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Impact of an acute 1-month cannabidiol treatment on pain and inflammation after a long bone fracture: a triple-blind randomized, placebo controlled, clinical trial protocol

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Impact of an acute 1-month cannabidiol treatment on pain and inflammation after a long bone fracture: a triple-blind randomized, placebo controlled, clinical trial protocol

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Abstract

Introduction. Acute pain levels following orthopedic injury (e.g., fracture) is a predictor of the onset of chronic pain, which affects nearly 50% of fracture patients and impairs functional recovery. Among current pharmacological treatments for acute pain, non-steroidal anti-inflammatory drugs have been associated with delayed bone healing, while opioids inhibit effective bone remodeling, increase the risk of pseudarthrosis, and carry a high risk of addiction. In light of this, the development of new pain treatments is essential.

Cannabidiol (CBD), a non-addictive and non-psychotropic cannabis component stands out as a potential therapeutic agent, given its analgesic and anti-inflammatory properties as well as its potential benefits for bone healing. This randomized controlled trial aims to investigate the effect of acute CBD treatment, compared to placebo, on patients' self-reported pain, inflammation and well-being following a fracture injury.

Methods and analysis. This is a triple-blind, randomized, placebo-controlled clinical trial. A total of 225 adults aged 18 to 70 years, who have suffered a long bone fracture and were treated at the Hôpital du Sacré-Coeur de Montréal, will be randomly assigned within one week to one of three treatment arms (25 mg or 50 mg of CBD or placebo) for one month. The primary outcome will be difference in the pain score between groups at one-month follow-up. Secondary outcomes will include measures of persistent pain, inflammation, opioid usage, quality of life, sleep quality, depression, anxiety, cognition and orthopaedic function. Data will be collected at baseline, 1- and 3-month follow-ups.

Ethics and dissemination. This study obtained a Health Canada license for use of cannabis products. It has also been approved by Health Canada and the Research Ethics Board of the CIUSSS du Nord-de-l'Île-de-Montréal (Project ID 2025-2105). The findings will be published in a peer-reviewed journal and presented at local, national, and international conferences. The trial's results will be made publicly available on the clinicaltrials.gov database.

Trial registration number: NCT06448923 (registered on [ClinicalTrials.gov](https://clinicaltrials.gov))

53 **Strengths and limitations of this study**

- 54 - This is the first human randomized clinical trial to assess the potential therapeutic
55 effects of cannabidiol on pain and inflammation following orthopaedic trauma.
- 56 - This trial includes a longitudinal assessment of CBD treatment on pain symptoms
57 and trauma-related outcomes up to three months post-fracture which marks the
58 critical period of transition to chronic pain.
- 59 - This study will assess potential interactions between pain mediators, such as
60 opioids, mild traumatic brain injury and sex, and response to CBD treatment. This
61 evaluation will help gain a more comprehensive understanding of the effects of pain
62 mediators on treatment response, as well as the effects of treatment on opioid
63 uptake.
- 64 - Therapeutic drug monitoring could be beneficial to account for inter-individual
65 variability as well as to optimize doses.

67 **Introduction**

68 Bone fractures are a prevalent condition affecting individuals of all ages and are the most
69 commonly treated trauma in hospitals (1, 2). In 2019, the estimated annual incidence of
70 new fractures worldwide was 178 million (3). The process of bone healing involves
71 multiple consecutive and interrelated phases including inflammation, repair, and
72 remodeling, which occur in a spatial and temporal series of dynamic processes (4, 5). The
73 skeletal system possesses a remarkable capacity for regeneration. The initial process of
74 bone healing typically occurs over a period of eight weeks (6), while bone remodeling
75 extends for months following a fracture (7).

Independent of body location, traumatic injury sets off an acute non-specific immune response characterized by the release of pro-inflammatory cytokines such as interleukins (IL-1 β , IL-6, IL-10) and the tumor necrosis factor (TNF- α) (8). In addition, systemic acute inflammation after bone fracture promotes the sustained release of cytokines disrupting the blood-brain barrier, thereby allowing toxic intruders such as pro-inflammatory cytokines to invade/migrate to the central nervous system (CNS) (9). Persistent CNS inflammation plays a key mediating role in central sensitization (10), a maladaptive plasticity process driven by an increased response to nociceptive inputs, involved in pain persistence and chronicity. Chronic pain, a condition associated with delayed functional recovery, sleep disturbances, mental health disorders, and poorer quality of life (10), is highly prevalent 3-6 months after trauma, affecting 30-50% of individuals with bone fractures (11). A number of variables have been identified as potential predictors of chronic pain after trauma, including pain intensity at three months post-accident, female gender, poor sleep, levels of anxiety and depression, and the concomitant occurrence of traumatic brain injury (TBI) or peripheral nerve injury at the time of fracture (12-16).

Following a fracture, patients frequently report a range of symptoms, including increased fatigue and motor impairment, which can exert a significant impact on their ability to perform activities of daily living (17). In addition, patients with orthopedic trauma report a deterioration in their quality of life up to twelve months following the injury (17, 18). However, pain emerges as the most prominent complaint, with 97% of patients reporting pain after an orthopedic injury (1, 19). Acute pain management is a crucial concern considering that inadequate pain control can lead to prolonged inflammation, which can

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3 99 perpetuate pain signals and lead to chronic pain (20, 21). Currently, a pharmacological
4
5 100 approach is widely recommended to manage acute post-trauma pain. Both non-steroidal
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7 101 anti-inflammatory drugs (NSAIDs) and opioids are frequently prescribed for their anti-
8
9 102 inflammatory and analgesic effects (22). Nevertheless, the use of NSAIDs has been
10
11 103 associated with delayed bone healing (23, 24) as well as digestive complication and kidney
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13 104 failure (25). As for opioids, in addition to major side effects, they pose a high risk of
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15 105 dependence and tolerance (4, 26). Furthermore, several studies show that opioids inhibit
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17 106 effective bone remodeling (27), increase the risk of pseudarthrosis (28), and heighten the
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19 107 risk of hyperalgesia, i.e. a paradoxical increase in pain sensitivity due to central
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21 108 sensitization (26).
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28 110 Interestingly, following the legalization of cannabis in Colorado, a reduction in chronic
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30 111 pain admissions was observed, leading experts to question the potentially beneficial effects
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32 112 of cannabis on pain (29). Indeed, one study found that 61% of medical cannabis users
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34 113 reported consuming it to alleviate pain (30, 31). However, the medical use of cannabis is
35
36 114 limited due to the undesirable psychotropic and addictive effects of tetrahydrocannabinol
37
38 115 (THC). Cannabidiol (CBD), an organic component of cannabis, is non-psychoactive due
39
40 116 to its low affinity with the CB1 receptor (32). It is of particular interest as it is devoid of
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42 117 addictive effects (33, 34) and has an excellent safety profile (35), and its use does not affect
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44 118 daily activities such as driving or working.
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51 120 CBD is highly lipophilic which facilitate its ability to cross the blood-brain barrier (36).
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53 121 However, the bioavailability of CBD varies greatly according to the method of
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122 administration. The bioavailability of oral CBD is lower due to the hepatic first-pass effect,
123 with approximately 5% of the product reaching the bloodstream (37-39). Food
124 consumption as well as nanotech and oil-based formulations of CBD have been shown to
125 increase bioavailability (40). However, compared to smoked CBD, oral administration of
126 CBD presents multiple advantages, including greater control over dosage, ease of
127 administration, and fewer side effects (38).

128
129 Mechanisms of action of CBD are complex, not yet fully understood and involve multiple
130 pharmacological targets. Emerging evidence suggests that CBD exerts a number of
131 important effects via its modulating role on several non-cannabinoid receptors and ion
132 channels including those of endogenous neurotransmitters, such as serotonin (41) as well
133 as several types of TRP channels, such as TRPV1 (42), and by modulating the binding
134 affinity of certain G protein-coupled receptors (43). Several in vitro and animal model
135 studies have demonstrated CBD's anti-inflammatory effect, notably by reducing pro-
136 inflammatory cytokines such as TNF- α , IL-1 β and IL-6, in addition to inhibiting microglial
137 activation (32, 42, 44-51). CBD has also shown analgesic potential in studies using
138 neuropathic and inflammatory pain models. These human and animal studies suggest a
139 reduction in pain, hyperalgesia, and allodynia following treatment with CBD (35, 52-59).
140 CBD is alleged to possess anxiolytic and anti-depressant properties, as shown in several
141 animal and human studies (60-66). In addition, a well-controlled preliminary animal study
142 showed that CBD, but not THC, enhanced the biomechanical properties of healing mid-
143 femoral fractures in rats, supporting a beneficial effect of CBD on bone healing (67).

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3 145 Epidemiological studies have suggested a reduction in opioid use for pain coinciding with
4
5 146 an increased use of medical cannabis (30), a trend also documented in Canada (68). While
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8 147 the interaction between CBD and opioids is not yet fully understood, studies have shown
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10 148 that CBD acts as an allosteric modulator of the mu- and delta-opioid receptors (69). CBD
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13 149 was also shown to potentially enhance the analgesic effects of endogenous and exogenous
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15 150 opioids. In one study, the use of CBD as a co-analgesic treatment for patients with chronic
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17 151 pain resulted in a reduction in opioid consumption and improvements in overall quality of
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19 152 life (70).

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24 154 Providing effective pain management for patients with fractures is not only a fundamental
25
26 155 right but also offers numerous benefits. It reduces stress, shortens hospitalization time,
27
28 156 decreases associated healthcare costs and lowers the risk of developing chronic pain (1).
29
30 157 Preventing chronic pain is easier than reversing the sensitization processes that cause it
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32 158 (71), making acute pain control a priority. Given its excellent safety profile (33, 35)
33
34 159 coupled with its downregulating effects on microglial and inflammatory activity, the
35
36 160 primary neuroinflammatory and pain mechanism, CBD represents an appealing
37
38 161 neuroprotective agent for pain-susceptible orthopedic trauma patients.
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45 163 **Study objectives**

46
47 164 The primary objective of this study is to evaluate the effects of CBD treatment on self-
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49 165 reported pain in patients following a long bone fracture injury. The second objective is to
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51 166 assess the effect of the CBD treatment on inflammation and patient well-being.
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54 167 Additionally, secondary analyses will look at the possible associations between pain
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mediators (such as opioids, sex, and mild traumatic brain injury (mTBI)) and response to CBD treatment. The aim is to better identify the effects of these pain mediators on treatment response and the impact of CBD treatment on opioid uptake.

Methods

Study design

This is a randomized, placebo controlled, triple-blind 1-month clinical trial evaluating the effects of two doses (low and moderate) of CBD compared to a placebo on pain and inflammation after a long bone fracture.

Participants

A total of 225 participants aged 18 to 70 will be recruited within one week after their long bone fracture injury and consultation to the Hôpital du Sacré-Coeur de Montréal (HSCM), one of the largest Level 1 trauma centres in Canada with approximately 3,500 orthopedic patients treated annually.

Inclusion criteria

Subjects meeting the following criteria are eligible for the trial:

- Patients with a long bone fracture of the lower limb (tibia, fibula, femur, metatarsals, and phalanges) or the upper limb (humerus, radius, ulna, metacarpals, and phalanges) treated to Hôpital du Sacré-Coeur de Montréal (HSCM) within one week of the accident
- Participants is between 18 and 70 years of age

191 - Patients with or without surgical procedures

192

193 *Exclusion criteria*

194 Patients presenting any of the following characteristics are not eligible for the trial:

195 - Moderate/severe traumatic brain injury (TBI)

196 - Diagnosis of any of the following mental disorders as defined by the DSM-5:
197 schizophrenia, intellectual disability, bipolar disorder, major depression, a
198 diagnosed and untreated sleep disorders

199 - History of alcohol or opioid misuse/abuse

200 - Evidence of severe renal (stage 4 or 5) or hepatic impairment (Child B or C)

201 - Pregnant or lactating women, women of childbearing potential who are not using
202 medically accepted forms of contraception, or women who are planning on
203 becoming pregnant

204 - History of adverse reactions to cannabis

205 - Patients taking warfarin, sildenafil, valproate or under opioids treatment prior to the
206 injury

207 - Patients experiencing on average mild-to-absent pain in the last 24h preceding
208 recruitment (as per a score <30 on a 0-100mm Visual Analogue Scale (VAS))

209 - Transport business drivers and heavy machinery operators

210 - A diagnosis of chronic pain, bone pathology (e.g., osteoporosis) or chronic
211 inflammatory disease (e.g., rheumatoid arthritis, arthritis, psoriasis)

212 - Not having French or English as a spoken language

213 - A weighted MoCA score of less than 24

214 - Regular cannabis use more than 5 times a week

215

216 **Recruitment**

217 Recruitment will begin in September 2024. Potential participants will be screened daily by
218 the research team and collaborators. Potentially eligible patients will be approached by a
219 research team member and provided with a consent form. Once the research team has
220 addressed any remaining questions and obtained a signed consent form, the participant will
221 be randomized. See figure 1 for an overview of the study timeline.

222

223 **Assignment of interventions**

224 Participants will undergo concealed randomization to avoid selection bias. The study
225 pharmacist will randomly assign participants to one of the three treatment groups (low or
226 moderate CBD or placebo) using a 1:1:1 ratio through block randomization, stratified by
227 sex, age and type of fracture (i.e., lower and upper limb). The randomization procedure
228 will be performed a priori by an independent biostatistician. Identical tablets for CBD and
229 placebo will ensure blinding of clinicians, researchers, patients, families, and biostatistician
230 to avoid unequal co-interventions, ascertainment bias, and analytic bias. The study
231 pharmacist will be aware of allocation but will have no clinical or interpretive role.
232 Assignments will be kept in sequentially numbered, sealed envelopes to ensure adequate
233 allocation concealment. In the event of a serious adverse event or reaction, the allocation
234 list can be retrieved.

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237 **Intervention**

238 Patients in the treatment group will receive either a low dose (25 mg) or a moderate dose
239 (50 mg) of CBD self-administered orally as a tablet twice daily with a meal for one month.
240 Patients in the placebo group will receive an identical amount of a matching placebo
241 administered with a meal twice daily for one month.

242

243 *Investigational product*

244 CBD tablets, along with matching placebos, will be supplied by EmpowerPharm (Toronto,
245 Canada). The pharmacokinetic profile of the CBD product has already been established,
246 and efforts to register the product with Health Canada have begun.

247

248 *Dose justification*

249 A wide range of CBD doses ranging from <1 to 50mg/kg has been used in various
250 conditions (72, 73). The low dose (25 mg) selected for our study is based on initial and
251 ongoing studies of CBD in chronic pain which used a mean dose of 22.5mg and 20mg per
252 day (65). This is also approximately the mean dose of CBD administered in a successful
253 trial of Sativex (THC/CBD) for neuropathic pain (74). Moreover, a higher but relatively
254 moderate dose of CBD (50 mg) will be evaluated to assess dose-response effect. CBD
255 doses in this range have shown no statistical difference in intoxication scores in healthy
256 volunteers (75) and doses of up to 800 mg per day for a minimum of 4 weeks showed an
257 excellent safety and tolerability profile (76 , 77) Participants will be advised to ingest the
258 treatment at mealtime, as studies have shown an increased bioavailability of CBD in
259 subjects after eating (78, 79). To achieve our primary goal of mitigating acute pain, a one-

month treatment period has been selected, aligning with the typical evolution of acute pain post-fracture (6).

Study procedure

Upon enrollment in the study, research staff will provide study instructions, collect baseline data (e.g., demographics and clinical characteristics), administer questionnaires and cognitive tests, and collect blood samples for quantification of pro-inflammatory cytokines. Patients will report their pain intensity at baseline, and then three times a week throughout the entire one-month treatment duration. Participants will be instructed to complete a daily medication diary for one month to monitor the administration of study product, as well as opioid, drugs, or other analgesic medication use. This data will be collected via questionnaires sent by e-mail or SMS message from the RedCap secure database. At 24h following treatment completion (one-month follow-up) and at the 3-month follow-up, participants will be evaluated at the research laboratory to collect measures of pain intensity and related outcomes including opioids intake, inflammation, cognition, orthopedic function and indicators of overall well-being. Participants will have to abstain from CBD consumption from the end of treatment until the last follow-up visit. See Table 1 for a detailed schedule of assessments.

Primary outcome

The main outcome is the difference between groups in the mean pain intensity score at one-month follow-up, as measured by the visual analog scale (VAS) (80). Pain intensity on the VAS will be gathered 24h following treatment completion. The VAS is a 100mm line with

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283 anchor words ranging from “no pain” to “worst imaginable pain”. Participants will indicate
284 the intensity of their pain at that moment by placing a mark along the line.

285
286 **Secondary outcomes**

287 At 1 and 3-month follow-ups, persistent pain, opioid consumption, inflammation markers,
288 quality of life, sleep quality, depression, anxiety, cognition, mTBI symptom resolution, and
289 orthopaedic function outcomes will be collected. In addition, at baseline, participants will
290 be asked to indicate their level of treatment expectation using the Treatment Expectation
291 Questionnaire (TEX-Q-F) (81), a fifteen-question questionnaire, considering the potential
292 modulation of therapeutic effects by patients' expectations of treatment (82, 83). After
293 treatment completion, participants will also be asked to indicate whether they felt they had
294 received active treatment or placebo.

295
296 **Measures**

297 *Demographic and clinical characteristics*

298 The following information will be collected at baseline to characterize participants: age,
299 sex, height, weight, percentage of adipose tissue using an impedance meter scale,
300 occupation, education level, ethnicity, language spoken, pre-morbid medical history
301 (including psychological health history), pre-morbid substance use (e.g., alcohol, drugs,
302 cigarettes, medications), recreational cannabis use, history of brain trauma, injury type and
303 severity, mechanism of injury.

306 *Pain*

307 At 1- and 3-month follow-up, persistent pain will be assessed using the Brief Pain
308 Inventory short form (BPI-sf) (84), a 9-item self-report questionnaire assessing for the
309 presence, intensity, and location(s) of pain, as well as perceived efficacy of pain relief
310 treatment, and pain interference with activities of daily living. In addition, pain will be
311 assessed using the VAS at several time points for comparison: baseline, three times per
312 week during treatment, 24h after the end of treatment and at the 3-month follow-up. Pain
313 catastrophizing will also be assessed during the initial visit using the Pain Catastrophizing
314 Scale (85), a 13-item questionnaire evaluated on Likert scales, given the significant
315 contribution of psychological factors in the experience of pain.

316

317 *Opioid usage*

318 Participants will continue their usual pain care regimen throughout the study. Opioid usage
319 and analgesic will be recorded in a daily medication diary for the initial month and through
320 the number of prescription refills for months two and three. Self-reported opioid use in a
321 diary has been shown to be an accurate assessment of the quantity of opioids consumed
322 (86).

323

324 *Inflammation*

325 Blood levels of pro-inflammatory cytokines including interleukins (IL-6, IL-10, IL-1 β) and
326 TNF- α will be collected at baseline and at the 1 and 3-month follow-up sessions. To assess
327 cytokine levels, blood samples will be separated in buffy coat, serum and plasma, and
328 stored at -80 °C in polypropylene tubes on average 1-2h after the blood draw. EDTA

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plasma will be tested with cutting-edge ultra-sensitive Quanterix ImmunoAssay Analyzer
Simoa HD-X to quantify biomarkers using the Cor-Plex-Cytokine-10-Plex assay panel as
per manufacturer recommendation. Simoa is a leader in the quantification of plasma
biomarkers with markedly lower detection threshold than traditional ELISA (87).

Cognition

At baseline, 1 and 3-months follow-ups, neuropsychological tests highly sensitive to pain,
and that do not require the use of the fractured limb, will be administered: a task assessing
information processing speed (Symbol Search from the WAIS-IV Battery), two memory
tests (California Verbal Learning Test and Digit Span from the WAIS-IV battery), two
executive function tests (D-KEFS Color-Word and Verbal Fluency), and an attention test
(Elevator counting with distraction and Elevator counting without distraction from the Test
of Everyday Attention battery) (see Lezac et al., 1995 for test descriptions).

Mild TBI symptoms resolution

Patients who sustained a concomitant mTBI with their fracture will be included in the
study. Additional measures will be documented to control for this variable. At 1 and 3-
months follow-up, information on mTBI symptoms resolution will be collected for patients
diagnosed with a mTBI concomitant to the fracture using the Rivermead Post-Concussion
Questionnaire (88).

352 *Orthopaedic function*

353 At 1 and 3-months follow-ups, the Short Musculoskeletal Function Assessment (SMFA)
354 Questionnaire (89) will be administered. The SMFA includes 34 questions that evaluate
355 patient's function, and 12 questions related to how bothered patients are by their symptoms.

357 *Well-being*

358 At 1 and 3-months follow-ups, various important domains of well-being significantly
359 modulated by pain will be measured including: quality of life using the Short Form (36)
360 Health Survey (90), a 36-item self-report questionnaire for measuring quality of life across
361 9 domains; sleep quality and quantity using the Pittsburgh Sleep Quality Index (PSQI) (91),
362 a self-report questionnaire that assesses sleep quality and quantity over the past 4 weeks.
363 Additionally, at baseline, 1 and 3-months follow-ups depression and anxiety symptoms
364 will be assessed using the Beck's Depression Inventory-II (BDI-II) (92) and the Beck's
365 Anxiety Inventory (BAI) (86). The BDI-II is a 21-item multiple-choice self-report
366 questionnaire for measuring depression symptoms. The BAI is a 21-question multiple-
367 choice self-report inventory used for measuring the severity of anxiety. Finally, symptoms
368 of post-traumatic stress disorder will be assessed at the first visit and at 1-month follow-up
369 using the PTSD Checklist for DSM-5 (PCL-5) questionnaire (93).

