared with WL+POTS, as well as if they have developed symptoms of CUD at 24 weeks. See [box 3](#) for a full list of outcome measures.

Box 3 All outcomes will be analysed as mean difference in scores between baseline and 24 weeks, unless otherwise noted.

Withdrawal from the study

All participants will be informed that participation in the research study is voluntary, and they can withdraw and end their participation at any time. Study staff will work

Box 3 Outcome measures

Primary outcome measures

Prescription monitoring programme-verified opioid dose (morphine milligram equivalent; MME) per day.

Pain intensity and interference (Pain, Enjoyment, General Activity (PEG) Scale³⁷ summed score).

Secondary outcome measures

Quality of life (Quality of Life, Enjoyment and Satisfaction Questionnaire-Short Form, Q-LES-Q-SF⁴⁴).

Depressive symptoms (Patient Reported Outcomes Measurement Information System-29, PROMIS-29 Depression subscale⁴⁵).

Anxiety symptoms (Patient Reported Outcomes Measurement Information System-29, PROMIS-29 Anxiety subscale⁴⁵).

Opioid use disorder symptoms (DSM-5 Opioid Use Disorder Checklist⁴⁶).

Cannabis use disorder symptoms (DSM-5 Cannabis Use Disorder Checklist⁴⁶).

Self-reported opioid dose (MME/day) collected daily via online survey and then averaged over each month at 24 weeks.

Exploratory outcome measures

Opioid misuse (Current Opioid Misuse Measure, COMM⁴⁷).

Opioid-related problems (Prescribed Opioid Difficulties Scale, PODS⁴⁸).

Opioid withdrawal symptoms (Clinical Opiate Withdrawal Scale, COWS,⁴⁹ Short Opioid Withdrawal Scale, SOWS⁵⁰).

Opioid use disorder symptoms (DSM-5 Opioid Use Disorder Checklist⁴⁶) at 12 months.

Cannabis use disorder symptoms (DSM-5 Cannabis Use Disorder Checklist⁴⁶) at 12 months.

Self-Efficacy (Pain Self-Efficacy Questionnaire, Disorder⁵¹).

Pain Catastrophising (Pain Catastrophising Scale, PCS⁵²).

Distress Tolerance (Distress Tolerance Scale, DTS⁵³).

Anhedonia (Snaith-Hamilton Pleasure Scale, SHAPS⁵⁴).

Delay Discounting (Monetary Choice Questionnaire, MCQ⁵⁵).

Psychotic Experiences (Peters Delusion Inventory, PDI⁵⁶).

Suicidal thoughts and behaviours (Concise Health Risk Tracking Scale, CHRT⁵⁷).

Readiness to change (Readiness Ruler⁵⁸).

Cognitive function: Verbal (California Verbal Learning Test-Third Edition).⁵⁹

Cognitive function: working memory (Wechsler Adult Intelligence Scale-IV Digit Span Task⁶⁰).

to ensure withdrawn participants stop the study safely and will arrange for follow-up care if needed.

Duration of the trial

It is anticipated that the study will be completed in 4 years (November 2021–March 2025). Primary and secondary outcomes will be accomplished by the end of year 3.

Confidentiality

Patient confidentiality will be protected according to the regulations set forth by the Mass General Brigham Institutional Review Board (IRB). Participants are informed that all records are kept confidential. Paper records are secured in a locked office, and computer data protected with passwords and file access standards.

Data management and statistical analysis

Data will be collected prospectively and managed using a REDCap^{41 42} database designed by the principal investigators and data manager at MGH. Data will be entered by IRB-approved study staff who are trained in best practices for human subjects research. Daily survey data will be entered directly by participants who will be trained on how to use the application and correctly enter data. The data manager will check data weekly for quality and accuracy.

Baseline patient characteristics by treatment group will be presented as mean (SD), median and count (%), depending on type.

Our coprimary outcomes will be the summed score (ranging from 0 to 30) of the three-item PEG scale, a measure of pain intensity and interference, and total opioid dose in mean daily MME. We will analyse both outcomes using a linear regression model. PEG will be collected daily via self-report through an online survey from baseline to the end of the 24-week period (ie, up to 168 observations per subject), and opioid dose will be verified through the PMP. All postbaseline daily observations for PEG scores will be analysed.

The confirmatory effect of interest for opioid dose will be the treatment (WL+POTS vs CB+POTS) by time (baseline vs week 24) interaction, testing whether there is a significant reduction in opioid dose at week 24 for CB+POTS above and beyond any reduction for WL+POTS. If participants decide to reduce dose at week 24, we will use the reduced dose even if the new dose cannot be immediately implemented (eg, due to delays in refilling prescription) to ensure accurate representation of change.

The confirmatory effect of interest for PEG scores will be 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. Additionally, as covariates we will include terms for (a) a quadratic time trend, (b) baseline PEG scores and (c) baseline opioid dose. We assume a conservative additive model, with main effects for the impact of CB and monthly trends, but no treatment by time interaction.

Coefficients and standard errors for the linear model will be obtained using generalised estimating equations.⁴³ The primary contrast testing for a constant effect of CB above and beyond POTS will be deemed statistically significant for $p < 0.025$, thereby adjusting for multiple comparisons given that we have two outcome measures.