371 **Data management**

372 Data collected will be transcribed from the source documents into the electronic Case
373 Report Form (eCRF) on the REDCap database hosted at CIUSSS du Nord-de-l'Île-de-
374 Montréal (94) and quality controlled by a second qualified staff member. Data will be

stored on a secure network with regular backups. An external, independent clinical monitor will conduct regular monitoring visits according to the monitoring plan, during which they will review and verify source data, informed consent forms, medical records, laboratory results, case report forms, medication dispensing logs and protocol deviations.

Statistical analyses

Sample size estimation

A 30% relative pain intensity reduction on the VAS (expected response of 50% or more in the CBD group and expected 20% in the placebo group) has been used extensively to reflect clinically significant pain relief in clinical trials. Based on a Fisher's exact test, a sample size of 225 participants (3 groups of 75) will be required to reach a power of 80% to detect a statistically significant difference in the proportion of patients who reaches 30% pain reduction between the CBD groups and placebo at 1-month post-injury, assuming a dropout rate of 20% and a significance level of 5%. These parameters are taken from a successful randomised, placebo-controlled clinical trial using Sativex® in treating 125 neuropathic pain patients (74).

Moreover, considering that the placebo group may ingest more opiates and that the anticipated inter-group effect at one month may be reduced to 20%, a total sample size of 225 subjects could be required to achieve 80% power, assuming a drop-out rate of 20% and a significance level of 5%.

398 *Primary outcome*

399 The primary outcome will be analyzed using an ANCOVA, with mTBI and orthopedic
400 surgery as covariables and treatment (low and moderate CBD vs. placebo) as factor in the
401 mean VAS pain score at the 1-month follow-up.

402

403 *Secondary outcomes*

404 For the secondary outcomes, a Kaplan Meier survival analysis with the log-rank test on
405 VAS pain data collected during treatment will be used to assess CBD treatment success
406 rate relative to placebo at achieving 50% pain intensity reduction during treatment duration.

407 The proportion of patients no longer experiencing significant pain symptoms at the 3-
408 month follow-up (i.e., patients who did not convert to chronic pain) will be compared, as
409 defined as VAS pain ≤ 30 between treatment with a chi-squared test. A mixed model for
410 repeated measures with covariables mTBI and orthopedic surgery and treatment as factor
411 will be used to assess between-group treatment effects on total opioids use at both 1 and 3-
412 month follow-ups. The same approach will be used to assess between-group treatment
413 effects at both 1- and 3-month follow-ups on secondary outcomes measures listed above.

414

415 **Discontinuation**

416 Participants may withdraw from this research project at any time without giving reasons.

417 Discontinuation of treatment does not imply withdrawal from the trial. The following
418 reasons will be considered as grounds for patient withdrawal from the trial: withdrawal of
419 consent by the participant, failure to pass the selection phase, meeting an exclusion
420 criterion, failure to participate in follow-up, termination of the trial by the investigator,

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421 major protocol deviation incompatible with trial participation, an adverse event or any
422 other condition which, in the opinion of the investigator, would expose the participant to
423 undue risk by continuing the treatment trial, any condition that the investigator considers
424 medically necessary to withdraw the patient from the trial.

425

426 **Adherence**

427 During the baseline visit, a research team member will conduct an information session to
428 discuss the significance of adhering to the guidelines related to doses, timing of drug
429 administration, the procedure to be followed in case of a missed dose, and the importance
430 of reporting any adverse event. Automatic SMS reminders will be sent to ensure
431 completion of the digital VAS and medication diary. A high protocol adherence is expected
432 given that cannabidiol has limited adverse side effects, and the administration is oral and
433 non-invasive. A 10% loss to follow-up is expected based on a 3-month trial with the same
434 patient characteristics. For adherence purposes, patients will be instructed to return all
435 treatment bottles, empty or not, to be monitored by the pharmacy staff. Each participant
436 will receive financial compensation for costs incurred during their participation in this
437 research study. Participants who withdraw or are withdrawn from the project prior to its
438 completion will receive an amount proportional to the length of their participation.

439

440 **Safety and serious adverse events**

441 Risks of adverse effects are considered low given the demonstrated excellent safety profile
442 of CBD (33, 35). Somnolence, fatigue, drowsiness, gastro-intestinal issue, and decreased
443 appetite are the most probable adverse events associated with CBD in adult patients (34).

444 Participants will be instructed to advise the research team of any adverse events which will
445 be thoroughly monitored and documented. Access to on-duty emergency physicians at
446 HSCM will be provided during the entire treatment duration.

447

448 **Patient and public involvement**

449 Neither patients nor the public were involved in the development, design and conduct of
450 this study.

451

452 **Confidentiality**

453 All data collected in our databases will be stored following a de-identification process.

454 Participants will be identified by a unique identification code, and nominal data will be
455 protected separately. Uncoded data will only be accessible to the principal investigator. No
456 identifying data will be disclosed in any scientific communication or publication.

457

458 **Ethics and dissemination**

459 Ethical approval has been granted by the CIUSSS du Nord-de-l'Île-de-Montréal ethics
460 board (#2025-2105 issued August 2024) and Health Canada (License, #LIC-
461 NKA1EX2TUA-202-3 issued on March 26, 2024, and No Objection Letter, HC6-024-
462 c275232 issued on May 30, 2024). This study adheres with the Declaration of Helsinki.
463 The results will be published in a peer-reviewed journal and presented at local, national,
464 and international conferences.

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Author Contributions

DB, DW, FB, CA, GL, AP, DR, LDB conceived the study. DB and AAD will ensure coordination, recruitment and conduct of the protocol. DB and LDB wrote the manuscript. All authors contributed to the revisions of the manuscript.

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Competing interests: None declared.

References

1. Ahmadi A, Bazargan-Hejazi S, Heidari Zadie Z, Euasobhon P, Ketumarn P, Karbasfrushan A, et al. Pain management in trauma: A review study. *J Inj Violence Res*. 2016;8(2):89-98.
2. Urquhart DM, Williamson OD, Gabbe BJ, Cicuttini FM, Cameron PA, Richardson MD, et al. Outcomes of patients with orthopaedic trauma admitted to level 1 trauma centres. *ANZ J Surg*. 2006;76(7):600-6.
3. Wu A-M, Bisignano C, James SL, Abady GG, Abedi A, Abu-Gharbieh E, et al. Global, regional, and national burden of bone fractures in 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019. *The Lancet Healthy Longevity*. 2021;2(9):e580-e92.
4. Alves CJ, Neto E, Sousa DM, Leitão L, Vasconcelos DM, Ribeiro-Silva M, et al. Fracture pain-Traveling unknown pathways. *Bone*. 2016;85:107-14.
5. Claes L, Recknagel S, Ignatius A. Fracture healing under healthy and inflammatory conditions. *Nat Rev Rheumatol*. 2012;8(3):133-43.
6. Einhorn TA, Gerstenfeld LC. Fracture healing: mechanisms and interventions. *Nat Rev Rheumatol*. 2015;11(1):45-54.
7. Marsell R, Einhorn TA. The biology of fracture healing. *Injury*. 2011;42(6):551-5.
8. Loi F, Córdova LA, Pajarinen J, Lin TH, Yao Z, Goodman SB. Inflammation, fracture and bone repair. *Bone*. 2016;86:119-30.
9. Huang X, Hussain B, Chang J. Peripheral inflammation and blood-brain barrier disruption: effects and mechanisms. *CNS Neurosci Ther*. 2021;27(1):36-47.
10. Fine PG. Long-term consequences of chronic pain: mounting evidence for pain as a neurological disease and parallels with other chronic disease states. *Pain Med*. 2011;12(7):996-1004.
11. Nampiaparampil DE. Prevalence of chronic pain after traumatic brain injury: a systematic review. *Jama*. 2008;300(6):711-9.
12. Castillo RC, MacKenzie EJ, Wegener ST, Bosse MJ. Prevalence of chronic pain seven years following limb threatening lower extremity trauma. *Pain*. 2006;124(3):321-9.
13. McDonald SJ, Sharkey JM, Sun M, Kaukas LM, Shultz SR, Turner RJ, et al. Beyond the Brain: Peripheral Interactions after Traumatic Brain Injury. *J Neurotrauma*. 2020;37(5):770-81.
14. Walker WC. Pain pathoetiology after TBI: neural and nonneural mechanisms. *The Journal of head trauma rehabilitation*. 2004;19(1):72-81.
15. Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. *Br J Anaesth*. 2013;111(1):52-8.
16. Molitoris KH, Balu AR, Huang M, Baht GS. The impact of age and sex on the inflammatory response during bone fracture healing. *JBMR Plus*. 2024;8(5).
17. Soleymanha M, Mobayen M, Asadi K, Adeli A, Haghparast-Ghadim-Limudahi Z. Survey of 2582 cases of acute orthopedic trauma. *Trauma Mon*. 2014;19(4):e16215.

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18. Sluys KP, Shults J, Richmond TS. Health related quality of life and return to work after minor extremity injuries: A longitudinal study comparing upper versus lower extremity injuries. *Injury*. 2016;47(4):824-31.

19. Archer KR, Castillo RC, Wegener ST, Abraham CM, Obremskey WT. Pain and satisfaction in hospitalized trauma patients: The importance of self-efficacy and psychological distress. *Journal of Trauma and Acute Care Surgery*. 2012;72(4):1068-77.

20. Mehta SP, MacDermid JC, Richardson J, MacIntyre NJ, Grewal R. Baseline pain intensity is a predictor of chronic pain in individuals with distal radius fracture. *J Orthop Sports Phys Ther*. 2015;45(2):119-27.

21. Powelson EB, Mills B, Henderson-Drager W, Boyd M, Vavilala MS, Curatolo M. Predicting chronic pain after major traumatic injury. *Scand J Pain*. 2019;19(3):453-64.

22. Majuta LA, Longo G, Fealk MN, McCaffrey G, Mantyh PW. Orthopedic surgery and bone fracture pain are both significantly attenuated by sustained blockade of nerve growth factor. *Pain*. 2015;156(1):157-65.

23. Atchison JW, Herndon CM, Rusie E. NSAIDs for musculoskeletal pain management: current perspectives and novel strategies to improve safety. *J Manag Care Pharm*. 2013;19(9 Suppl A):S3-19.

24. Maruyama M, Rhee C, Utsunomiya T, Zhang N, Ueno M, Yao Z, et al. Modulation of the Inflammatory Response and Bone Healing. *Front Endocrinol (Lausanne)*. 2020;11:386.

25. Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. *Biochem Pharmacol*. 2020;180:114147.

26. Lembke A, Humphreys K, Newmark J. Weighing the Risks and Benefits of Chronic Opioid Therapy. *Am Fam Physician*. 2016;93(12):982-90.

27. Raphael-Mizrahi B, Gabet Y. The Cannabinoids Effect on Bone Formation and Bone Healing. *Curr Osteoporos Rep*. 2020;18(5):433-8.

28. Buchheit T, Zura R, Wang Z, Mehta S, Della Rocca GJ, Steen RG. Opioid exposure is associated with nonunion risk in a traumatically injured population: An inception cohort study. *Injury*. 2018;49(7):1266-71.

29. RMHIDTA. The Legalization of Marijuana in Colorado: The Impact: Volume 6, September 2019. *Mo Med*. 2019;116(6):450.

30. Hill KP, Palastro MD, Johnson B, Ditre JW. Cannabis and Pain: A Clinical Review. *Cannabis Cannabinoid Res*. 2017;2(1):96-104.

31. Khan SP, Pickens TA, Berlau DJ. Perspectives on cannabis as a substitute for opioid analgesics. *Pain Manag*. 2019;9(2):191-203.

32. Burstein S. Cannabidiol (CBD) and its analogs: a review of their effects on inflammation. *Bioorg Med Chem*. 2015;23(7):1377-85.

33. Gray RA, Heal DJ, Maguire DR, Gerak LR, Javors MA, Smith S, et al. Preclinical Assessment of the Abuse Potential of Purified Botanical Cannabidiol: Self-Administration, Drug Discrimination, and Physical Dependence. *J Pharmacol Exp Ther*. 2022;382(1):54-65.

34. Micallef J, Batisse A, Revol B. [Pharmacology of cannabidiol: Red flags, consequences and risks in humans]. *Therapie*. 2022;77(5):585-90.

35. Alaia MJ, Hurley ET, Vasavada K, Markus DH, Britton B, Gonzalez-Lomas G, et al. Buccally Absorbed Cannabidiol Shows Significantly Superior Pain Control and Improved Satisfaction Immediately After Arthroscopic Rotator Cuff Repair: A Placebo-Controlled, Double-Blinded, Randomized Trial. *Am J Sports Med.* 2022;50(11):3056-63.
36. Calapai F, Cardia L, Sorbara EE, Navarra M, Gangemi S, Calapai G, et al. Cannabinoids, Blood–Brain Barrier, and Brain Disposition. *Pharmaceutics.* 2020;12(3):265.
37. Atsmon J, Heffetz D, Deutsch L, Deutsch F, Sacks H. Single-Dose Pharmacokinetics of Oral Cannabidiol Following Administration of PTL101: A New Formulation Based on Gelatin Matrix Pellets Technology. *Clin Pharmacol Drug Dev.* 2018;7(7):751-8.
38. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet.* 2003;42(4):327-60.
39. Hosseini A, McLachlan AJ, Lickliter JD. A phase I trial of the safety, tolerability and pharmacokinetics of cannabidiol administered as single-dose oil solution and single and multiple doses of a sublingual wafer in healthy volunteers. *Br J Clin Pharmacol.* 2021;87(4):2070-7.
40. Moazen-Zadeh E, Chisholm A, Bachi K, Hurd YL. Pharmacokinetics of Cannabidiol: A systematic review and meta-regression analysis. *medRxiv.* 2023.
41. Russo EB, Burnett A, Hall B, Parker KK. Agonistic Properties of Cannabidiol at 5-HT1a Receptors. *Neurochemical Research.* 2005;30(8):1037-43.
42. Costa B, Colleoni M, Conti S, Parolaro D, Franke C, Trovato AE, et al. Oral anti-inflammatory activity of cannabidiol, a non-psychoactive constituent of cannabis, in acute carrageenan-induced inflammation in the rat paw. *Naunyn Schmiedebergs Arch Pharmacol.* 2004;369(3):294-9.
43. Laun AS, Shrader SH, Brown KJ, Song ZH. GPR3, GPR6, and GPR12 as novel molecular targets: their biological functions and interaction with cannabidiol. *Acta Pharmacol Sin.* 2019;40(3):300-8.
44. Kuret T, Kreft ME, Romih R, Veranič P. Cannabidiol as a Promising Therapeutic Option in IC/BPS: In Vitro Evaluation of Its Protective Effects against Inflammation and Oxidative Stress. *Int J Mol Sci.* 2023;24(5).
45. Kongkadee K, Wisuitiprot W, Ingkaninan K, Waranuch N. Anti-inflammation and gingival wound healing activities of Cannabis sativa L. subsp. sativa (hemp) extract and cannabidiol: An in vitro study. *Arch Oral Biol.* 2022;140:105464.
46. Yndart Arias A, Kolishetti N, Vashist A, Madepalli L, Llaguno L, Nair M. Anti-inflammatory effects of CBD in human microglial cell line infected with HIV-1. *Sci Rep.* 2023;13(1):7376.
47. Li H, Kong W, Chambers CR, Yu D, Ganea D, Tuma RF, et al. The non-psychoactive phytocannabinoid cannabidiol (CBD) attenuates pro-inflammatory mediators, T cell infiltration, and thermal sensitivity following spinal cord injury in mice. *Cell Immunol.* 2018;329:1-9.
48. Kozela E, Juknat A, Vogel Z. Modulation of Astrocyte Activity by Cannabidiol, a Nonpsychoactive Cannabinoid. *Int J Mol Sci.* 2017;18(8).

49. Kozela E, Lev N, Kaushansky N, Eilam R, Rimmerman N, Levy R, et al. Cannabidiol inhibits pathogenic T cells, decreases spinal microglial activation and ameliorates multiple sclerosis-like disease in C57BL/6 mice. *Br J Pharmacol*. 2011;163(7):1507-19.
50. Giacoppo S, Galuppo M, Pollastro F, Grassi G, Bramanti P, Mazzon E. A new formulation of cannabidiol in cream shows therapeutic effects in a mouse model of experimental autoimmune encephalomyelitis. *Daru*. 2015;23:48.
51. Dopkins N, Miranda K, Wilson K, Holloman BL, Nagarkatti P, Nagarkatti M. Effects of Orally Administered Cannabidiol on Neuroinflammation and Intestinal Inflammation in the Attenuation of Experimental Autoimmune Encephalomyelitis. *J Neuroimmune Pharmacol*. 2022;17(1-2):15-32.
52. Britch SC, Craft RM. Cannabidiol and Delta-9-Tetrahydrocannabinol Interactions in Male and Female Rats With Persistent Inflammatory Pain. *J Pain*. 2023;24(1):98-111.
53. Costa B, Trovato AE, Comelli F, Giagnoni G, Colleoni M. The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. *Eur J Pharmacol*. 2007;556(1-3):75-83.
54. Aguiar DD, da Costa Oliveira C, Fonseca FCS, de Almeida DL, Campos Pereira WV, Guimarães FS, et al. Peripherally injected cannabidiol reduces neuropathic pain in mice: Role of the 5-HT(1A) and TRPV1 receptors. *Biochem Biophys Res Commun*. 2023;660:58-64.
55. Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clin Rehabil*. 2003;17(1):21-9.
56. Wanasuntronwong A, Kaewsrising S, Rotpenpian N, Arayapisit T, Pavasant P, Suprongsinchai W. Efficacy and mechanism of the antinociceptive effects of cannabidiol on acute orofacial nociception induced by Complete Freund's Adjuvant in male *Mus musculus* mice. *Arch Oral Biol*. 2022;144:105570.
57. Urits I, Gress K, Charipova K, Habib K, Lee D, Lee C, et al. Use of cannabidiol (CBD) for the treatment of chronic pain. *Best Pract Res Clin Anaesthesiol*. 2020;34(3):463-77.
58. Gulbransen G, Xu W, Arroll B. Cannabidiol prescription in clinical practice: an audit on the first 400 patients in New Zealand. *BJGP Open*. 2020;4(1).
59. Verrico CD, Wesson S, Konduri V, Hofferek CJ, Vazquez-Perez J, Blair E, et al. A randomized, double-blind, placebo-controlled study of daily cannabidiol for the treatment of canine osteoarthritis pain. *Pain*. 2020;161(9):2191-202.
60. Guimarães FS, Chiaretti TM, Graeff FG, Zuardi AW. Antianxiety effect of cannabidiol in the elevated plus-maze. *Psychopharmacology (Berl)*. 1990;100(4):558-9.
61. de Mello Schier AR, de Oliveira Ribeiro NP, Coutinho DS, Machado S, Arias-Carrión O, Crippa JA, et al. Antidepressant-like and anxiolytic-like effects of cannabidiol: a chemical compound of *Cannabis sativa*. *CNS Neurol Disord Drug Targets*. 2014;13(6):953-60.
62. Resstel LB, Tavares RF, Lisboa SF, Joca SR, Corrêa FM, Guimarães FS. 5-HT1A receptors are involved in the cannabidiol-induced attenuation of behavioural and cardiovascular responses to acute restraint stress in rats. *Br J Pharmacol*. 2009;156(1):181-8.

- 663 63. Zanelati TV, Biojone C, Moreira FA, Guimarães FS, Joca SR. Antidepressant-like
664 effects of cannabidiol in mice: possible involvement of 5-HT_{1A} receptors. *Br J Pharmacol*.
665 2010;159(1):122-8.
- 666 64. Bergamaschi MM, Queiroz RH, Chagas MH, de Oliveira DC, De Martinis BS,
667 Kapczinski F, et al. Cannabidiol reduces the anxiety induced by simulated public speaking
668 in treatment-naïve social phobia patients. *Neuropsychopharmacology*. 2011;36(6):1219-
669 26.
- 670 65. Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmons S, et al. Initial
671 experiences with medicinal extracts of cannabis for chronic pain: Results from 34 'N of 1'
672 studies. *Anaesthesia*. 2004;59(5):440-52.
- 673 66. Shannon S, Lewis N, Lee H, Hughes S. Cannabidiol in Anxiety and Sleep: A Large
674 Case Series. *Perm J*. 2019;23:18-041.
- 675 67. Kogan NM, Melamed E, Wasserman E, Raphael B, Breuer A, Stok KS, et al.
676 Cannabidiol, a Major Non-Psychotropic Cannabis Constituent Enhances Fracture Healing
677 and Stimulates Lysyl Hydroxylase Activity in Osteoblasts. *J Bone Miner Res*.
678 2015;30(10):1905-13.
- 679 68. Lucas P, Baron EP, Jikomes N. Medical cannabis patterns of use and substitution
680 for opioids & other pharmaceutical drugs, alcohol, tobacco, and illicit substances; results
681 from a cross-sectional survey of authorized patients. *Harm Reduct J*. 2019;16(1):9.
- 682 69. Kathmann M, Flau K, Redmer A, Tränkle C, Schlicker E. Cannabidiol is an allosteric
683 modulator at mu- and delta-opioid receptors. *Naunyn Schmiedebergs Arch Pharmacol*.
684 2006;372(5):354-61.
- 685 70. Capano A, Weaver R, Burkman E. Evaluation of the effects of CBD hemp extract on
686 opioid use and quality of life indicators in chronic pain patients: a prospective cohort
687 study. *Postgrad Med*. 2020;132(1):56-61.
- 688 71. Loggia ML, Chonde DB, Akeju O, Arabasz G, Catana C, Edwards RR, et al. Evidence
689 for brain glial activation in chronic pain patients. *Brain*. 2015;138(Pt 3):604-15.
- 690 72. Hendricks O, Andersen TE, Christiansen AA, Primdahl J, Hauge EM, Ellingsen T, et
691 al. Efficacy and safety of cannabidiol followed by an open label add-on of
692 tetrahydrocannabinol for the treatment of chronic pain in patients with rheumatoid
693 arthritis or ankylosing spondylitis: protocol for a multicentre, randomised, placebo-
694 controlled study. *BMJ open* [Internet]. 2019 2019/06//; 9(6):[e028197 p.]. Available from:
695 <http://europepmc.org/abstract/MED/31167870>.
- 696 73. Millar SA, Stone NL, Bellman ZD, Yates AS, England TJ, O'Sullivan SE. A systematic
697 review of cannabidiol dosing in clinical populations. *Br J Clin Pharmacol*. 2019;85(9):1888-
698 900.
- 699 74. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex
700 successfully treats neuropathic pain characterised by allodynia: a randomised, double-
701 blind, placebo-controlled clinical trial. *Pain*. 2007;133(1-3):210-20.
- 702 75. Solowij N, Broyd S, Greenwood L-m, van Hell H, Martellozzo D, Rueb K, et al. A
703 randomised controlled trial of vaporised Δ⁹-tetrahydrocannabinol and cannabidiol alone
704 and in combination in frequent and infrequent cannabis users: acute intoxication effects.
705 *European Archives of Psychiatry and Clinical Neuroscience*. 2019;269(1):17-35.

76. Freeman TP, Hindocha C, Baio G, Shaban NDC, Thomas EM, Astbury D, et al. Cannabidiol for the treatment of cannabis use disorder: a phase 2a, double-blind, placebo-controlled, randomised, adaptive Bayesian trial. *Lancet Psychiatry*. 2020;7(10):865-74.
77. Mongeau-Pérusse V, Brissette S, Bruneau J, Conrod P, Dubreucq S, Gazil G, et al. Cannabidiol as a treatment for craving and relapse in individuals with cocaine use disorder: a randomized placebo-controlled trial. *Addiction*. 2021;116(9):2431-42.
78. Mozaffari K, Willette S, Lucker BF, Kovar SE, Holguin FO, Guzman I. The Effects of Food on Cannabidiol Bioaccessibility. *Molecules*. 2021;26(12).
79. Silmore LH, Willmer AR, Capparelli EV, Rosania GR. Food effects on the formulation, dosing, and administration of cannabidiol (CBD) in humans: A systematic review of clinical studies. *Pharmacotherapy*. 2021;41(4):405-20.
80. Delgado DA, Lambert BS, Boutris N, McCulloch PC, Robbins AB, Moreno MR, et al. Validation of Digital Visual Analog Scale Pain Scoring With a Traditional Paper-based Visual Analog Scale in Adults. *JAAOS Global Research & Reviews*. 2018;2(3):e088.
81. Shedden-Mora MC, Alberts J, Petrie KJ, Laferton JAC, von Blanckenburg P, Kohlmann S, et al. The Treatment Expectation Questionnaire (TEX-Q): Validation of a generic multidimensional scale measuring patients' treatment expectations. *PLoS One*. 2023;18(1):e0280472.
82. Benedetti F, Carlino E, Piedimonte A. Increasing uncertainty in CNS clinical trials: the role of placebo, nocebo, and Hawthorne effects. *Lancet Neurol*. 2016;15(7):736-47.
83. Spinella TC, Stewart SH, Naugler J, Yakovenko I, Barrett SP. Evaluating cannabidiol (CBD) expectancy effects on acute stress and anxiety in healthy adults: a randomized crossover study. *Psychopharmacology (Berl)*. 2021;238(7):1965-77.
84. Jumbo SU, MacDermid JC, Kalu ME, Packham TL, Athwal GS, Faber KJ. Measurement Properties of the Brief Pain Inventory-Short Form (BPI-SF) and Revised Short McGill Pain Questionnaire Version-2 (SF-MPQ-2) in Pain-related Musculoskeletal Conditions: A Systematic Review. *Clin J Pain*. 2021;37(6):454-74.
85. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. *Psychological Assessment*. 1995;7:524-32.
86. Daoust R, Paquet J, Williamson D, Perry JJ, Iseppon M, Castonguay V, et al. Accuracy of a self-report prescription opioid use diary for patients discharge from the emergency department with acute pain: a multicentre prospective cohort study. *BMJ Open*. 2022;12(10):e062984.
87. Li D, Mielke MM. An Update on Blood-Based Markers of Alzheimer's Disease Using the SiMoA Platform. *Neurol Ther*. 2019;8(Suppl 2):73-82.
88. King NS, Crawford S, Wenden FJ, Moss NE, Wade DT. The Rivermead Post Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced after head injury and its reliability. *J Neurol*. 1995;242(9):587-92.
89. Swiontkowski MF, Engelberg R, Martin DP, Agel J. Short musculoskeletal function assessment questionnaire: validity, reliability, and responsiveness. *J Bone Joint Surg Am*. 1999;81(9):1245-60.

90. Garratt AM, Ruta DA, Abdalla MI, Buckingham JK, Russell IT. The SF36 health survey questionnaire: an outcome measure suitable for routine use within the NHS? *Bmj*. 1993;306(6890):1440-4.
91. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193-213.
92. Beck AT, Steer RA, Brown G. Beck depression inventory : manual. . Psychological Corporation: San Antonio, TX. 1996.
93. Ashbaugh AR, Houle-Johnson S, Herbert C, El-Hage W, Brunet A. Psychometric Validation of the English and French Versions of the Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5). *PLoS One*. 2016;11(10):e0161645.
94. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*. 2009;42(2):377-81.

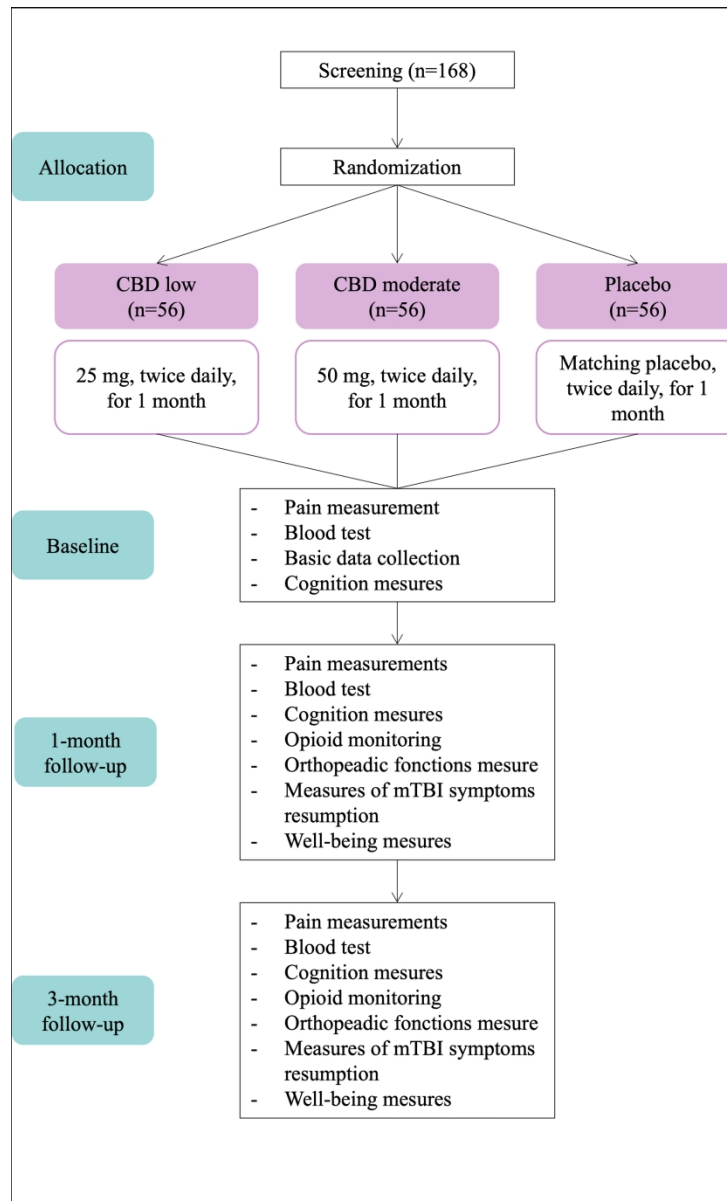


Figure 1 - Study schema

171x281mm (300 x 300 DPI)

Domain	Mesure	Screening	Baseline	During Treatment	1-month follow-up	3-month follow-up
Eligibility	Demographic questionnaire	X	X			
	Consent form	X				
	Medical history	X				
	MoCA	X				
	Medication	X	X	X	X	X
Primary outcome	Visual Analog Scale	X	X	X	X	X
	Brief Pain Inventory short form (BPI-sf)				X	X
	Blood sample - Inflammation markers		X		X	X
	Cognition		X		X	X
	Rivermead TBI symptoms				X	X
	Short Musculoskeletal Function Assessment (SMFA)				X	X
	Short Form Health Survey				X	X
	Pittsburgh Sleep Quality Index (PSQI)				X	X
	Beck's Depression Inventory-II		X		X	X
	Beck's Anxiety Inventory		X		X	X
	Pain Catastrophizing Scale (PCS)		X			
	Treatment Expectation Questionnaire (TEX-Q)		X			
	PTSD Checklist for DSM-5 (PCL-5)		X		X	
	Treatment assignment hypothesis				X	
Other	Opioid consumption	X	X	X	X	X
	Adverse events			X	X	

Table 1. Schedule of assessment

172x213mm (144 x 144 DPI)

BMJ Open

Impact of an acute 1-month cannabidiol treatment on pain and inflammation after a long bone fracture: a triple-blind randomized, placebo controlled, clinical trial protocol

Journal:	<i>BMJ Open</i>
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Impact of an acute 1-month cannabidiol treatment on pain and inflammation after a long bone fracture: a triple-blind randomized, placebo controlled, clinical trial protocol

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Abstract

Introduction. Acute pain levels following orthopedic injury (e.g., fracture) is a predictor of the onset of chronic pain, which affects nearly 50% of fracture patients and impairs functional recovery. Among current pharmacological treatments for acute pain, non-steroidal anti-inflammatory drugs have been associated with delayed bone healing, while opioids inhibit effective bone remodeling, increase the risk of pseudarthrosis, and carry a high risk of addiction. In light of this, the development of new pain treatments is essential.

Cannabidiol (CBD), a non-addictive and non-psychotropic cannabis component stands out as a potential therapeutic agent, given its analgesic and anti-inflammatory properties as well as its potential benefits for bone healing. This randomized controlled trial aims to investigate the effect of acute CBD treatment, compared to placebo, on patients' self-reported pain, inflammation and well-being following a fracture injury.

Methods and analysis. This is a triple-blind, randomized, placebo-controlled clinical trial. A total of 225 adults aged 18 to 70 years, who have suffered a long bone fracture and were treated at the Hôpital du Sacré-Coeur de Montréal, will be randomly assigned within one week to one of three treatment arms (25 mg or 50 mg of CBD or placebo) for one month. The primary outcome will be difference in the pain score between groups at one-month follow-up. Secondary outcomes will include measures of persistent pain, inflammation, opioid usage, quality of life, sleep quality, depression, anxiety, cognition and orthopaedic function. Data will be collected at baseline, 1- and 3-month follow-ups.

Ethics and dissemination. This study obtained a Health Canada license for use of cannabis products. It has also been approved by Health Canada and the Research Ethics Board of the CIUSSS du Nord-de-l'Île-de-Montréal (Project ID 2025-2105). The findings will be published in a peer-reviewed journal and presented at local, national, and international conferences. The trial's results will be made publicly available on the clinicaltrials.gov database.

Trial registration number: NCT06448923 (registered on [ClinicalTrials.gov](https://clinicaltrials.gov))

53 **Strengths and limitations of this study**

- 54 - This is the first human randomized clinical trial to assess the potential therapeutic
- 55 effects of cannabidiol on pain and inflammation following orthopaedic trauma.
- 56 - This trial includes a longitudinal assessment of CBD treatment on pain symptoms
- 57 and trauma-related outcomes up to three months post-fracture which marks the
- 58 critical period of transition to chronic pain.
- 59 - To help gain a more comprehensive understanding of the effects of pain mediators
- 60 on treatment response, as well as the effects of treatment on opioid uptake, this
- 61 study will assess potential interactions between pain mediators, such as opioids,
- 62 mild traumatic brain injury and sex, and response to CBD treatment.
- 63 - One limitation of this study is that therapeutic drug monitoring was not performed,
- 64 which could have helped account for inter-individual variability and optimize
- 65 dosing.

66 **Introduction**

67 Bone fractures are a prevalent condition affecting individuals of all ages and are the most
68 commonly treated trauma in hospitals [1, 2]. In 2019, the estimated annual incidence of
69 new fractures worldwide was 178 million [3]. The process of bone healing involves
70 multiple consecutive and interrelated phases including inflammation, repair, and
71 remodeling, which occur in a spatial and temporal series of dynamic processes [4, 5]. The
72 skeletal system possesses a remarkable capacity for regeneration. The initial process of
73 bone healing typically occurs over a period of eight weeks [6], while bone remodeling
74 extends for months following a fracture [7].

Independent of body location, traumatic injury sets off an acute non-specific immune response characterized by the release of pro-inflammatory cytokines such as interleukins (IL-1 β , IL-6, IL-10) and the tumor necrosis factor (TNF- α) [8]. In addition, systemic acute inflammation after bone fracture promotes the sustained release of cytokines disrupting the blood-brain barrier, thereby allowing toxic intruders such as pro-inflammatory cytokines to invade/migrate to the central nervous system (CNS) [9]. Persistent CNS inflammation plays a key mediating role in central sensitization [10], a maladaptive plasticity process driven by an increased response to nociceptive inputs, involved in pain persistence and chronicity. Chronic pain, a condition associated with delayed functional recovery, sleep disturbances, mental health disorders, and poorer quality of life [10], is highly prevalent 3-6 months after trauma, affecting 30-50% of individuals with bone fractures [11]. A number of variables have been identified as potential predictors of chronic pain after trauma, including pain intensity at three months post-accident, female sex, poor sleep, levels of anxiety and depression, and the concomitant occurrence of traumatic brain injury (TBI) or peripheral nerve injury at the time of fracture [12-16].

Following a fracture, patients frequently report a range of symptoms, including increased fatigue and motor impairment, which can exert a significant impact on their ability to perform activities of daily living [17]. In addition, patients with orthopedic trauma report a deterioration in their quality of life up to twelve months following the injury [17, 18]. However, pain emerges as the most prominent complaint, with 97% of patients reporting pain after an orthopedic injury [1, 19]. Acute pain management is a crucial concern considering that inadequate pain control can lead to prolonged inflammation, which can

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98 perpetuate pain signals and lead to chronic pain [20, 21]. Currently, a pharmacological
99 approach is widely recommended to manage acute post-trauma pain. Both non-steroidal
100 anti-inflammatory drugs (NSAIDs) and opioids are frequently prescribed for their anti-
101 inflammatory and analgesic effects [22]. Nevertheless, the use of NSAIDs has been
102 associated with delayed bone healing [23, 24] as well as digestive complication and kidney
103 failure [25]. As for opioids, in addition to major side effects, they pose a high risk of
104 dependence and tolerance [4, 26]. Furthermore, several studies show that opioids inhibit
105 effective bone remodeling [27], increase the risk of pseudarthrosis [28], and heighten the
106 risk of hyperalgesia, i.e. a paradoxical increase in pain sensitivity due to central
107 sensitization [26].
108
109 Interestingly, following the legalization of cannabis in Colorado, a reduction in chronic
110 pain admissions was observed, leading experts to question the potentially beneficial effects
111 of cannabis on pain [29]. Indeed, one study found that 61% of medical cannabis users
112 reported consuming it to alleviate pain [30, 31]. However, the medical use of cannabis is
113 limited due to the undesirable psychotropic and addictive effects of tetrahydrocannabinol
114 (THC). Cannabidiol (CBD), an organic component of cannabis, is non-psychoactive due
115 to its low affinity with the CB1 receptor [32]. It is of particular interest as it is devoid of
116 addictive effects [33, 34] and has an excellent safety profile [35], and its use does not affect
117 daily activities such as driving or working.
118
119 CBD is highly lipophilic which facilitates its ability to cross the blood-brain barrier [36].
120 However, the bioavailability of CBD varies greatly according to the method of

121 administration. The bioavailability of oral CBD is lower due to the hepatic first-pass effect,
122 with approximately 5% of the product reaching the bloodstream [37-39]. Food
123 consumption as well as nanotech and oil-based formulations of CBD have been shown to
124 increase bioavailability [40]. However, compared to smoked CBD, oral administration of
125 CBD presents multiple advantages, including greater control over dosage, ease of
126 administration, and fewer side effects [38].

127
128 Mechanisms of action of CBD are complex, not yet fully understood and involve multiple
129 pharmacological targets. Emerging evidence suggests that CBD exerts a number of
130 important effects via its modulating role on several non-cannabinoid receptors and ion
131 channels including those of endogenous neurotransmitters, such as serotonin [41] as well
132 as several types of transient receptor potential channels (TRP), such as TRPV1 [42], and
133 by modulating the binding affinity of certain G protein-coupled receptors [43]. Several in
134 vitro and animal model studies have demonstrated CBD's anti-inflammatory effect, notably
135 by reducing pro-inflammatory cytokines such as TNF- α , IL-1 β and IL-6, in addition to
136 inhibiting microglial activation [32, 42, 44-51]. CBD has also shown analgesic potential in
137 studies using neuropathic and inflammatory pain models. These human and animal studies
138 suggest a reduction in pain, hyperalgesia, and allodynia following treatment with CBD [35,
139 52-59]. CBD is alleged to possess anxiolytic and anti-depressant properties, as shown in
140 several animal and human studies [60-66]. In addition, a well-controlled preliminary
141 animal study showed that CBD, but not THC, enhanced the biomechanical properties of
142 healing mid-femoral fractures in rats, supporting a beneficial effect of CBD on bone
143 healing [67].

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145 Epidemiological studies have suggested a reduction in opioid use for pain coinciding with

146 an increased use of medical cannabis [30], a trend also documented in Canada [68]. While

147 the interaction between CBD and opioids is not yet fully understood, studies have shown

148 that CBD acts as an allosteric modulator of the mu- and delta-opioid receptors [69]. CBD

149 was also shown to potentially enhance the analgesic effects of endogenous and exogenous

150 opioids. In one study, the use of CBD as a co-analgesic treatment for patients with chronic

151 pain resulted in a reduction in opioid consumption and improvements in overall quality of

152 life [70].

153

154 Providing effective pain management for patients with fractures is not only a fundamental

155 right but also offers numerous benefits. It reduces stress, shortens hospitalization time,

156 decreases associated healthcare costs and lowers the risk of developing chronic pain [1].

157 Preventing chronic pain is easier than reversing the sensitization processes that cause it

158 [71], making acute pain control a priority. Given its excellent safety profile [33, 35]

159 coupled with its downregulating effects on microglial and inflammatory activity, the

160 primary neuroinflammatory and pain mechanism, CBD represents an appealing

161 neuroprotective agent for pain-susceptible orthopedic trauma patients.

162

163 **Study objectives**

164 The primary objective of this study is to evaluate the effects of CBD treatment on self-

165 reported pain in patients following a long bone fracture injury. The second objective is to

166 assess the effect of the CBD treatment on inflammation and patient well-being.