We will also conduct sensitivity analyses for each outcome. First, we will examine if the direction and significance of the primary contrast for CB+POTS and WL+POTS is robust to the inclusion of additional covariates that includes a treatment by time interaction. Second, we will examine if the direction and significance of the primary contrast for CB+POTS is robust to our treatment of missing data by fitting the statistical model to the observed data only. Finally, we will conduct an as-treated

analysis examining those who used CB regularly (weekly or more) versus those who did not use (verified by negative urine screens and no self-reported use), correcting for “confounding by indication” by weighting data by the inverse probability of being in the CB or non-user group. Additional sensitivity analyses may be required to address unanticipated developments throughout the course of the study.

Examination of PEG scores and opioid dose means that a combination of clinical outcomes is possible (see table 2), which will indicate whether cannabis is helpful, cannabis is harmful or that cannabis has no clear effect on opioid dose/PEG scores. In the third condition, an exploratory analysis will evaluate costs/benefits of cannabis to the individual patient, measured via secondary outcomes, (eg, effect of cannabis on sleep, mood).

Secondary outcomes will consist of measures collected at each monthly study visit (measures of quality of life, depression, anxiety, OUD, CUD and self-reported opioid dose). Secondary outcomes will be analysed using the same statistical model as PEG scores, but with the quadratic time trend defined over the monthly visits.

We will use multiple imputation via chained equations to address missing data for both primary and secondary outcomes. Subjects with fewer than 14 days of daily diary entries will be excluded. For daily PEG scores, for runs of missing data (multiple days in a row with missingness), the first and last entry of the run will be imputed.

Sample size

While final analyses will rely on 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 sample t-tests. The target sample size was 125 subjects per group, or 100 subjects under a worse-case scenario of 20% attrition. A power curve for each outcome was computed, plotting the required sample size for 80% power against the associated minimum detectable percent reduction in the outcome measure.

For PEG scores, power curve estimates were based on preliminary data, 3205 daily pain scores (a component of PEG scores) reported by 46 subjects in our previous cannabis use study²⁰ over a period of 84 days (roughly 3 months). The mean (6.3) and SD (3.1) for pain scores in the first 2 weeks was used to compute percent reduction. For 125 subjects 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 subjects 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.

For opioid dose, power curve estimates were based on opioid dose data extracted from 2017 MGH records for the 145 PEG score patients. We used the mean (88) and SD (32) in MME to compute per cent reduction.

Table 2 Clinical significance table

Decision	PEG scores at 6 months compared with baseline	Opioid dose at 6 months compared with 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

CB, cannabis; ns, not significant; PEG, Pain, Enjoyment and General Activity; POTS, Prescription Opioid Taper Support; WL, waitlist.

For 125 subjects 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 subjects 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.

For our secondary outcome variables, which seek to address other behavioural measures such as OUD symptoms, pain interference, PEG score self-efficacy, pain-related function and psychological functioning (quality of life, depression, anxiety and sleep) in the active group compared with the WL+POTS group, we determined that with 100 participants in each group and 30% attrition (final n=70), we have 89% power to detect a difference in the slopes between baseline and the 6-month visit, at two-tailed p=0.05 level if the true difference in slopes is a 10% improvement on any of these measures in the CB group, and 0%–5% increase in the WL+POTS group.

More information is available in the trial statistical analysis plan (online supplemental file 3).

Adverse events

Research coordinators will ask subjects to report adverse events (AEs) possibly related to cannabis, opioid use and the study intervention at all study visits and at the 12-month follow-up call. AEs will also be reviewed by the Data Safety Monitoring Board (DSMB) every 3 months. The DSMB will consist of one psychiatrist, one statistician and one addiction neuroscientist. Each member of the DSMB will not otherwise be associated with the trial. The DSMB charter is available as supplementary information

(online supplemental file 4). Reporting and handling of AEs will be in concordance with IRB regulations and good clinical practice guidelines.

Unblinding

We anticipate the need for assessor unblinding to be unlikely. Study physicians will be unblinded to manage cannabis-related AEs.

Early termination of the trial

The DSMB will conduct a blind analysis of efficacy and safety data when half of the sample is enrolled. If there is a need to terminate this trial early, this decision will be made by the DSMB and submitted to the NIDA Project Officer.

Patient and public involvement

Patients and the public were not involved in the development of the research question, the design, recruitment or conduct of the study, and the burden of the intervention was not assessed by the patients or the public.

Ethics and Dissemination

This study has ethical approval by the Massachusetts General Brigham (MGB) Institutional Review Board (Protocol Number 2021P000871). Informed consent will be obtained from all participants by a trained member of study staff. Important protocol modifications will be submitted to the Institutional Review Board for approval and will be communicated with all participants. Results will be disseminated to participants by email and shared with the public through publication in peer-reviewed

journals and presentations at national conferences. Data will be deidentified in all cases.

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Contributors JG and AEE developed and designed the trial and obtained funding for the trial. JJ wrote the first draft of this manuscript. JG, AEE, CC, EG, AQ and JJ assisted with the study design. DAS and KP designed the statistical aspects of this protocol. All were involved in the revision of the manuscript. All authors approved the final version to be submitted.

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Competing interests AEE reported receiving grants from Charles River Analytics and non-financial support from Pfizer as well as serving as the chair of the data monitoring board of Karuna Pharmaceuticals outside the submitted work.

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

Patient consent for publication Not required.

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