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3 167 Additionally, secondary analyses will look at the possible associations between pain
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5 168 mediators (such as opioids, sex, and mild traumatic brain injury (mTBI)) and response to
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8 169 CBD treatment. The aim is to better identify the effects of these pain mediators on treatment
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10 170 response and the impact of CBD treatment on opioid uptake.
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14 172 **Methods**

15 173 **Study design**

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18 174 This is a randomized, placebo controlled, triple-blind 1-month clinical trial evaluating the
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20 175 effects of two doses (low and moderate) of CBD compared to a placebo on pain and
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23 176 inflammation after a long bone fracture.
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27 178 **Participants**

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29 179 A total of 225 participants aged 18 to 70 will be recruited within one week after their long
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31 180 bone fracture injury and consultation to the Hôpital du Sacré-Coeur de Montréal (HSCM),
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33 181 one of the largest Level 1 trauma centres in Canada with approximately 3,500 orthopedic
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36 182 patients treated annually. The planned age range, targeting a population representative of
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38 183 individuals who frequently experience traumatic fractures, was chosen as it allows for a
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41 184 more homogenous evaluation of fracture healing and pain recovery. Including participants
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44 185 over 70 introduces additional challenges, such as increased comorbidities, chronic diseases,
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46 186 bone fragility, polymedication and increased complications, which could slow the healing
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49 187 process, influence pain perception and complicate result interpretation.
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190 *Inclusion criteria*

191 Subjects meeting the following criteria are eligible for the trial:

- 192 - Patients with a long bone fracture of the lower limb (tibia, fibula, femur,
193 metatarsals, and phalanges) or the upper limb (humerus, radius, ulna, metacarpals,
194 and phalanges) treated to Hôpital du Sacré-Coeur de Montréal (HSCM) within one
195 week of the accident
- 196 - Participants is between 18 and 70 years of age
- 197 - Patients with or without surgical procedures

199 *Exclusion criteria*

200 Patients presenting any of the following characteristics are not eligible for the trial:

- 201 - Moderate/severe traumatic brain injury (TBI)
- 202 - Diagnosis of any of the following mental disorders as defined by the DSM-5:
203 schizophrenia, intellectual disability, bipolar disorder, major depression, a
204 diagnosed and untreated sleep disorders
- 205 - History of alcohol or opioid misuse/abuse, as defined by the DSM-5
- 206 - Evidence of severe renal (stage 4 or 5) or hepatic impairment (Child B or C)
- 207 - Pregnant or lactating women, women of childbearing potential who are not using
208 medically accepted forms of contraception (e.g., condoms, oral contraceptive or
209 intrauterine device), or women who are actively planning on becoming pregnant
- 210 - History of adverse reactions to cannabis
- 211 - Patients taking warfarin, sildenafil, valproate or under opioids treatment prior to the
212 injury

- 213 - Patients experiencing on average mild-to-absent pain in the last 24h preceding
- 214 recruitment (as per a score <30 on a 0-100mm Visual Analogue Scale (VAS))
- 215 - Transport business drivers and heavy machinery operators
- 216 - A diagnosis of chronic pain, bone pathology (e.g., osteoporosis) or chronic
- 217 inflammatory disease (e.g., rheumatoid arthritis, arthritis, psoriasis)
- 218 - Not having French or English as a spoken language
- 219 - A weighted MoCA score of less than 24
- 220 - Regular cannabis use more than 5 times a week

221

222 Recruitment

223 Recruitment will begin in January 2025 and end in January 2027. Potential participants will
224 be screened daily by the research team and collaborators. Potentially eligible patients will
225 be approached by a research team member and provided with a consent form. Once the
226 research team has addressed any remaining questions and obtained a signed consent form,
227 the participant will be randomized. See figure 1 for an overview of the study timeline.

228

229 Assignment of interventions

230 Participants will undergo concealed randomization to avoid selection bias. The study
231 pharmacist will randomly assign participants to one of the three treatment groups (low or
232 moderate CBD or placebo) using a 1:1:1 ratio through block randomization with randomly
233 selected block sizes, stratified by sex, age (i.e., participants aged 45 and under, and those
234 over 45) and type of fracture (i.e., lower and upper limb). The randomization procedure
235 will be performed a priori by an independent biostatistician. Identical tablets for CBD and

236 placebo will ensure blinding of clinicians, researchers, patients, families, and biostatistician
237 to avoid unequal co-interventions, ascertainment bias, and analytic bias. The study
238 pharmacist will be aware of allocation but will have no clinical or interpretive role.
239 Assignments will be kept in sequentially numbered, sealed envelopes to ensure adequate
240 allocation concealment. In the event of a serious adverse event or reaction, the allocation
241 list can be retrieved.

243 **Intervention**

244 Patients in the treatment group will receive either a low dose (25 mg per tablet) or a
245 moderate dose (50 mg per tablet) of CBD self-administered orally as a tablet twice daily
246 with a meal for one month. Patients in the placebo group will receive an identical amount
247 of a matching placebo administered with a meal twice daily for one month.

249 *Investigational product*

250 CBD tablets, along with matching placebos, will be supplied by EmpowerPharm (Toronto,
251 Canada). The pharmacokinetic profile of the CBD product has already been established,
252 and efforts to register the product with Health Canada have begun.

254 *Dose justification*

255 A wide range of CBD doses ranging from <1 to 50mg/kg has been used in various
256 conditions [72, 73]. The low dose (25 mg) selected for our study is based on initial and
257 ongoing studies of CBD in chronic pain which used a mean dose of 22.5mg and 20mg per
258 day [65]. This is also approximately the mean dose of CBD administered in a successful

trial of Sativex (THC/CBD) for neuropathic pain [74]. Moreover, a higher but relatively moderate dose of CBD (50 mg) will be evaluated to assess dose-response effect. CBD doses in this range have shown no statistical difference in intoxication scores in healthy volunteers [75] and doses of up to 800 mg per day for a minimum of 4 weeks showed an excellent safety and tolerability profile [76, 77]. Participants will be advised to ingest the treatment at mealtime, as studies have shown an increased bioavailability of CBD in subjects after eating [78, 79]. To achieve our primary goal of mitigating acute pain, a one-month treatment period has been selected, aligning with the typical evolution of acute pain post-fracture [6].

Study procedure

Upon enrollment in the study, research staff will provide study instructions, collect baseline data (e.g., demographics and clinical characteristics), administer questionnaires and cognitive tests, and collect blood samples for quantification of pro-inflammatory cytokines. Patients will report their pain intensity at baseline, and then three times a week throughout the entire one-month treatment duration. Participants will be instructed to complete a daily medication diary for one month to monitor the administration of study product, as well as opioid, drugs, or other analgesic medication use. This data will be collected via questionnaires sent by e-mail or SMS message from the RedCap secure database. At 24h following treatment completion (one-month follow-up) and at the 3-month follow-up, participants will be evaluated at the research laboratory to collect measures of pain intensity and related outcomes including opioids intake, inflammation, cognition, orthopedic function and indicators of overall well-being. Participants will have to abstain from CBD

consumption from the end of treatment until the last follow-up visit. See Table 1 for a detailed schedule of assessments.

Table 1. Schedule of assessment

Domain	Mesure	Screening	Baseline	During Treatment	1-month follow-up	3-month follow-up
Eligibility	Demographic questionnaire	X	X			
	Consent form	X				
	Medical history	X				
	MoCA	X				
	Medication	X	X	X	X	X
Primary outcome	Visual Analog Scale	X	X	X	X	X
Secondary outcomes	Brief Pain Inventory short form (BPI-sf)				X	X
	Blood sample - Inflammation markers		X		X	X
	Cognition		X		X	X
	Rivermead TBI symptoms				X	X
	Short Musculoskeletal Function Assessment (SMFA)				X	X
	Short Form Health Survey				X	X
	Pittsburgh Sleep Quality Index (PSQI)				X	X
	Beck's Depression Inventory-II		X		X	X
	Beck's Anxiety Inventory		X		X	X
Other	Pain Catastrophizing Scale (PCS)		X			

Treatment Expectation Questionnaire (TEX-Q)		X			
PTSD Checklist for DSM-5 (PCL-5)		X		X	
Treatment assignment hypothesis				X	
Opioid consumption	X	X	X	X	X
Adverse events			X	X	

Primary outcome

The main outcome is the difference between groups in the mean pain intensity score at one-month follow-up, as measured by the visual analog scale (VAS) [80]. Pain intensity on the VAS will be gathered 24h following treatment completion. The VAS is a 100mm line with anchor words ranging from “no pain” to “worst imaginable pain”. Participants will indicate the intensity of their pain at that moment by placing a mark along the line.

Secondary outcomes

At 1 and 3-month follow-ups, persistent pain, opioid consumption, inflammation markers, quality of life, sleep quality, depression, anxiety, cognition, mTBI symptom resolution, and orthopaedic function outcomes will be collected. In addition, at baseline, participants will be asked to indicate their level of treatment expectation using the Treatment Expectation Questionnaire (TEX-Q-F) [81], a fifteen-question questionnaire, considering the potential modulation of therapeutic effects by patients' expectations of treatment [82, 83]. After treatment completion, participants will also be asked to indicate whether they felt they had received active treatment or placebo.

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304 **Measures**

305 *Demographic and clinical characteristics*

306 The following information will be collected at baseline to characterize participants: age,
307 sex, height, weight, percentage of adipose tissue using an impedance meter scale,
308 occupation, education level, ethnicity, language spoken, pre-morbid medical history
309 (including psychological health history), pre-morbid substance use (e.g., alcohol, drugs,
310 cigarettes, medications), recreational cannabis use, history of brain trauma, injury type and
311 severity, mechanism of injury.

312

313 *Pain*

314 At 1- and 3-month follow-up, persistent pain will be assessed using the Brief Pain
315 Inventory short form (BPI-sf) [84], a 9-item self-report questionnaire assessing for the
316 presence, intensity, and location(s) of pain, as well as perceived efficacy of pain relief
317 treatment, and pain interference with activities of daily living. In addition, pain will be
318 assessed using the VAS at several time points for comparison: baseline, three times per
319 week during treatment, 24h after the end of treatment and at the 3-month follow-up. Pain
320 catastrophizing will also be assessed during the initial visit using the Pain Catastrophizing
321 Scale [85], a 13-item questionnaire evaluated on Likert scales, given the significant
322 contribution of psychological factors in the experience of pain.

323

324 *Opioid usage*

325 Participants will continue their usual pain care regimen throughout the study. Opioid usage
326 and analgesic will be recorded in a daily medication diary for the initial month and through

the number of prescription refills for months two and three. Self-reported opioid use in a diary has been shown to be an accurate assessment of the quantity of opioids consumed [86].

Inflammation

Blood levels of pro-inflammatory cytokines including interleukins (IL-6, IL-10, IL-1 β) and TNF- α will be collected at baseline and at the 1 and 3-month follow-up sessions. To assess cytokine levels, blood samples will be separated in buffy coat, serum and plasma, and stored at -80 °C in polypropylene tubes on average 1-2h after the blood draw. EDTA plasma will be tested with cutting-edge ultra-sensitive Quanterix ImmunoAssay Analyzer Simoa HD-X to quantify biomarkers using the Cor-Plex-Cytokine-10-Plex assay panel as per manufacturer recommendation. Simoa is a leader in the quantification of plasma biomarkers with markedly lower detection threshold than traditional ELISA [87].

Cognition

At baseline, 1 and 3-months follow-ups, neuropsychological tests highly sensitive to pain, and that do not require the use of the fractured limb, will be administered: a task assessing information processing speed (Symbol Search from the WAIS-IV Battery), two memory tests (California Verbal Learning Test and Digit Span from the WAIS-IV battery), two executive function tests (D-KEFS Color-Word and Verbal Fluency), and an attention test (Elevator counting with distraction and Elevator counting without distraction from the Test of Everyday Attention battery) (see Lezac et al., 1995 for test descriptions).

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350 *Mild TBI symptoms resolution*

351 Patients who sustained a concomitant mTBI with their fracture will be included in the
352 study. Additional measures will be documented to control for this variable. At 1 and 3-
353 months follow-up, information on mTBI symptoms resolution will be collected for patients
354 diagnosed with a mTBI concomitant to the fracture using the Rivermead Post-Concussion
355 Questionnaire [88].

357 *Orthopaedic function*

358 At 1 and 3-months follow-ups, the Short Musculoskeletal Function Assessment (SMFA)
359 Questionnaire [89] will be administered. The SMFA includes 34 questions that evaluate
360 patient's function, and 12 questions related to how bothered patients are by their symptoms.

362 *Well-being*

363 At 1 and 3-months follow-ups, various important domains of well-being significantly
364 modulated by pain will be measured including: quality of life using the Short Form (36)
365 Health Survey [90], a 36-item self-report questionnaire for measuring quality of life across
366 9 domains; sleep quality and quantity using the Pittsburgh Sleep Quality Index (PSQI) [91],
367 a self-report questionnaire that assesses sleep quality and quantity over the past 4 weeks.
368 Additionally, at baseline, 1 and 3-months follow-ups depression and anxiety symptoms
369 will be assessed using the Beck's Depression Inventory-II (BDI-II) [92] and the Beck's
370 Anxiety Inventory (BAI) (86). The BDI-II is a 21-item multiple-choice self-report
371 questionnaire for measuring depression symptoms. The BAI is a 21-question multiple-
372 choice self-report inventory used for measuring the severity of anxiety. Finally, symptoms

of post-traumatic stress disorder will be assessed at the first visit and at 1-month follow-up using the PTSD Checklist for DSM-5 (PCL-5) questionnaire [93].

Data management

Data collected will be transcribed from the source documents into the electronic Case Report Form (eCRF) on the REDCap database hosted at CIUSSS du Nord-de-l'Île-de-Montréal [94] and quality controlled by a second qualified staff member. Data will be stored on a secure network with regular backups. An external, independent clinical monitor will conduct regular monitoring visits according to the monitoring plan, during which they will review and verify source data, informed consent forms, medical records, laboratory results, case report forms, medication dispensing logs and protocol deviations.

Statistical analyses

Sample size estimation

A 30% relative pain intensity reduction on the VAS (expected response of 50% or more in the CBD group and expected 20% in the placebo group) has been used extensively to reflect clinically significant pain relief in clinical trials. Based on a Fisher's exact test, a sample size of 225 participants (3 groups of 75) will be required to reach a power of 80% to detect a statistically significant difference in the proportion of patients who reaches 30% pain reduction between the CBD groups and placebo at 1-month post-injury, assuming a dropout rate of 20% and a significance level of 5%. These parameters are taken from a successful randomised, placebo-controlled clinical trial using Sativex© in treating 125 neuropathic pain patients [74].

Moreover, considering that the placebo group may ingest more opiates and that the anticipated inter-group effect at one month may be reduced to 20%, a total sample size of 225 subjects could be required to achieve 80% power, assuming a drop-out rate of 20% and a significance level of 5%.

400

401 *Primary outcome*

The primary outcome will be analyzed using an ANCOVA, with mTBI and orthopedic surgery as covariables and treatment (low and moderate CBD vs. placebo) as factor in the mean VAS pain score at the 1-month follow-up.

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406 *Secondary outcomes*

For the secondary outcomes, a Kaplan Meier survival analysis with the log-rank test on VAS pain data collected during treatment will be used to assess CBD treatment success rate relative to placebo at achieving 50% pain intensity reduction during treatment duration. The proportion of patients no longer experiencing significant pain symptoms at the 3-month follow-up (i.e., patients who did not convert to chronic pain) will be compared, as defined as VAS pain ≤ 30 between treatment with a chi-squared test. A mixed model for repeated measures with covariables mTBI and orthopedic surgery and treatment as factor will be used to assess between-group treatment effects on total opioids use at both 1 and 3-month follow-ups. The same approach will be used to assess between-group treatment effects at both 1- and 3-month follow-ups on secondary outcomes measures listed above.

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Analyses will be performed on an intention-to-treat (ITT) dataset. The ITT dataset will include all participants randomized in the analysis, whether or not they have completed treatment in order to limit bias and reflect results under real treatment conditions.

Missing data will be reported and justified in the results. The multiple imputation method, which has been recognized in clinical studies involving experimental treatment, will be applied. Additionally, a sensitivity analysis will be performed to assess the impact of missing data on the results.

Discontinuation

Participants may withdraw from this research project at any time without giving reasons. Discontinuation of treatment does not imply withdrawal from the trial. The following reasons will be considered as grounds for patient withdrawal from the trial: withdrawal of consent by the participant, failure to pass the selection phase, meeting an exclusion criterion, failure to participate in follow-up, termination of the trial by the investigator, major protocol deviation incompatible with trial participation, an adverse event or any other condition which, in the opinion of the investigator, would expose the participant to undue risk by continuing the treatment trial, any condition that the investigator considers medically necessary to withdraw the patient from the trial.

Adherence

During the baseline visit, a research team member will conduct an information session to discuss the significance of adhering to the guidelines related to doses, timing of drug

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administration, the procedure to be followed in case of a missed dose, and the importance of reporting any adverse event. Automatic SMS reminders will be sent to ensure completion of the digital VAS and medication diary. A high protocol adherence is expected given that cannabidiol has limited adverse side effects, and the administration is oral and non-invasive. A 10% loss to follow-up is expected based on a 3-month trial with the same patient characteristics[95]. For adherence purposes, patients will be instructed to return all treatment bottles, empty or not, to be monitored by the pharmacy staff. Each participant will receive financial compensation for costs incurred during their participation in this research study. Participants who withdraw or are withdrawn from the project prior to its completion will receive an amount proportional to the length of their participation.

Safety and serious adverse events

Risks of adverse effects are considered low given the demonstrated excellent safety profile of CBD [33, 35]. Somnolence, fatigue, drowsiness, gastro-intestinal issue, and decreased appetite are the most probable adverse events associated with CBD in adult patients [34]. Participants will be instructed to advise the research team of any adverse events which will be thoroughly monitored and documented. Access to on-duty emergency physicians at HSCM will be provided during the entire treatment duration.

Patient and public involvement

Neither patients nor the public were involved in the development, design and conduct of this study.

Confidentiality

All data collected in our databases will be stored following a de-identification process. Participants will be identified by a unique identification code, and nominal data will be protected separately. Uncoded data will only be accessible to the principal investigator. No identifying data will be disclosed in any scientific communication or publication.

Ethics and dissemination

Ethical approval has been granted by the CIUSSS du Nord-de-l'Île-de-Montréal ethics board (#2025-2105 issued August 2024) and Health Canada (License, #LIC-NKA1EX2TUA-202-3 issued on March 26, 2024, and No Objection Letter, HC6-024-c275232 issued on May 30, 2024). This study adheres with the Declaration of Helsinki. The results will be published in a peer-reviewed journal and presented at local, national, and international conferences.

Author Contributions

DB, DW, FB, CA, GL, AP, DR, LDB conceived the study. DB and AAD will ensure coordination, recruitment and conduct of the protocol. DB and LDB wrote the manuscript. All authors contributed to the revisions of the manuscript. LDB is guarantor.

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EmpowerPharm (Ontario, Canada). The study's design, management, analysis, and reporting are entirely independent of the CBD manufacturers.

Competing interests: None declared.

Figure 1. Study Schema. CBD, cannabidiol; mTBI, mild traumatic brain injury.

References

[1] Ahmadi A, Bazargan-Hejazi S, Heidari Zadie Z, Euasobhon P, Ketumarn P, Karbasfrushan A, et al. Pain management in trauma: A review study. *J Inj Violence Res*. 2016;8(2):89-98.

[2] Urquhart DM, Williamson OD, Gabbe BJ, Cicuttini FM, Cameron PA, Richardson MD, et al. Outcomes of patients with orthopaedic trauma admitted to level 1 trauma centres. *ANZ J Surg*. 2006;76(7):600-6.

[3] Wu A-M, Bisignano C, James SL, Abady GG, Abedi A, Abu-Gharbieh E, et al. Global, regional, and national burden of bone fractures in 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019. *The Lancet Healthy Longevity*. 2021;2(9):e580-e92.

[4] Alves CJ, Neto E, Sousa DM, Leitão L, Vasconcelos DM, Ribeiro-Silva M, et al. Fracture pain-Traveling unknown pathways. *Bone*. 2016;85:107-14.

[5] Claes L, Recknagel S, Ignatius A. Fracture healing under healthy and inflammatory conditions. *Nat Rev Rheumatol*. 2012;8(3):133-43.

[6] Einhorn TA, Gerstenfeld LC. Fracture healing: mechanisms and interventions. *Nat Rev Rheumatol*. 2015;11(1):45-54.

[7] Marsell R, Einhorn TA. The biology of fracture healing. *Injury*. 2011;42(6):551-5.

[8] Loi F, Córdova LA, Pajarinen J, Lin TH, Yao Z, Goodman SB. Inflammation, fracture and bone repair. *Bone*. 2016;86:119-30.

[9] Huang X, Hussain B, Chang J. Peripheral inflammation and blood-brain barrier disruption: effects and mechanisms. *CNS Neurosci Ther*. 2021;27(1):36-47.

[10] Fine PG. Long-term consequences of chronic pain: mounting evidence for pain as a neurological disease and parallels with other chronic disease states. *Pain Med*. 2011;12(7):996-1004.

[11] Nampiaparampil DE. Prevalence of chronic pain after traumatic brain injury: a systematic review. *Jama*. 2008;300(6):711-9.

- [12] Castillo RC, MacKenzie EJ, Wegener ST, Bosse MJ. Prevalence of chronic pain seven years following limb threatening lower extremity trauma. *Pain*. 2006;124(3):321-9.
- [13] McDonald SJ, Sharkey JM, Sun M, Kaukas LM, Shultz SR, Turner RJ, et al. Beyond the Brain: Peripheral Interactions after Traumatic Brain Injury. *J Neurotrauma*. 2020;37(5):770-81.
- [14] Walker WC. Pain pathoetiology after TBI: neural and nonneural mechanisms. *The Journal of head trauma rehabilitation*. 2004;19(1):72-81.
- [15] Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. *Br J Anaesth*. 2013;111(1):52-8.
- [16] Molitoris KH, Balu AR, Huang M, Baht GS. The impact of age and sex on the inflammatory response during bone fracture healing. *JBMR Plus*. 2024;8(5).
- [17] Soleymanha M, Mobayen M, Asadi K, Adeli A, Haghparast-Ghadim-Limudahi Z. Survey of 2582 cases of acute orthopedic trauma. *Trauma Mon*. 2014;19(4):e16215.
- [18] Sluys KP, Shults J, Richmond TS. Health related quality of life and return to work after minor extremity injuries: A longitudinal study comparing upper versus lower extremity injuries. *Injury*. 2016;47(4):824-31.
- [19] Archer KR, Castillo RC, Wegener ST, Abraham CM, Obremskey WT. Pain and satisfaction in hospitalized trauma patients: The importance of self-efficacy and psychological distress. *Journal of Trauma and Acute Care Surgery*. 2012;72(4):1068-77.
- [20] Mehta SP, MacDermid JC, Richardson J, MacIntyre NJ, Grewal R. Baseline pain intensity is a predictor of chronic pain in individuals with distal radius fracture. *J Orthop Sports Phys Ther*. 2015;45(2):119-27.
- [21] Powelson EB, Mills B, Henderson-Drager W, Boyd M, Vavilala MS, Curatolo M. Predicting chronic pain after major traumatic injury. *Scand J Pain*. 2019;19(3):453-64.
- [22] Majuta LA, Longo G, Fealk MN, McCaffrey G, Mantyh PW. Orthopedic surgery and bone fracture pain are both significantly attenuated by sustained blockade of nerve growth factor. *Pain*. 2015;156(1):157-65.
- [23] Atchison JW, Herndon CM, Rusie E. NSAIDs for musculoskeletal pain management: current perspectives and novel strategies to improve safety. *J Manag Care Pharm*. 2013;19(9 Suppl A):S3-19.
- [24] Maruyama M, Rhee C, Utsunomiya T, Zhang N, Ueno M, Yao Z, et al. Modulation of the Inflammatory Response and Bone Healing. *Front Endocrinol (Lausanne)*. 2020;11:386.
- [25] Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. *Biochem Pharmacol*. 2020;180:114147.
- [26] Lembke A, Humphreys K, Newmark J. Weighing the Risks and Benefits of Chronic Opioid Therapy. *Am Fam Physician*. 2016;93(12):982-90.
- [27] Raphael-Mizrahi B, Gabet Y. The Cannabinoids Effect on Bone Formation and Bone Healing. *Curr Osteoporos Rep*. 2020;18(5):433-8.
- [28] Buchheit T, Zura R, Wang Z, Mehta S, Della Rocca GJ, Steen RG. Opioid exposure is associated with nonunion risk in a traumatically injured population: An inception cohort study. *Injury*. 2018;49(7):1266-71.

- [29] RMHIDTA. The Legalization of Marijuana in Colorado: The Impact: Volume 6, September 2019. *Mo Med*. 2019;116(6):450.
- [30] Hill KP, Palastro MD, Johnson B, Ditre JW. Cannabis and Pain: A Clinical Review. *Cannabis Cannabinoid Res*. 2017;2(1):96-104.
- [31] Khan SP, Pickens TA, Berlau DJ. Perspectives on cannabis as a substitute for opioid analgesics. *Pain Manag*. 2019;9(2):191-203.
- [32] Burstein S. Cannabidiol (CBD) and its analogs: a review of their effects on inflammation. *Bioorg Med Chem*. 2015;23(7):1377-85.
- [33] Gray RA, Heal DJ, Maguire DR, Gerak LR, Javors MA, Smith S, et al. Preclinical Assessment of the Abuse Potential of Purified Botanical Cannabidiol: Self-Administration, Drug Discrimination, and Physical Dependence. *J Pharmacol Exp Ther*. 2022;382(1):54-65.
- [34] Micallef J, Batisse A, Revol B. [Pharmacology of cannabidiol: Red flags, consequences and risks in humans]. *Thérapie*. 2022;77(5):585-90.
- [35] Alaia MJ, Hurley ET, Vasavada K, Markus DH, Britton B, Gonzalez-Lomas G, et al. Buccally Absorbed Cannabidiol Shows Significantly Superior Pain Control and Improved Satisfaction Immediately After Arthroscopic Rotator Cuff Repair: A Placebo-Controlled, Double-Blinded, Randomized Trial. *Am J Sports Med*. 2022;50(11):3056-63.
- [36] Calapai F, Cardia L, Sorbara EE, Navarra M, Gangemi S, Calapai G, et al. Cannabinoids, Blood-Brain Barrier, and Brain Disposition. *Pharmaceutics*. 2020;12(3):265.
- [37] Atsmon J, Heffetz D, Deutsch L, Deutsch F, Sacks H. Single-Dose Pharmacokinetics of Oral Cannabidiol Following Administration of PTL101: A New Formulation Based on Gelatin Matrix Pellets Technology. *Clin Pharmacol Drug Dev*. 2018;7(7):751-8.
- [38] Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet*. 2003;42(4):327-60.
- [39] Hosseini A, McLachlan AJ, Lickliter JD. A phase I trial of the safety, tolerability and pharmacokinetics of cannabidiol administered as single-dose oil solution and single and multiple doses of a sublingual wafer in healthy volunteers. *Br J Clin Pharmacol*. 2021;87(4):2070-7.
- [40] Moazen-Zadeh E, Chisholm A, Bachi K, Hurd YL. Pharmacokinetics of Cannabidiol: A systematic review and meta-regression analysis. *medRxiv*. 2023.
- [41] Russo EB, Burnett A, Hall B, Parker KK. Agonistic Properties of Cannabidiol at 5-HT1a Receptors. *Neurochemical Research*. 2005;30(8):1037-43.
- [42] Costa B, Colleoni M, Conti S, Parolaro D, Franke C, Trovato AE, et al. Oral anti-inflammatory activity of cannabidiol, a non-psychoactive constituent of cannabis, in acute carrageenan-induced inflammation in the rat paw. *Naunyn Schmiedeberg Arch Pharmacol*. 2004;369(3):294-9.
- [43] Laun AS, Shrader SH, Brown KJ, Song ZH. GPR3, GPR6, and GPR12 as novel molecular targets: their biological functions and interaction with cannabidiol. *Acta Pharmacol Sin*. 2019;40(3):300-8.
- [44] Kuret T, Kreft ME, Romih R, Veranič P. Cannabidiol as a Promising Therapeutic Option in IC/BPS: In Vitro Evaluation of Its Protective Effects against Inflammation and Oxidative Stress. *Int J Mol Sci*. 2023;24(5).

- [45] Kongkadee K, Wisuitiprot W, Ingkaninan K, Waranuch N. Anti-inflammation and gingival wound healing activities of *Cannabis sativa* L. subsp. *sativa* (hemp) extract and cannabidiol: An in vitro study. *Arch Oral Biol*. 2022;140:105464.
- [46] Yndart Arias A, Kolishetti N, Vashist A, Madepalli L, Llaguno L, Nair M. Anti-inflammatory effects of CBD in human microglial cell line infected with HIV-1. *Sci Rep*. 2023;13(1):7376.
- [47] Li H, Kong W, Chambers CR, Yu D, Ganea D, Tuma RF, et al. The non-psychoactive phytocannabinoid cannabidiol (CBD) attenuates pro-inflammatory mediators, T cell infiltration, and thermal sensitivity following spinal cord injury in mice. *Cell Immunol*. 2018;329:1-9.
- [48] Kozela E, Juknat A, Vogel Z. Modulation of Astrocyte Activity by Cannabidiol, a Nonpsychoactive Cannabinoid. *Int J Mol Sci*. 2017;18(8).
- [49] Kozela E, Lev N, Kaushansky N, Eilam R, Rimmerman N, Levy R, et al. Cannabidiol inhibits pathogenic T cells, decreases spinal microglial activation and ameliorates multiple sclerosis-like disease in C57BL/6 mice. *Br J Pharmacol*. 2011;163(7):1507-19.
- [50] Giacoppo S, Galuppo M, Pollastro F, Grassi G, Bramanti P, Mazzon E. A new formulation of cannabidiol in cream shows therapeutic effects in a mouse model of experimental autoimmune encephalomyelitis. *Daru*. 2015;23:48.
- [51] Dopkins N, Miranda K, Wilson K, Holloman BL, Nagarkatti P, Nagarkatti M. Effects of Orally Administered Cannabidiol on Neuroinflammation and Intestinal Inflammation in the Attenuation of Experimental Autoimmune Encephalomyelitis. *J Neuroimmune Pharmacol*. 2022;17(1-2):15-32.
- [52] Britch SC, Craft RM. Cannabidiol and Delta-9-Tetrahydrocannabinol Interactions in Male and Female Rats With Persistent Inflammatory Pain. *J Pain*. 2023;24(1):98-111.
- [53] Costa B, Trovato AE, Comelli F, Giagnoni G, Colleoni M. The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. *Eur J Pharmacol*. 2007;556(1-3):75-83.
- [54] Aguiar DD, da Costa Oliveira C, Fonseca FCS, de Almeida DL, Campos Pereira WV, Guimarães FS, et al. Peripherally injected cannabidiol reduces neuropathic pain in mice: Role of the 5-HT(1A) and TRPV1 receptors. *Biochem Biophys Res Commun*. 2023;660:58-64.
- [55] Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clin Rehabil*. 2003;17(1):21-9.
- [56] Wanasuntronwong A, Kaewsrising S, Rotpenpian N, Arayapisit T, Pavasant P, Suprongsinchai W. Efficacy and mechanism of the antinociceptive effects of cannabidiol on acute orofacial nociception induced by Complete Freund's Adjuvant in male *Mus musculus* mice. *Arch Oral Biol*. 2022;144:105570.
- [57] Urits I, Gress K, Charipova K, Habib K, Lee D, Lee C, et al. Use of cannabidiol (CBD) for the treatment of chronic pain. *Best Pract Res Clin Anaesthesiol*. 2020;34(3):463-77.
- [58] Gulbransen G, Xu W, Arroll B. Cannabidiol prescription in clinical practice: an audit on the first 400 patients in New Zealand. *BJGP Open*. 2020;4(1).

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[59] Verrico CD, Wesson S, Konduri V, Hofferek CJ, Vazquez-Perez J, Blair E, et al. A randomized, double-blind, placebo-controlled study of daily cannabidiol for the treatment of canine osteoarthritis pain. *Pain*. 2020;161(9):2191-202.

[60] Guimarães FS, Chiaretti TM, Graeff FG, Zuairi AW. Antianxiety effect of cannabidiol in the elevated plus-maze. *Psychopharmacology (Berl)*. 1990;100(4):558-9.

[61] de Mello Schier AR, de Oliveira Ribeiro NP, Coutinho DS, Machado S, Arias-Carrión O, Crippa JA, et al. Antidepressant-like and anxiolytic-like effects of cannabidiol: a chemical compound of *Cannabis sativa*. *CNS Neurol Disord Drug Targets*. 2014;13(6):953-60.

[62] Resstel LB, Tavares RF, Lisboa SF, Joca SR, Corrêa FM, Guimarães FS. 5-HT1A receptors are involved in the cannabidiol-induced attenuation of behavioural and cardiovascular responses to acute restraint stress in rats. *Br J Pharmacol*. 2009;156(1):181-8.

[63] Zanelati TV, Biojone C, Moreira FA, Guimarães FS, Joca SR. Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT1A receptors. *Br J Pharmacol*. 2010;159(1):122-8.

[64] Bergamaschi MM, Queiroz RH, Chagas MH, de Oliveira DC, De Martinis BS, Kapczinski F, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. *Neuropsychopharmacology*. 2011;36(6):1219-26.

[65] Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmons S, et al. Initial experiences with medicinal extracts of cannabis for chronic pain: Results from 34 'N of 1' studies. *Anaesthesia*. 2004;59(5):440-52.

[66] Shannon S, Lewis N, Lee H, Hughes S. Cannabidiol in Anxiety and Sleep: A Large Case Series. *Perm J*. 2019;23:18-041.

[67] Kogan NM, Melamed E, Wasserman E, Raphael B, Breuer A, Stok KS, et al. Cannabidiol, a Major Non-Psychotropic Cannabis Constituent Enhances Fracture Healing and Stimulates Lysyl Hydroxylase Activity in Osteoblasts. *J Bone Miner Res*. 2015;30(10):1905-13.

[68] Lucas P, Baron EP, Jikomes N. Medical cannabis patterns of use and substitution for opioids & other pharmaceutical drugs, alcohol, tobacco, and illicit substances; results from a cross-sectional survey of authorized patients. *Harm Reduct J*. 2019;16(1):9.

[69] Kathmann M, Flau K, Redmer A, Tränkle C, Schlicker E. Cannabidiol is an allosteric modulator at mu- and delta-opioid receptors. *Naunyn Schmiedeberg's Arch Pharmacol*. 2006;372(5):354-61.

[70] Capano A, Weaver R, Burkman E. Evaluation of the effects of CBD hemp extract on opioid use and quality of life indicators in chronic pain patients: a prospective cohort study. *Postgrad Med*. 2020;132(1):56-61.

[71] Loggia ML, Chonde DB, Akeju O, Arabasz G, Catana C, Edwards RR, et al. Evidence for brain glial activation in chronic pain patients. *Brain*. 2015;138(Pt 3):604-15.

[72] Hendricks O, Andersen TE, Christiansen AA, Primdahl J, Hauge EM, Ellingsen T, et al. Efficacy and safety of cannabidiol followed by an open label add-on of tetrahydrocannabinol for the treatment of chronic pain in patients with rheumatoid arthritis or ankylosing spondylitis: protocol for a multicentre, randomised, placebo-

- controlled study. BMJ open [Internet]. 2019 2019/06//; 9(6):[e028197 p.]. Available from: <http://europepmc.org/abstract/MED/31167870>.
- [73] Millar SA, Stone NL, Bellman ZD, Yates AS, England TJ, O'Sullivan SE. A systematic review of cannabidiol dosing in clinical populations. *Br J Clin Pharmacol*. 2019;85(9):1888-900.
- [74] Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain*. 2007;133(1-3):210-20.
- [75] Solowij N, Broyd S, Greenwood L-m, van Hell H, Martellozzo D, Rueb K, et al. A randomised controlled trial of vaporised $\Delta 9$ -tetrahydrocannabinol and cannabidiol alone and in combination in frequent and infrequent cannabis users: acute intoxication effects. *European Archives of Psychiatry and Clinical Neuroscience*. 2019;269(1):17-35.
- [76] Freeman TP, Hindocha C, Baio G, Shaban NDC, Thomas EM, Astbury D, et al. Cannabidiol for the treatment of cannabis use disorder: a phase 2a, double-blind, placebo-controlled, randomised, adaptive Bayesian trial. *Lancet Psychiatry*. 2020;7(10):865-74.
- [77] Mongeau-Pérusse V, Brissette S, Bruneau J, Conrod P, Dubreucq S, Gazil G, et al. Cannabidiol as a treatment for craving and relapse in individuals with cocaine use disorder: a randomized placebo-controlled trial. *Addiction*. 2021;116(9):2431-42.
- [78] Mozaffari K, Willette S, Lucker BF, Kovar SE, Holguin FO, Guzman I. The Effects of Food on Cannabidiol Bioaccessibility. *Molecules*. 2021;26(12).
- [79] Silmore LH, Willmer AR, Capparelli EV, Rosania GR. Food effects on the formulation, dosing, and administration of cannabidiol (CBD) in humans: A systematic review of clinical studies. *Pharmacotherapy*. 2021;41(4):405-20.
- [80] Delgado DA, Lambert BS, Boutris N, McCulloch PC, Robbins AB, Moreno MR, et al. Validation of Digital Visual Analog Scale Pain Scoring With a Traditional Paper-based Visual Analog Scale in Adults. *JAAOS Global Research & Reviews*. 2018;2(3):e088.
- [81] Shedden-Mora MC, Alberts J, Petrie KJ, Laferton JAC, von Blanckenburg P, Kohlmann S, et al. The Treatment Expectation Questionnaire (TEX-Q): Validation of a generic multidimensional scale measuring patients' treatment expectations. *PLoS One*. 2023;18(1):e0280472.
- [82] Benedetti F, Carlino E, Piedimonte A. Increasing uncertainty in CNS clinical trials: the role of placebo, nocebo, and Hawthorne effects. *Lancet Neurol*. 2016;15(7):736-47.
- [83] Spinella TC, Stewart SH, Naugler J, Yakovenko I, Barrett SP. Evaluating cannabidiol (CBD) expectancy effects on acute stress and anxiety in healthy adults: a randomized crossover study. *Psychopharmacology (Berl)*. 2021;238(7):1965-77.
- [84] Jumbo SU, MacDermid JC, Kalu ME, Packham TL, Athwal GS, Faber KJ. Measurement Properties of the Brief Pain Inventory-Short Form (BPI-SF) and Revised Short McGill Pain Questionnaire Version-2 (SF-MPQ-2) in Pain-related Musculoskeletal Conditions: A Systematic Review. *Clin J Pain*. 2021;37(6):454-74.
- [85] Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. *Psychological Assessment*. 1995;7:524-32.
- [86] Daoust R, Paquet J, Williamson D, Perry JJ, Iseppon M, Castonguay V, et al. Accuracy of a self-report prescription opioid use diary for patients discharge from the

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emergency department with acute pain: a multicentre prospective cohort study. *BMJ Open*. 2022;12(10):e062984.

[87] Li D, Mielke MM. An Update on Blood-Based Markers of Alzheimer's Disease Using the SiMoA Platform. *Neurol Ther*. 2019;8(Suppl 2):73-82.

[88] King NS, Crawford S, Wenden FJ, Moss NE, Wade DT. The Rivermead Post Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced after head injury and its reliability. *J Neurol*. 1995;242(9):587-92.

[89] Swiontkowski MF, Engelberg R, Martin DP, Agel J. Short musculoskeletal function assessment questionnaire: validity, reliability, and responsiveness. *J Bone Joint Surg Am*. 1999;81(9):1245-60.

[90] Garratt AM, Ruta DA, Abdalla MI, Buckingham JK, Russell IT. The SF36 health survey questionnaire: an outcome measure suitable for routine use within the NHS? *Bmj*. 1993;306(6890):1440-4.

[91] Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193-213.

[92] Beck AT, Steer RA, Brown G. Beck depression inventory : manual. . Psychological Corporation: San Antonio, TX. 1996.

[93] Ashbaugh AR, Houle-Johnson S, Herbert C, El-Hage W, Brunet A. Psychometric Validation of the English and French Versions of the Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5). *PLoS One*. 2016;11(10):e0161645.

[94] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*. 2009;42(2):377-81.

[95] Jodoin M, Herrero Babiloni A, Provost C, Blais H, Bellemare A, Desjardins M, et al. 10-Day Theta Burst Stimulation Intervention Facilitates the Clinical Rehabilitation of Patients After an Isolated Limb Fracture: A Longitudinal SHAM-Controlled Pilot Study. *American Journal of Physical Medicine & Rehabilitation*. 2024;103(11):e152-e61.

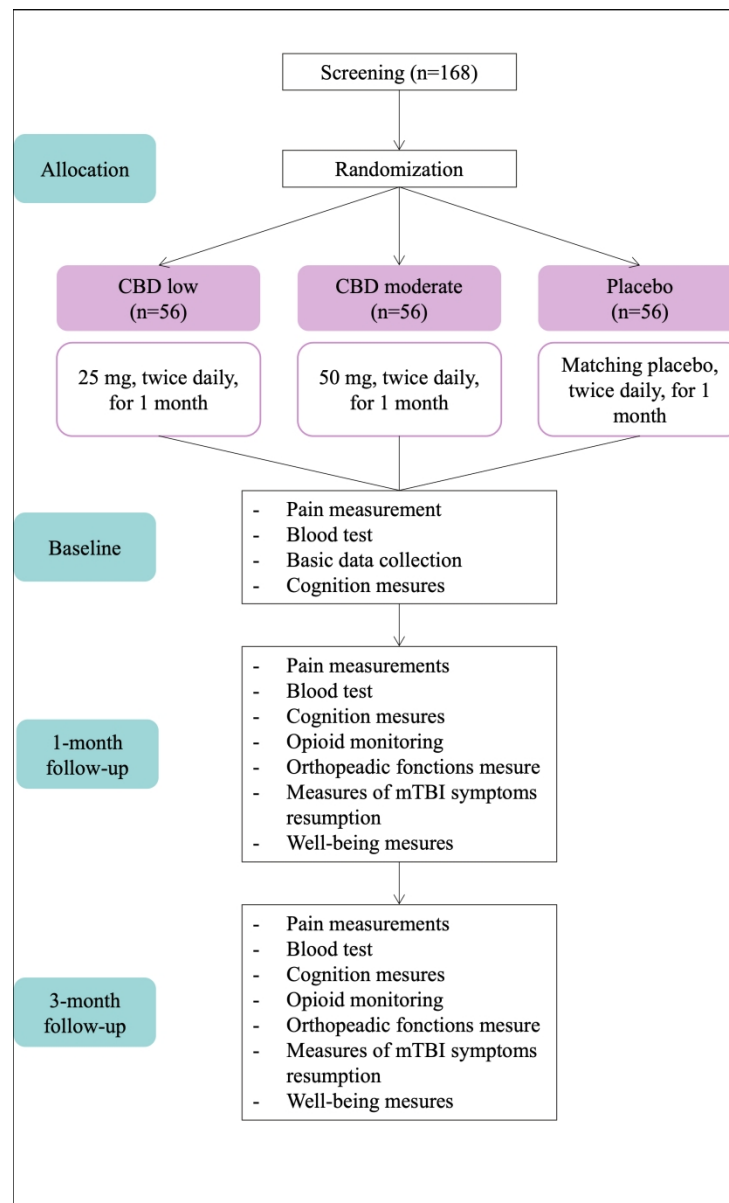


Figure 1 - Study schema

171x281mm (330 x 330 DPI)

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Impact of an acute 1-month cannabidiol treatment on pain and inflammation after a long bone fracture: a triple-blind randomized, placebo controlled, clinical trial protocol

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Impact of an acute 1-month cannabidiol treatment on pain and inflammation after a long bone fracture: a triple-blind randomized, placebo controlled, clinical trial protocol

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Abstract

Introduction. Acute pain levels following orthopedic injury (e.g., fracture) is a predictor of the onset of chronic pain, which affects nearly 50% of fracture patients and impairs functional recovery. Among current pharmacological treatments for acute pain, non-steroidal anti-inflammatory drugs have been associated with delayed bone healing, while opioids inhibit effective bone remodeling, increase the risk of pseudarthrosis, and carry a high risk of addiction. In light of this, the development of new pain treatments is essential.

Cannabidiol (CBD), a non-addictive and non-psychotropic cannabis component stands out as a potential therapeutic agent, given its analgesic and anti-inflammatory properties as well as its potential benefits for bone healing. This randomized controlled trial aims to investigate the effect of acute CBD treatment, compared to placebo, on patients' self-reported pain, inflammation and well-being following a fracture injury.

Methods and analysis. This is a triple-blind, randomized, placebo-controlled clinical trial. A total of 225 adults aged 18 to 70 years, who have suffered a long bone fracture and were treated at the Hôpital du Sacré-Coeur de Montréal, will be randomly assigned within one week to one of three treatment arms (25 mg or 50 mg of CBD or placebo) for one month. The primary outcome will be difference in the pain score between groups at one-month follow-up. Secondary outcomes will include measures of persistent pain, inflammation, opioid usage, quality of life, sleep quality, depression, anxiety, cognition and orthopaedic function. Data will be collected at baseline, 1- and 3-month follow-ups.

Ethics and dissemination. This study obtained a Health Canada license for use of cannabis products. It has also been approved by Health Canada and the Research Ethics Board of the CIUSSS du Nord-de-l'Île-de-Montréal (Project ID 2025-2105). The findings will be published in a peer-reviewed journal and presented at local, national, and international conferences. The trial's results will be made publicly available on the clinicaltrials.gov database.

Trial registration number: NCT06448923 (registered on [ClinicalTrials.gov](https://clinicaltrials.gov))

53 **Strengths and limitations of this study**

- 54 - This study is robust due to its triple-blind randomized, placebo-controlled design,
55 which assesses the effects of two different doses of pharmaceutical-grade CBD.
- 56 - The extensive number of measurements allows for a comprehensive assessment of
57 the treatment's impact, not only by evaluating patients' perceived well-being and
58 recovery but also by objectively quantifying CBD's effect on inflammation through
59 inflammatory markers.
- 60 - This trial includes a longitudinal assessment of CBD treatment on pain symptoms
61 and trauma-related outcomes up to three months post-fracture, a critical period
62 marking the transition to chronic pain, however, the long-term effects of the
63 treatment will not be assessed.
- 64 - One limitation is the exclusion of osteoporotic patients, as well as a potential
65 restriction in the inclusion of women, since those of childbearing age who are not
66 using contraception will have to be excluded due to limited knowledge on the
67 teratogenic effects of CBD.
- 68 - One limitation of this study is that therapeutic drug monitoring was not performed,
69 which could have helped account for inter-individual variability and optimize
70 dosing.

71 **Introduction**

72 Bone fractures are a prevalent condition affecting individuals of all ages and are the most
73 commonly treated trauma in hospitals [1, 2]. In 2019, the estimated annual incidence of
74 new fractures worldwide was 178 million [3]. The process of bone healing involves
75 multiple consecutive and interrelated phases including inflammation, repair, and

remodeling, which occur in a spatial and temporal series of dynamic processes [4, 5]. The skeletal system possesses a remarkable capacity for regeneration. The initial process of bone healing typically occurs over a period of eight weeks [6], while bone remodeling extends for months following a fracture [7].

Independent of body location, traumatic injury sets off an acute non-specific immune response characterized by the release of pro-inflammatory cytokines such as interleukins (IL-1 β , IL-6, IL-10) and the tumor necrosis factor (TNF- α) [8]. In addition, systemic acute inflammation after bone fracture promotes the sustained release of cytokines disrupting the blood-brain barrier, thereby allowing toxic intruders such as pro-inflammatory cytokines to invade/migrate to the central nervous system (CNS) [9]. Persistent CNS inflammation plays a key mediating role in central sensitization [10], a maladaptive plasticity process driven by an increased response to nociceptive inputs, involved in pain persistence and chronicity. Chronic pain, a condition associated with delayed functional recovery, sleep disturbances, mental health disorders, and poorer quality of life [10], is highly prevalent 3-6 months after trauma, affecting 30-50% of individuals with bone fractures [11]. A number of variables have been identified as potential predictors of chronic pain after trauma, including pain intensity at three months post-accident, female sex, poor sleep, levels of anxiety and depression, and the concomitant occurrence of traumatic brain injury (TBI) or peripheral nerve injury at the time of fracture [12-16].

Following a fracture, patients frequently report a range of symptoms, including increased fatigue and motor impairment, which can exert a significant impact on their ability to perform activities of daily living [17]. In addition, patients with orthopedic trauma report

99 a deterioration in their quality of life up to twelve months following the injury [17, 18].

100 However, pain emerges as the most prominent complaint, with 97% of patients reporting

101 pain after an orthopedic injury [1, 19]. Acute pain management is a crucial concern

102 considering that inadequate pain control can lead to prolonged inflammation, which can

103 perpetuate pain signals and lead to chronic pain [20, 21]. Currently, a pharmacological

104 approach is widely recommended to manage acute post-trauma pain. Both non-steroidal

105 anti-inflammatory drugs (NSAIDs) and opioids are frequently prescribed for their anti-

106 inflammatory and analgesic effects [22]. Nevertheless, the use of NSAIDs has been

107 associated with delayed bone healing [23, 24] as well as digestive complication and kidney

108 failure [25]. As for opioids, in addition to major side effects, they pose a high risk of

109 dependence and tolerance [4, 26]. Furthermore, several studies show that opioids inhibit

110 effective bone remodeling [27], increase the risk of pseudarthrosis [28], and heighten the

111 risk of hyperalgesia, i.e. a paradoxical increase in pain sensitivity due to central

112 sensitization [26].

113

114 Interestingly, following the legalization of cannabis in Colorado, a reduction in chronic

115 pain admissions was observed, leading experts to question the potentially beneficial effects

116 of cannabis on pain [29]. Indeed, one study found that 61% of medical cannabis users

117 reported consuming it to alleviate pain [30, 31]. However, the medical use of cannabis is

118 limited due to the undesirable psychotropic and addictive effects of tetrahydrocannabinol

119 (THC). Cannabidiol (CBD), an organic component of cannabis, is non-psychoactive due

120 to its low affinity with the CB1 receptor [32]. It is of particular interest as it is devoid of

121 addictive effects [33, 34] and has an excellent safety profile [35], and its use does not affect
122 daily activities such as driving or working.

123

124 CBD is highly lipophilic which facilitates its ability to cross the blood-brain barrier [36].

125 However, the bioavailability of CBD varies greatly according to the method of
126 administration. The bioavailability of oral CBD is lower due to the hepatic first-pass effect,
127 with approximately 5% of the product reaching the bloodstream [37-39]. Food
128 consumption as well as nanotech and oil-based formulations of CBD have been shown to
129 increase bioavailability [40]. However, compared to smoked CBD, oral administration of
130 CBD presents multiple advantages, including greater control over dosage, ease of
131 administration, and fewer side effects [38].

132

133 Mechanisms of action of CBD are complex, not yet fully understood and involve multiple
134 pharmacological targets. Emerging evidence suggests that CBD exerts a number of
135 important effects via its modulating role on several non-cannabinoid receptors and ion
136 channels including those of endogenous neurotransmitters, such as serotonin [41] as well
137 as several types of transient receptor potential channels (TRP), such as TRPV1 [42], and
138 by modulating the binding affinity of certain G protein-coupled receptors [43]. Several in
139 vitro and animal model studies have demonstrated CBD's anti-inflammatory effect, notably
140 by reducing pro-inflammatory cytokines such as TNF- α , IL-1 β and IL-6, in addition to
141 inhibiting microglial activation [32, 42, 44-51]. CBD has also shown analgesic potential in
142 studies using neuropathic and inflammatory pain models. These human and animal studies
143 suggest a reduction in pain, hyperalgesia, and allodynia following treatment with CBD [35,

144 52-59]. CBD is alleged to possess anxiolytic and anti-depressant properties, as shown in
145 several animal and human studies [60-66]. In addition, a well-controlled preliminary
146 animal study showed that CBD, but not THC, enhanced the biomechanical properties of
147 healing mid-femoral fractures in rats, supporting a beneficial effect of CBD on bone
148 healing [67].

149

150 Epidemiological studies have suggested a reduction in opioid use for pain coinciding with
151 an increased use of medical cannabis [30], a trend also documented in Canada [68]. While
152 the interaction between CBD and opioids is not yet fully understood, studies have shown
153 that CBD acts as an allosteric modulator of the mu- and delta-opioid receptors [69]. CBD
154 was also shown to potentially enhance the analgesic effects of endogenous and exogenous
155 opioids. In one study, the use of CBD as a co-analgesic treatment for patients with chronic
156 pain resulted in a reduction in opioid consumption and improvements in overall quality of
157 life [70].

158

159 Providing effective pain management for patients with fractures is not only a fundamental
160 right but also offers numerous benefits. It reduces stress, shortens hospitalization time,
161 decreases associated healthcare costs and lowers the risk of developing chronic pain [1].
162 Preventing chronic pain is easier than reversing the sensitization processes that cause it
163 [71], making acute pain control a priority. Given its excellent safety profile [33, 35]
164 coupled with its downregulating effects on microglial and inflammatory activity, the
165 primary neuroinflammatory and pain mechanism, CBD represents an appealing
166 neuroprotective agent for pain-susceptible orthopedic trauma patients.

167

168 **Study objectives**

169 The primary objective of this study is to evaluate the effects of CBD treatment on self-
170 reported pain in patients following a long bone fracture injury. The second objective is to
171 assess the effect of the CBD treatment on inflammation and patient well-being.
172 Additionally, secondary analyses will look at the possible associations between pain
173 mediators (such as opioids, sex, and mild traumatic brain injury (mTBI)) and response to
174 CBD treatment. The aim is to better identify the effects of these pain mediators on treatment
175 response and the impact of CBD treatment on opioid uptake.

176

177 **Methods**

178 **Study design**

179 This is a randomized, placebo controlled, triple-blind 1-month clinical trial evaluating the
180 effects of two doses (low and moderate) of CBD compared to a placebo on pain and
181 inflammation after a long bone fracture.

182

183 **Participants**

184 A total of 225 participants aged 18 to 70 will be recruited within one week after their long
185 bone fracture injury and consultation to the Hôpital du Sacré-Coeur de Montréal (HSCM),
186 one of the largest Level 1 trauma centres in Canada with approximately 3,500 orthopedic
187 patients treated annually. The planned age range, targeting a population representative of
188 individuals who frequently experience traumatic fractures, was chosen as it allows for a
189 more homogenous evaluation of fracture healing and pain recovery. Including participants

over 70 introduces additional challenges, such as increased comorbidities, chronic diseases, bone fragility, polymedication and increased complications, which could slow the healing process, influence pain perception and complicate result interpretation.

Inclusion criteria

Subjects meeting the following criteria are eligible for the trial:

- Patients with a long bone fracture of the lower limb (tibia, fibula, femur, metatarsals, and phalanges) or the upper limb (humerus, radius, ulna, metacarpals, and phalanges) treated to Hôpital du Sacré-Coeur de Montréal (HSCM) within one week of the accident
- Participants is between 18 and 70 years of age
- Patients with or without surgical procedures

Exclusion criteria

Patients presenting any of the following characteristics are not eligible for the trial:

- Moderate/severe traumatic brain injury (TBI)
- Diagnosis of any of the following mental disorders as defined by the DSM-5: schizophrenia, intellectual disability, bipolar disorder, major depression, a diagnosed and untreated sleep disorders
- History of alcohol or opioid misuse/abuse, as defined by the DSM-5
- Evidence of severe renal (stage 4 or 5) or hepatic impairment (Child B or C)

- 211 - Pregnant or lactating women, women of childbearing potential who are not using
- 212 medically accepted forms of contraception (e.g., condoms, oral contraceptive or
- 213 intrauterine device), or women who are actively planning on becoming pregnant
- 214 - History of adverse reactions to cannabis
- 215 - Patients taking warfarin, sildenafil, valproate or under opioids treatment prior to the
- 216 injury
- 217 - Patients experiencing on average mild-to-absent pain in the last 24h preceding
- 218 recruitment (as per a score <30 on a 0-100mm Visual Analogue Scale (VAS))
- 219 - Transport business drivers and heavy machinery operators
- 220 - A diagnosis of chronic pain, bone pathology (e.g., osteoporosis) or chronic
- 221 inflammatory disease (e.g., rheumatoid arthritis, arthritis, psoriasis)
- 222 - Not having French or English as a spoken language
- 223 - A weighted MoCA score of less than 24
- 224 - Regular cannabis use more than 5 times a week

225

226 Recruitment

227 Recruitment will begin in January 2025 and end in January 2027. Potential participants will

228 be screened daily by the research team and collaborators. Potentially eligible patients will

229 be approached by a research team member and provided with a consent form. Once the

230 research team has addressed any remaining questions and obtained a signed consent form,

231 the participant will be randomized. See figure 1 for an overview of the study timeline.

232

233 Assignment of interventions

Participants will undergo concealed randomization to avoid selection bias. The study pharmacist will randomly assign participants to one of the three treatment groups (low or moderate CBD or placebo) using a 1:1:1 ratio through block randomization with randomly selected block sizes (9 and 12), stratified by sex, age (i.e., participants aged 45 and under, and those over 45) and type of fracture (i.e., lower and upper limb). The randomization procedure will be performed a priori by an independent biostatistician. Identical tablets for CBD and placebo will ensure blinding of clinicians, researchers, patients, families, and biostatistician to avoid unequal co-interventions, ascertainment bias, and analytic bias. The study pharmacist will be aware of allocation but will have no clinical or interpretive role. Assignments will be kept in sequentially numbered, sealed envelopes to ensure adequate allocation concealment. In the event of a serious adverse event or reaction, the allocation list can be retrieved.

Intervention

Patients in the treatment group will receive either a low dose (25 mg per tablet) or a moderate dose (50 mg per tablet) of CBD self-administered orally as a tablet twice daily with a meal for one month. Patients in the placebo group will receive an identical amount of a matching placebo administered with a meal twice daily for one month.

Investigational product

CBD tablets, along with matching placebos, will be supplied by EmpowerPharm (Toronto, Canada). The pharmacokinetic profile of the CBD product has already been established, and efforts to register the product with Health Canada have begun.

257

258 *Dose justification*

259 A wide range of CBD doses ranging from <1 to 50mg/kg has been used in various
260 conditions [72, 73]. The low dose (25 mg) selected for our study is based on initial and
261 ongoing studies of CBD in chronic pain which used a mean dose of 22.5mg and 20mg per
262 day [65]. This is also approximately the mean dose of CBD administered in a successful
263 trial of Sativex (THC/CBD) for neuropathic pain [74]. Moreover, a higher but relatively
264 moderate dose of CBD (50 mg) will be evaluated to assess dose-response effect. CBD
265 doses in this range have shown no statistical difference in intoxication scores in healthy
266 volunteers [75] and doses of up to 800 mg per day for a minimum of 4 weeks showed an
267 excellent safety and tolerability profile [76 , 77]. Participants will be advised to ingest the
268 treatment at mealtime, as studies have shown an increased bioavailability of CBD in
269 subjects after eating [78, 79]. To achieve our primary goal of mitigating acute pain, a one-
270 month treatment period has been selected, aligning with the typical evolution of acute pain
271 post-fracture [6].

272

273 **Study procedure**

274 Upon enrollment in the study, research staff will provide study instructions, collect baseline
275 data (e.g., demographics and clinical characteristics), administer questionnaires and
276 cognitive tests, and collect blood samples for quantification of pro-inflammatory cytokines.
277 Patients will report their pain intensity at baseline, and then three times a week throughout
278 the entire one-month treatment duration. Participants will be instructed to complete a daily
279 medication diary for one month to monitor the administration of study product, as well as

opioid, drugs, or other analgesic medication use. This data will be collected via questionnaires sent by e-mail or SMS message from the RedCap secure database. At 24h following treatment completion (one-month follow-up) and at the 3-month follow-up, participants will be evaluated at the research laboratory to collect measures of pain intensity and related outcomes including opioids intake, inflammation, cognition, orthopedic function and indicators of overall well-being. Participants will have to abstain from CBD consumption from the end of treatment until the last follow-up visit. See Table 1 for a detailed schedule of assessments.

Table 1. Schedule of assessment

Domain	Mesure	Screening	Baseline	During Treatment	1-month follow-up	3-month follow-up
Eligibility	Demographic questionnaire	X	X			
	Consent form	X				
	Medical history	X				
	MoCA	X				
	Medication	X	X	X	X	X
Primary outcome	Visual Analog Scale	X	X	X	X	X
Secondary outcomes	Brief Pain Inventory short form (BPI-sf)				X	X
	Blood sample - Inflammation markers		X		X	X
	Cognition		X		X	X
	Rivermead TBI symptoms				X	X
	Short Musculoskeletal Function Assessment (SMFA)				X	X

	Short Form Health Survey				X	X
	Pittsburgh Sleep Quality Index (PSQI)				X	X
	Beck's Depression Inventory-II		X		X	X
	Beck's Anxiety Inventory		X		X	X
Other	Pain Catastrophizing Scale (PCS)		X			
	Treatment Expectation Questionnaire (TEX-Q)		X			
	PTSD Checklist for DSM-5 (PCL-5)		X		X	
	Treatment assignment hypothesis				X	
	Opioid consumption	X	X	X	X	X
	Adverse events			X	X	

Primary outcome

The main outcome is the difference between groups in the mean pain intensity score at one-month follow-up, as measured by the visual analog scale (VAS) [80]. Pain intensity on the VAS will be gathered 24h following treatment completion. The VAS is a 100mm line with anchor words ranging from “no pain” to “worst imaginable pain”. Participants will indicate the intensity of their pain at that moment by placing a mark along the line.

Secondary outcomes

At 1 and 3-month follow-ups, persistent pain, opioid consumption, inflammation markers, quality of life, sleep quality, depression, anxiety, cognition, mTBI symptom resolution, and orthopaedic function outcomes will be collected. In addition, at baseline, participants will

1
2
3 302 be asked to indicate their level of treatment expectation using the Treatment Expectation
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5 303 Questionnaire (TEX-Q-F) [81], a fifteen-question questionnaire, considering the potential
6
7 304 modulation of therapeutic effects by patients' expectations of treatment [82, 83]. After
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9
10 305 treatment completion, participants will also be asked to indicate whether they felt they had
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12 306 received active treatment or placebo.
13

14 307
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16
17 308 **Measures**
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19 309 *Demographic and clinical characteristics*
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21
22 310 The following information will be collected at baseline to characterize participants: age,
23
24 311 sex, height, weight, percentage of adipose tissue using an impedance meter scale,
25
26 312 occupation, education level, ethnicity, language spoken, pre-morbid medical history
27
28 313 (including psychological health history), pre-morbid substance use (e.g., alcohol, drugs,
29
30 314 cigarettes, medications), recreational cannabis use, history of brain trauma, injury type and
31
32 315 severity, mechanism of injury.
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34 316
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36
37 317 *Pain*
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39
40 318 At 1- and 3-month follow-up, persistent pain will be assessed using the Brief Pain
41
42 319 Inventory short form (BPI-sf) [84], a 9-item self-report questionnaire assessing for the
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44 320 presence, intensity, and location(s) of pain, as well as perceived efficacy of pain relief
45
46 321 treatment, and pain interference with activities of daily living. In addition, pain will be
47
48 322 assessed using the VAS at several time points for comparison: baseline, three times per
49
50 323 week during treatment, 24h after the end of treatment and at the 3-month follow-up. Pain
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52 324 catastrophizing will also be assessed during the initial visit using the Pain Catastrophizing
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Scale [85], a 13-item questionnaire evaluated on Likert scales, given the significant contribution of psychological factors in the experience of pain.

Opioid usage

Participants will continue their usual pain care regimen throughout the study. Opioid usage and analgesic will be recorded in a daily medication diary for the initial month and through the number of prescription refills for months two and three. Self-reported opioid use in a diary has been shown to be an accurate assessment of the quantity of opioids consumed [86].

Inflammation

Blood levels of pro-inflammatory cytokines including interleukins (IL-6, IL-10, IL-1 β) and TNF- α will be collected at baseline and at the 1 and 3-month follow-up sessions. To assess cytokine levels, blood samples will be separated in buffy coat, serum and plasma, and stored at -80 °C in polypropylene tubes on average 1-2h after the blood draw. EDTA plasma will be tested with cutting-edge ultra-sensitive Quanterix ImmunoAssay Analyzer Simoa HD-X to quantify biomarkers using the Cor-Plex-Cytokine-10-Plex assay panel as per manufacturer recommendation. Simoa is a leader in the quantification of plasma biomarkers with markedly lower detection threshold than traditional ELISA [87].

Cognition

At baseline, 1 and 3-months follow-ups, neuropsychological tests highly sensitive to pain, and that do not require the use of the fractured limb, will be administered: a task assessing

1
2
3 348 information processing speed (Symbol Search from the WAIS-IV Battery), two memory
4
5 349 tests (California Verbal Learning Test and Digit Span from the WAIS-IV battery), two
6
7
8 350 executive function tests (D-KEFS Color-Word and Verbal Fluency), and an attention test
9
10 351 (Elevator counting with distraction and Elevator counting without distraction from the Test
11
12 352 of Everyday Attention battery) (see Lezac et al., 1995 for test descriptions).
13
14

15 353
16
17 354 *Mild TBI symptoms resolution*
18

19 355 Patients who sustained a concomitant mTBI with their fracture will be included in the
20
21 356 study. Additional measures will be documented to control for this variable. At 1 and 3-
22
23 357 months follow-up, information on mTBI symptoms resolution will be collected for patients
24
25 358 diagnosed with a mTBI concomitant to the fracture using the Rivermead Post-Concussion
26
27 359 Questionnaire [88].
28
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31 360
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33 361 *Orthopaedic function*
34

35 362 At 1 and 3-months follow-ups, the Short Musculoskeletal Function Assessment (SMFA)
36
37 363 Questionnaire [89] will be administered. The SMFA includes 34 questions that evaluate
38
39 364 patient's function, and 12 questions related to how bothered patients are by their symptoms.
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43 365
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45 366 *Well-being*
46

47 367 At 1 and 3-months follow-ups, various important domains of well-being significantly
48
49 368 modulated by pain will be measured including: quality of life using the Short Form (36)
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51 369 Health Survey [90], a 36-item self-report questionnaire for measuring quality of life across
52
53 370 9 domains; sleep quality and quantity using the Pittsburgh Sleep Quality Index (PSQI) [91],
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a self-report questionnaire that assesses sleep quality and quantity over the past 4 weeks. Additionally, at baseline, 1 and 3-months follow-ups depression and anxiety symptoms will be assessed using the Beck's Depression Inventory-II (BDI-II) [92] and the Beck's Anxiety Inventory (BAI) (86). The BDI-II is a 21-item multiple-choice self-report questionnaire for measuring depression symptoms. The BAI is a 21-question multiple-choice self-report inventory used for measuring the severity of anxiety. Finally, symptoms of post-traumatic stress disorder will be assessed at the first visit and at 1-month follow-up using the PTSD Checklist for DSM-5 (PCL-5) questionnaire [93].

Data management

Data collected will be transcribed from the source documents into the electronic Case Report Form (eCRF) on the REDCap database hosted at CIUSSS du Nord-de-l'Île-de-Montréal [94] and quality controlled by a second qualified staff member. Data will be stored on a secure network with regular backups. An external, independent clinical monitor will conduct regular monitoring visits according to the monitoring plan, during which they will review and verify source data, informed consent forms, medical records, laboratory results, case report forms, medication dispensing logs and protocol deviations.

Statistical analyses

Sample size estimation

A 30% relative pain intensity reduction on the VAS (expected response of 50% or more in the CBD group and expected 20% in the placebo group) has been used extensively to reflect clinically significant pain relief in clinical trials. Based on a Fisher's exact test, a sample

size of 225 participants (3 groups of 75) will be required to reach a power of 80% to detect a statistically significant difference in the proportion of patients who reaches 30% pain reduction between the CBD groups and placebo at 1-month post-injury, assuming a dropout rate of 20% and a significance level of 5%. These parameters are taken from a successful randomised, placebo-controlled clinical trial using Sativex© in treating 125 neuropathic pain patients [74].

Moreover, considering that the placebo group may ingest more opiates and that the anticipated inter-group effect at one month may be reduced to 20%, a total sample size of 225 subjects could be required to achieve 80% power, assuming a drop-out rate of 20% and a significance level of 5%.

Primary outcome

The primary outcome will be analyzed using an ANCOVA, with mTBI and orthopedic surgery as covariables and treatment (low and moderate CBD vs. placebo) as factor in the mean VAS pain score at the 1-month follow-up.

Secondary outcomes

For the secondary outcomes, a Kaplan Meier survival analysis with the log-rank test on VAS pain data collected during treatment will be used to assess CBD treatment success rate relative to placebo at achieving 50% pain intensity reduction during treatment duration. The proportion of patients no longer experiencing significant pain symptoms at the 3-month follow-up (i.e., patients who did not convert to chronic pain) will be compared, as defined as VAS pain ≤ 30 between treatment with a chi-squared test. A mixed model for

repeated measures with covariables mTBI and orthopedic surgery and treatment as factor will be used to assess between-group treatment effects on total opioids use at both 1 and 3-month follow-ups. The same approach will be used to assess between-group treatment effects at both 1- and 3-month follow-ups on secondary outcomes measures listed above.

Analyses will be performed on an intention-to-treat (ITT) dataset. The ITT dataset will include all participants randomized in the analysis, whether or not they have completed treatment in order to limit bias and reflect results under real treatment conditions.

Missing data will be reported and justified in the results. The multiple imputation method, which has been recognized in clinical studies involving experimental treatment, will be applied. Additionally, a sensitivity analysis will be performed to assess the impact of missing data on the results.

Discontinuation

Participants may withdraw from this research project at any time without giving reasons. Discontinuation of treatment does not imply withdrawal from the trial. The following reasons will be considered as grounds for patient withdrawal from the trial: withdrawal of consent by the participant, failure to pass the selection phase, meeting an exclusion criterion, failure to participate in follow-up, termination of the trial by the investigator, major protocol deviation incompatible with trial participation, an adverse event or any other condition which, in the opinion of the investigator, would expose the participant to

undue risk by continuing the treatment trial, any condition that the investigator considers medically necessary to withdraw the patient from the trial.

Adherence

During the baseline visit, a research team member will conduct an information session to discuss the significance of adhering to the guidelines related to doses, timing of drug administration, the procedure to be followed in case of a missed dose, and the importance of reporting any adverse event. Automatic SMS reminders will be sent to ensure completion of the digital VAS and medication diary. A high protocol adherence is expected given that cannabidiol has limited adverse side effects, and the administration is oral and non-invasive. A 10% loss to follow-up is expected based on a 3-month trial with the same patient characteristics[95]. For adherence purposes, patients will be instructed to return all treatment bottles, empty or not, to be monitored by the pharmacy staff. Each participant will receive financial compensation for costs incurred during their participation in this research study. Participants who withdraw or are withdrawn from the project prior to its completion will receive an amount proportional to the length of their participation.

Safety and serious adverse events

Risks of adverse effects are considered low given the demonstrated excellent safety profile of CBD [33, 35]. Somnolence, fatigue, drowsiness, gastro-intestinal issue, and decreased appetite are the most probable adverse events associated with CBD in adult patients [34]. Participants will be instructed to advise the research team of any adverse events which will

be thoroughly monitored and documented. Access to on-duty emergency physicians at HSCM will be provided during the entire treatment duration.

Patient and public involvement

Neither patients nor the public were involved in the development, design and conduct of this study.

Confidentiality

All data collected in our databases will be stored following a de-identification process. Participants will be identified by a unique identification code, and nominal data will be protected separately. Uncoded data will only be accessible to the principal investigator. No identifying data will be disclosed in any scientific communication or publication.

Ethics and dissemination

Ethical approval has been granted by the CIUSSS du Nord-de-l'Île-de-Montréal ethics board (#2025-2105 issued August 2024) and Health Canada (License, #LIC-NKA1EX2TUA-202-3 issued on March 26, 2024, and No Objection Letter, HC6-024-c275232 issued on May 30, 2024). This study adheres with the Declaration of Helsinki. The results will be published in a peer-reviewed journal and presented at local, national, and international conferences.

Author Contributions

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483 DB, DW, FB, CA, GL, AP, DR, LDB conceived the study. DB and AAD will ensure
484 coordination, recruitment and conduct of the protocol. DB and LDB wrote the manuscript.
485 All authors contributed to the revisions of the manuscript. LDB is guarantor.

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491 EmpowerPharm (Ontario, Canada). The study's design, management, analysis, and
492 reporting are entirely independent of the CBD manufacturers.

494 **Competing interests:** None declared.

496 **Figure 1. Study Schema. CBD, cannabidiol; mTBI, mild traumatic brain injury.**

501 **References**

502 [1] Ahmadi A, Bazargan-Hejazi S, Heidari Zadie Z, Euasobhon P, Ketumarn P,
503 Karbasfrushan A, et al. Pain management in trauma: A review study. J Inj Violence Res.
504 2016;8(2):89-98.
505 [2] Urquhart DM, Williamson OD, Gabbe BJ, Cicuttini FM, Cameron PA, Richardson
506 MD, et al. Outcomes of patients with orthopaedic trauma admitted to level 1 trauma
507 centres. ANZ J Surg. 2006;76(7):600-6.
508 [3] Wu A-M, Bisignano C, James SL, Abady GG, Abedi A, Abu-Gharbieh E, et al. Global,
509 regional, and national burden of bone fractures in 204 countries and territories, 1990–
510 2019: a systematic analysis from the Global Burden of Disease Study 2019. The Lancet
511 Healthy Longevity. 2021;2(9):e580-e92.

- [4] Alves CJ, Neto E, Sousa DM, Leitão L, Vasconcelos DM, Ribeiro-Silva M, et al. Fracture pain-Traveling unknown pathways. *Bone*. 2016;85:107-14.
- [5] Claes L, Recknagel S, Ignatius A. Fracture healing under healthy and inflammatory conditions. *Nat Rev Rheumatol*. 2012;8(3):133-43.
- [6] Einhorn TA, Gerstenfeld LC. Fracture healing: mechanisms and interventions. *Nat Rev Rheumatol*. 2015;11(1):45-54.
- [7] Marsell R, Einhorn TA. The biology of fracture healing. *Injury*. 2011;42(6):551-5.
- [8] Loi F, Córdova LA, Pajarinen J, Lin TH, Yao Z, Goodman SB. Inflammation, fracture and bone repair. *Bone*. 2016;86:119-30.
- [9] Huang X, Hussain B, Chang J. Peripheral inflammation and blood-brain barrier disruption: effects and mechanisms. *CNS Neurosci Ther*. 2021;27(1):36-47.
- [10] Fine PG. Long-term consequences of chronic pain: mounting evidence for pain as a neurological disease and parallels with other chronic disease states. *Pain Med*. 2011;12(7):996-1004.
- [11] Nampiaparampil DE. Prevalence of chronic pain after traumatic brain injury: a systematic review. *Jama*. 2008;300(6):711-9.
- [12] Castillo RC, MacKenzie EJ, Wegener ST, Bosse MJ. Prevalence of chronic pain seven years following limb threatening lower extremity trauma. *Pain*. 2006;124(3):321-9.
- [13] McDonald SJ, Sharkey JM, Sun M, Kaukas LM, Shultz SR, Turner RJ, et al. Beyond the Brain: Peripheral Interactions after Traumatic Brain Injury. *J Neurotrauma*. 2020;37(5):770-81.
- [14] Walker WC. Pain pathoetiology after TBI: neural and nonneural mechanisms. *The Journal of head trauma rehabilitation*. 2004;19(1):72-81.
- [15] Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. *Br J Anaesth*. 2013;111(1):52-8.
- [16] Molitoris KH, Balu AR, Huang M, Baht GS. The impact of age and sex on the inflammatory response during bone fracture healing. *JBMR Plus*. 2024;8(5).
- [17] Soleymanha M, Mobayen M, Asadi K, Adeli A, Haghparast-Ghadim-Limudahi Z. Survey of 2582 cases of acute orthopedic trauma. *Trauma Mon*. 2014;19(4):e16215.
- [18] Sluys KP, Shults J, Richmond TS. Health related quality of life and return to work after minor extremity injuries: A longitudinal study comparing upper versus lower extremity injuries. *Injury*. 2016;47(4):824-31.
- [19] Archer KR, Castillo RC, Wegener ST, Abraham CM, Obremskey WT. Pain and satisfaction in hospitalized trauma patients: The importance of self-efficacy and psychological distress. *Journal of Trauma and Acute Care Surgery*. 2012;72(4):1068-77.
- [20] Mehta SP, MacDermid JC, Richardson J, MacIntyre NJ, Grewal R. Baseline pain intensity is a predictor of chronic pain in individuals with distal radius fracture. *J Orthop Sports Phys Ther*. 2015;45(2):119-27.
- [21] Powelson EB, Mills B, Henderson-Drager W, Boyd M, Vavilala MS, Curatolo M. Predicting chronic pain after major traumatic injury. *Scand J Pain*. 2019;19(3):453-64.
- [22] Majuta LA, Longo G, Fealk MN, McCaffrey G, Mantyh PW. Orthopedic surgery and bone fracture pain are both significantly attenuated by sustained blockade of nerve growth factor. *Pain*. 2015;156(1):157-65.

1
2
3 555 [23] Atchison JW, Herndon CM, Rusie E. NSAIDs for musculoskeletal pain
4 556 management:current perspectives and novel strategies to improve safety. J Manag Care
5 557 Pharm. 2013;19(9 Suppl A):S3-19.
6
7 558 [24] Maruyama M, Rhee C, Utsunomiya T, Zhang N, Ueno M, Yao Z, et al. Modulation
8 559 of the Inflammatory Response and Bone Healing. Front Endocrinol (Lausanne).
9 560 2020;11:386.
10 561 [25] Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs
11 562 (NSAIDs) and organ damage: A current perspective. Biochem Pharmacol.
12 563 2020;180:114147.
13 564 [26] Lembke A, Humphreys K, Newmark J. Weighing the Risks and Benefits of Chronic
14 565 Opioid Therapy. Am Fam Physician. 2016;93(12):982-90.
15 566 [27] Raphael-Mizrahi B, Gabet Y. The Cannabinoids Effect on Bone Formation and Bone
16 567 Healing. Curr Osteoporos Rep. 2020;18(5):433-8.
17 568 [28] Buchheit T, Zura R, Wang Z, Mehta S, Della Rocca GJ, Steen RG. Opioid exposure is
18 569 associated with nonunion risk in a traumatically injured population: An inception cohort
19 570 study. Injury. 2018;49(7):1266-71.
20 571 [29] RMHIDTA. The Legalization of Marijuana in Colorado: The Impact: Volume 6,
21 572 September 2019. Mo Med. 2019;116(6):450.
22 573 [30] Hill KP, Palastro MD, Johnson B, Ditre JW. Cannabis and Pain: A Clinical Review.
23 574 Cannabis Cannabinoid Res. 2017;2(1):96-104.
24 575 [31] Khan SP, Pickens TA, Berlau DJ. Perspectives on cannabis as a substitute for opioid
25 576 analgesics. Pain Manag. 2019;9(2):191-203.
26 577 [32] Burstein S. Cannabidiol (CBD) and its analogs: a review of their effects on
27 578 inflammation. Bioorg Med Chem. 2015;23(7):1377-85.
28 579 [33] Gray RA, Heal DJ, Maguire DR, Gerak LR, Javors MA, Smith S, et al. Preclinical
29 580 Assessment of the Abuse Potential of Purified Botanical Cannabidiol: Self-Administration,
30 581 Drug Discrimination, and Physical Dependence. J Pharmacol Exp Ther. 2022;382(1):54-65.
31 582 [34] Micallef J, Batisse A, Revol B. [Pharmacology of cannabidiol: Red flags,
32 583 consequences and risks in humans]. Therapie. 2022;77(5):585-90.
33 584 [35] Alaia MJ, Hurley ET, Vasavada K, Markus DH, Britton B, Gonzalez-Lomas G, et al.
34 585 Buccally Absorbed Cannabidiol Shows Significantly Superior Pain Control and Improved
35 586 Satisfaction Immediately After Arthroscopic Rotator Cuff Repair: A Placebo-Controlled,
36 587 Double-Blinded, Randomized Trial. Am J Sports Med. 2022;50(11):3056-63.
37 588 [36] Calapai F, Cardia L, Sorbara EE, Navarra M, Gangemi S, Calapai G, et al.
38 589 Cannabinoids, Blood–Brain Barrier, and Brain Disposition. Pharmaceuticals.
39 590 2020;12(3):265.
40 591 [37] Atsmon J, Heffetz D, Deutsch L, Deutsch F, Sacks H. Single-Dose Pharmacokinetics
41 592 of Oral Cannabidiol Following Administration of PTL101: A New Formulation Based on
42 593 Gelatin Matrix Pellets Technology. Clin Pharmacol Drug Dev. 2018;7(7):751-8.
43 594 [38] Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin
44 595 Pharmacokinet. 2003;42(4):327-60.
45 596 [39] Hosseini A, McLachlan AJ, Lickliter JD. A phase I trial of the safety, tolerability and
46 597 pharmacokinetics of cannabidiol administered as single-dose oil solution and single and

- multiple doses of a sublingual wafer in healthy volunteers. *Br J Clin Pharmacol*. 2021;87(4):2070-7.
- [40] Moazen-Zadeh E, Chisholm A, Bachi K, Hurd YL. Pharmacokinetics of Cannabidiol: A systematic review and meta-regression analysis. *medRxiv*. 2023.
- [41] Russo EB, Burnett A, Hall B, Parker KK. Agonistic Properties of Cannabidiol at 5-HT1a Receptors. *Neurochemical Research*. 2005;30(8):1037-43.
- [42] Costa B, Colleoni M, Conti S, Parolaro D, Franke C, Trovato AE, et al. Oral anti-inflammatory activity of cannabidiol, a non-psychoactive constituent of cannabis, in acute carrageenan-induced inflammation in the rat paw. *Naunyn Schmiedebergs Arch Pharmacol*. 2004;369(3):294-9.
- [43] Laun AS, Shrader SH, Brown KJ, Song ZH. GPR3, GPR6, and GPR12 as novel molecular targets: their biological functions and interaction with cannabidiol. *Acta Pharmacol Sin*. 2019;40(3):300-8.
- [44] Kuret T, Kreft ME, Romih R, Veranič P. Cannabidiol as a Promising Therapeutic Option in IC/BPS: In Vitro Evaluation of Its Protective Effects against Inflammation and Oxidative Stress. *Int J Mol Sci*. 2023;24(5).
- [45] Kongkadee K, Wisuitiprot W, Ingkaninan K, Waranuch N. Anti-inflammation and gingival wound healing activities of Cannabis sativa L. subsp. sativa (hemp) extract and cannabidiol: An in vitro study. *Arch Oral Biol*. 2022;140:105464.
- [46] Yndart Arias A, Kolishetti N, Vashist A, Madepalli L, Llaguno L, Nair M. Anti-inflammatory effects of CBD in human microglial cell line infected with HIV-1. *Sci Rep*. 2023;13(1):7376.
- [47] Li H, Kong W, Chambers CR, Yu D, Ganea D, Tuma RF, et al. The non-psychoactive phytocannabinoid cannabidiol (CBD) attenuates pro-inflammatory mediators, T cell infiltration, and thermal sensitivity following spinal cord injury in mice. *Cell Immunol*. 2018;329:1-9.
- [48] Kozela E, Juknat A, Vogel Z. Modulation of Astrocyte Activity by Cannabidiol, a Nonpsychoactive Cannabinoid. *Int J Mol Sci*. 2017;18(8).
- [49] Kozela E, Lev N, Kaushansky N, Eilam R, Rimmerman N, Levy R, et al. Cannabidiol inhibits pathogenic T cells, decreases spinal microglial activation and ameliorates multiple sclerosis-like disease in C57BL/6 mice. *Br J Pharmacol*. 2011;163(7):1507-19.
- [50] Giacoppo S, Galuppo M, Pollastro F, Grassi G, Bramanti P, Mazzon E. A new formulation of cannabidiol in cream shows therapeutic effects in a mouse model of experimental autoimmune encephalomyelitis. *Daru*. 2015;23:48.
- [51] Dopkins N, Miranda K, Wilson K, Holloman BL, Nagarkatti P, Nagarkatti M. Effects of Orally Administered Cannabidiol on Neuroinflammation and Intestinal Inflammation in the Attenuation of Experimental Autoimmune Encephalomyelitis. *J Neuroimmune Pharmacol*. 2022;17(1-2):15-32.
- [52] Britch SC, Craft RM. Cannabidiol and Delta-9-Tetrahydrocannabinol Interactions in Male and Female Rats With Persistent Inflammatory Pain. *J Pain*. 2023;24(1):98-111.
- [53] Costa B, Trovato AE, Comelli F, Giagnoni G, Colleoni M. The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. *Eur J Pharmacol*. 2007;556(1-3):75-83.

- [54] Aguiar DD, da Costa Oliveira C, Fonseca FCS, de Almeida DL, Campos Pereira WV, Guimarães FS, et al. Peripherally injected cannabidiol reduces neuropathic pain in mice: Role of the 5-HT(1A) and TRPV1 receptors. *Biochem Biophys Res Commun*. 2023;660:58-64.
- [55] Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clin Rehabil*. 2003;17(1):21-9.
- [56] Wanasuntronwong A, Kaewsrisung S, Rotpenpian N, Arayapisit T, Pavasant P, Suprongsinchai W. Efficacy and mechanism of the antinociceptive effects of cannabidiol on acute orofacial nociception induced by Complete Freund's Adjuvant in male *Mus musculus* mice. *Arch Oral Biol*. 2022;144:105570.
- [57] Urits I, Gress K, Charipova K, Habib K, Lee D, Lee C, et al. Use of cannabidiol (CBD) for the treatment of chronic pain. *Best Pract Res Clin Anaesthesiol*. 2020;34(3):463-77.
- [58] Gulbransen G, Xu W, Arroll B. Cannabidiol prescription in clinical practice: an audit on the first 400 patients in New Zealand. *BJGP Open*. 2020;4(1).
- [59] Verrico CD, Wesson S, Konduri V, Hofferek CJ, Vazquez-Perez J, Blair E, et al. A randomized, double-blind, placebo-controlled study of daily cannabidiol for the treatment of canine osteoarthritis pain. *Pain*. 2020;161(9):2191-202.
- [60] Guimarães FS, Chiaretti TM, Graeff FG, Zuardi AW. Antianxiety effect of cannabidiol in the elevated plus-maze. *Psychopharmacology (Berl)*. 1990;100(4):558-9.
- [61] de Mello Schier AR, de Oliveira Ribeiro NP, Coutinho DS, Machado S, Arias-Carrión O, Crippa JA, et al. Antidepressant-like and anxiolytic-like effects of cannabidiol: a chemical compound of *Cannabis sativa*. *CNS Neurol Disord Drug Targets*. 2014;13(6):953-60.
- [62] Resstel LB, Tavares RF, Lisboa SF, Joca SR, Corrêa FM, Guimarães FS. 5-HT1A receptors are involved in the cannabidiol-induced attenuation of behavioural and cardiovascular responses to acute restraint stress in rats. *Br J Pharmacol*. 2009;156(1):181-8.
- [63] Zanelati TV, Biojone C, Moreira FA, Guimarães FS, Joca SR. Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT1A receptors. *Br J Pharmacol*. 2010;159(1):122-8.
- [64] Bergamaschi MM, Queiroz RH, Chagas MH, de Oliveira DC, De Martinis BS, Kapczinski F, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. *Neuropsychopharmacology*. 2011;36(6):1219-26.
- [65] Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmons S, et al. Initial experiences with medicinal extracts of cannabis for chronic pain: Results from 34 'N of 1' studies. *Anaesthesia*. 2004;59(5):440-52.
- [66] Shannon S, Lewis N, Lee H, Hughes S. Cannabidiol in Anxiety and Sleep: A Large Case Series. *Perm J*. 2019;23:18-041.
- [67] Kogan NM, Melamed E, Wasserman E, Raphael B, Breuer A, Stok KS, et al. Cannabidiol, a Major Non-Psychotropic Cannabis Constituent Enhances Fracture Healing and Stimulates Lysyl Hydroxylase Activity in Osteoblasts. *J Bone Miner Res*. 2015;30(10):1905-13.

- [68] Lucas P, Baron EP, Jikomes N. Medical cannabis patterns of use and substitution for opioids & other pharmaceutical drugs, alcohol, tobacco, and illicit substances; results from a cross-sectional survey of authorized patients. *Harm Reduct J*. 2019;16(1):9.
- [69] Kathmann M, Flau K, Redmer A, Tränkle C, Schlicker E. Cannabidiol is an allosteric modulator at mu- and delta-opioid receptors. *Naunyn Schmiedebergs Arch Pharmacol*. 2006;372(5):354-61.
- [70] Capano A, Weaver R, Burkman E. Evaluation of the effects of CBD hemp extract on opioid use and quality of life indicators in chronic pain patients: a prospective cohort study. *Postgrad Med*. 2020;132(1):56-61.
- [71] Loggia ML, Chonde DB, Akeju O, Arabasz G, Catana C, Edwards RR, et al. Evidence for brain glial activation in chronic pain patients. *Brain*. 2015;138(Pt 3):604-15.
- [72] Hendricks O, Andersen TE, Christiansen AA, Primdahl J, Hauge EM, Ellingsen T, et al. Efficacy and safety of cannabidiol followed by an open label add-on of tetrahydrocannabinol for the treatment of chronic pain in patients with rheumatoid arthritis or ankylosing spondylitis: protocol for a multicentre, randomised, placebo-controlled study. *BMJ open* [Internet]. 2019 2019/06//; 9(6):[e028197 p.]. Available from: <http://europepmc.org/abstract/MED/31167870>.
- [73] Millar SA, Stone NL, Bellman ZD, Yates AS, England TJ, O'Sullivan SE. A systematic review of cannabidiol dosing in clinical populations. *Br J Clin Pharmacol*. 2019;85(9):1888-900.
- [74] Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain*. 2007;133(1-3):210-20.
- [75] Solowij N, Broyd S, Greenwood L-m, van Hell H, Martellozzo D, Rueb K, et al. A randomised controlled trial of vaporised Δ^9 -tetrahydrocannabinol and cannabidiol alone and in combination in frequent and infrequent cannabis users: acute intoxication effects. *European Archives of Psychiatry and Clinical Neuroscience*. 2019;269(1):17-35.
- [76] Freeman TP, Hindocha C, Baio G, Shaban NDC, Thomas EM, Astbury D, et al. Cannabidiol for the treatment of cannabis use disorder: a phase 2a, double-blind, placebo-controlled, randomised, adaptive Bayesian trial. *Lancet Psychiatry*. 2020;7(10):865-74.
- [77] Mongeau-Pérusse V, Brissette S, Bruneau J, Conrod P, Dubreucq S, Gazil G, et al. Cannabidiol as a treatment for craving and relapse in individuals with cocaine use disorder: a randomized placebo-controlled trial. *Addiction*. 2021;116(9):2431-42.
- [78] Mozaffari K, Willette S, Lucker BF, Kovar SE, Holguin FO, Guzman I. The Effects of Food on Cannabidiol Bioaccessibility. *Molecules*. 2021;26(12).
- [79] Silmore LH, Willmer AR, Capparelli EV, Rosania GR. Food effects on the formulation, dosing, and administration of cannabidiol (CBD) in humans: A systematic review of clinical studies. *Pharmacotherapy*. 2021;41(4):405-20.
- [80] Delgado DA, Lambert BS, Boutris N, McCulloch PC, Robbins AB, Moreno MR, et al. Validation of Digital Visual Analog Scale Pain Scoring With a Traditional Paper-based Visual Analog Scale in Adults. *JAAOS Global Research & Reviews*. 2018;2(3):e088.
- [81] Shedden-Mora MC, Alberts J, Petrie KJ, Laferton JAC, von Blanckenburg P, Kohlmann S, et al. The Treatment Expectation Questionnaire (TEX-Q): Validation of a

- generic multidimensional scale measuring patients' treatment expectations. PLoS One. 2023;18(1):e0280472.
- [82] Benedetti F, Carlino E, Piedimonte A. Increasing uncertainty in CNS clinical trials: the role of placebo, nocebo, and Hawthorne effects. Lancet Neurol. 2016;15(7):736-47.
- [83] Spinella TC, Stewart SH, Naugler J, Yakovenko I, Barrett SP. Evaluating cannabidiol (CBD) expectancy effects on acute stress and anxiety in healthy adults: a randomized crossover study. Psychopharmacology (Berl). 2021;238(7):1965-77.
- [84] Jumbo SU, MacDermid JC, Kalu ME, Packham TL, Athwal GS, Faber KJ. Measurement Properties of the Brief Pain Inventory-Short Form (BPI-SF) and Revised Short McGill Pain Questionnaire Version-2 (SF-MPQ-2) in Pain-related Musculoskeletal Conditions: A Systematic Review. Clin J Pain. 2021;37(6):454-74.
- [85] Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. Psychological Assessment. 1995;7:524-32.
- [86] Daoust R, Paquet J, Williamson D, Perry JJ, Iseppon M, Castonguay V, et al. Accuracy of a self-report prescription opioid use diary for patients discharge from the emergency department with acute pain: a multicentre prospective cohort study. BMJ Open. 2022;12(10):e062984.
- [87] Li D, Mielke MM. An Update on Blood-Based Markers of Alzheimer's Disease Using the SiMoA Platform. Neurol Ther. 2019;8(Suppl 2):73-82.
- [88] King NS, Crawford S, Wenden FJ, Moss NE, Wade DT. The Rivermead Post Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced after head injury and its reliability. J Neurol. 1995;242(9):587-92.
- [89] Swiontkowski MF, Engelberg R, Martin DP, Agel J. Short musculoskeletal function assessment questionnaire: validity, reliability, and responsiveness. J Bone Joint Surg Am. 1999;81(9):1245-60.
- [90] Garratt AM, Ruta DA, Abdalla MI, Buckingham JK, Russell IT. The SF36 health survey questionnaire: an outcome measure suitable for routine use within the NHS? Bmj. 1993;306(6890):1440-4.
- [91] Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193-213.
- [92] Beck AT, Steer RA, Brown G. Beck depression inventory : manual. . Psychological Corporation: San Antonio, TX. 1996.
- [93] Ashbaugh AR, Houle-Johnson S, Herbert C, El-Hage W, Brunet A. Psychometric Validation of the English and French Versions of the Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5). PLoS One. 2016;11(10):e0161645.
- [94] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics. 2009;42(2):377-81.
- [95] Jodoin M, Herrero Babiloni A, Provost C, Blais H, Bellemare A, Desjardins M, et al. 10-Day Theta Burst Stimulation Intervention Facilitates the Clinical Rehabilitation of Patients After an Isolated Limb Fracture: A Longitudinal SHAM-Controlled Pilot Study. American Journal of Physical Medicine & Rehabilitation. 2024;103(11):e152-e61.

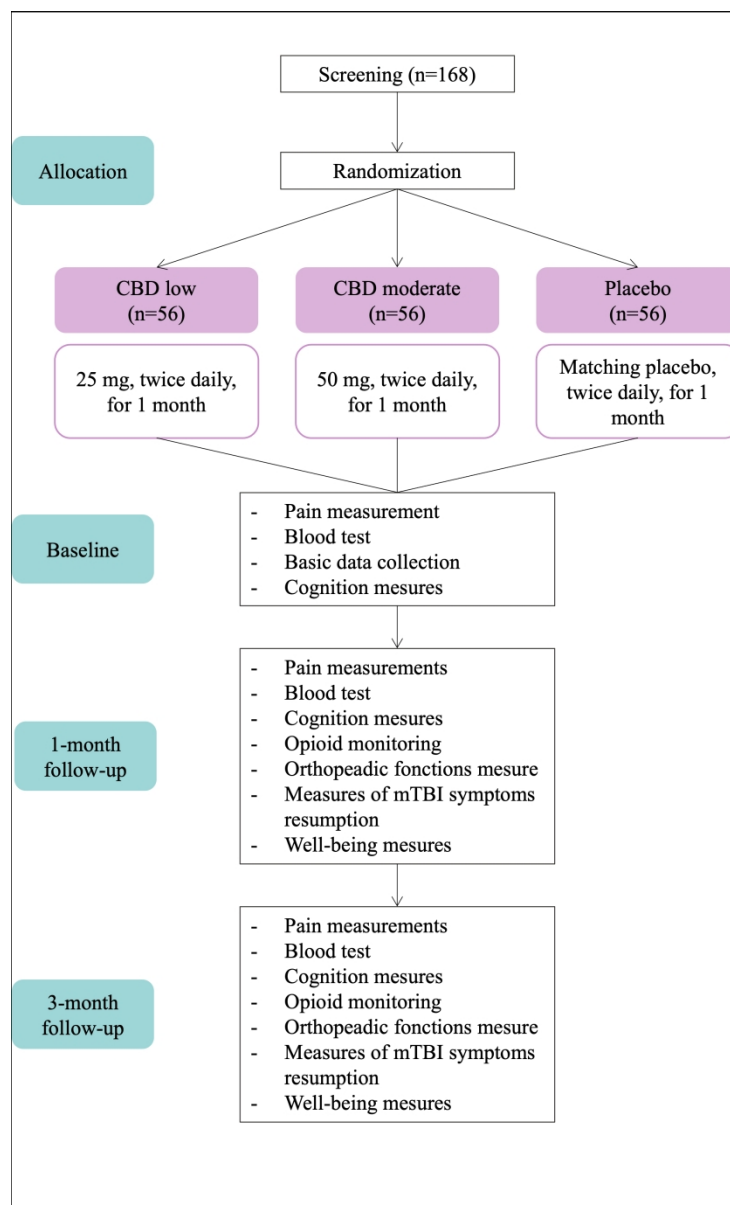


Figure 1 - Study schema

171x281mm (330 x 330 DPI)

BMJ Open

Impact of an acute 1-month cannabidiol treatment on pain and inflammation after a long bone fracture: a triple-blind randomized, placebo controlled, clinical trial protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2024-092919.R3
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Impact of an acute 1-month cannabidiol treatment on pain and inflammation after a long bone fracture: a triple-blind randomized, placebo controlled, clinical trial protocol

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Abstract

Introduction. Acute pain levels following orthopedic injury (e.g., fracture) is a predictor of the onset of chronic pain, which affects nearly 50% of fracture patients and impairs functional recovery. Among current pharmacological treatments for acute pain, non-steroidal anti-inflammatory drugs have been associated with delayed bone healing, while opioids inhibit effective bone remodeling, increase the risk of pseudarthrosis, and carry a high risk of addiction. In light of this, the development of new pain treatments is essential.

Cannabidiol (CBD), a non-addictive and non-psychotropic cannabis component stands out as a potential therapeutic agent, given its analgesic and anti-inflammatory properties as well as its potential benefits for bone healing. This randomized controlled trial aims to investigate the effect of acute CBD treatment, compared to placebo, on patients' self-reported pain, inflammation and well-being following a fracture injury.

Methods and analysis. This is a triple-blind, randomized, placebo-controlled clinical trial. A total of 225 adults aged 18 to 70 years, who have suffered a long bone fracture and were treated at the Hôpital du Sacré-Coeur de Montréal, will be randomly assigned within one week to one of three treatment arms (25 mg or 50 mg of CBD or placebo) for one month. The primary outcome will be difference in the pain score between groups at one-month follow-up. Secondary outcomes will include measures of persistent pain, inflammation, opioid usage, quality of life, sleep quality, depression, anxiety, cognition and orthopaedic function. Data will be collected at baseline, 1- and 3-month follow-ups.

Ethics and dissemination. This study obtained a Health Canada license for use of cannabis products. It has also been approved by Health Canada and the Research Ethics Board of the CIUSSS du Nord-de-l'Île-de-Montréal (Project ID 2025-2105). The findings will be published in a peer-reviewed journal and presented at local, national, and international conferences. The trial's results will be made publicly available on the clinicaltrials.gov database.

Trial registration number: NCT06448923 (registered on [ClinicalTrials.gov](https://clinicaltrials.gov))

53 **Strengths and limitations of this study**

- 54 - This study is robust due to its triple-blind randomized, placebo-controlled design,
55 which assesses the effects of two different doses of pharmaceutical-grade CBD.
- 56 - The extensive number of measurements allows for a comprehensive assessment of
57 the treatment's impact, not only by evaluating patients' perceived well-being and
58 recovery but also by objectively quantifying CBD's effect on inflammation through
59 inflammatory markers.
- 60 - This trial includes a longitudinal assessment of CBD treatment on pain symptoms
61 and trauma-related outcomes up to three months post-fracture, a critical period
62 marking the transition to chronic pain, however, the long-term effects of the
63 treatment will not be assessed.
- 64 - A limitation is the exclusion of osteoporotic patients, as well as a potential
65 restriction in the inclusion of women, since those of childbearing age who are not
66 using contraception will have to be excluded due to limited knowledge on the
67 teratogenic effects of CBD.
- 68 - Another limitation of this study is that therapeutic drug monitoring was not
69 performed, which could have helped account for inter-individual variability and
70 optimize dosing.

71 **Introduction**

72 Bone fractures are a prevalent condition affecting individuals of all ages and are the most
73 commonly treated trauma in hospitals [1, 2]. In 2019, the estimated annual incidence of
74 new fractures worldwide was 178 million [3]. The process of bone healing involves
75 multiple consecutive and interrelated phases including inflammation, repair, and

remodeling, which occur in a spatial and temporal series of dynamic processes [4, 5]. The skeletal system possesses a remarkable capacity for regeneration. The initial process of bone healing typically occurs over a period of eight weeks [6], while bone remodeling extends for months following a fracture [7].

Independent of body location, traumatic injury sets off an acute non-specific immune response characterized by the release of pro-inflammatory cytokines such as interleukins (IL-1 β , IL-6, IL-10) and the tumor necrosis factor (TNF- α) [8]. In addition, systemic acute inflammation after bone fracture promotes the sustained release of cytokines disrupting the blood-brain barrier, thereby allowing toxic intruders such as pro-inflammatory cytokines to invade/migrate to the central nervous system (CNS) [9]. Persistent CNS inflammation plays a key mediating role in central sensitization [10], a maladaptive plasticity process driven by an increased response to nociceptive inputs, involved in pain persistence and chronicity. Chronic pain, a condition associated with delayed functional recovery, sleep disturbances, mental health disorders, and poorer quality of life [10], is highly prevalent 3-6 months after trauma, affecting 30-50% of individuals with bone fractures [11]. A number of variables have been identified as potential predictors of chronic pain after trauma, including pain intensity at three months post-accident, female sex, poor sleep, levels of anxiety and depression, and the concomitant occurrence of traumatic brain injury (TBI) or peripheral nerve injury at the time of fracture [12-16].

Following a fracture, patients frequently report a range of symptoms, including increased fatigue and motor impairment, which can exert a significant impact on their ability to perform activities of daily living [17]. In addition, patients with orthopedic trauma report

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99 a deterioration in their quality of life up to twelve months following the injury [17, 18].

100 However, pain emerges as the most prominent complaint, with 97% of patients reporting

101 pain after an orthopedic injury [1, 19]. Acute pain management is a crucial concern

102 considering that inadequate pain control can lead to prolonged inflammation, which can

103 perpetuate pain signals and lead to chronic pain [20, 21]. Currently, a pharmacological

104 approach is widely recommended to manage acute post-trauma pain. Both non-steroidal

105 anti-inflammatory drugs (NSAIDs) and opioids are frequently prescribed for their anti-

106 inflammatory and analgesic effects [22]. Nevertheless, the use of NSAIDs has been

107 associated with delayed bone healing [23, 24] as well as digestive complication and kidney

108 failure [25]. As for opioids, in addition to major side effects, they pose a high risk of

109 dependence and tolerance [4, 26]. Furthermore, several studies show that opioids inhibit

110 effective bone remodeling [27], increase the risk of pseudarthrosis [28], and heighten the

111 risk of hyperalgesia, i.e. a paradoxical increase in pain sensitivity due to central

112 sensitization [26].

113

114 Interestingly, following the legalization of cannabis in Colorado, a reduction in chronic

115 pain admissions was observed, leading experts to question the potentially beneficial effects

116 of cannabis on pain [29]. Indeed, one study found that 61% of medical cannabis users

117 reported consuming it to alleviate pain [30, 31]. However, the medical use of cannabis is

118 limited due to the undesirable psychotropic and addictive effects of tetrahydrocannabinol

119 (THC). Cannabidiol (CBD), an organic component of cannabis, is non-psychoactive due

120 to its low affinity with the CB1 receptor [32]. It is of particular interest as it is devoid of

121 addictive effects [33, 34] and has an excellent safety profile [35], and its use does not affect
122 daily activities such as driving or working.

123

124 CBD is highly lipophilic which facilitates its ability to cross the blood-brain barrier [36].

125 However, the bioavailability of CBD varies greatly according to the method of
126 administration. The bioavailability of oral CBD is lower due to the hepatic first-pass effect,
127 with approximately 5% of the product reaching the bloodstream [37-39]. Food
128 consumption as well as nanotech and oil-based formulations of CBD have been shown to
129 increase bioavailability [40]. However, compared to smoked CBD, oral administration of
130 CBD presents multiple advantages, including greater control over dosage, ease of
131 administration, and fewer side effects [38].

132

133 Mechanisms of action of CBD are complex, not yet fully understood and involve multiple
134 pharmacological targets. Emerging evidence suggests that CBD exerts a number of
135 important effects via its modulating role on several non-cannabinoid receptors and ion
136 channels including those of endogenous neurotransmitters, such as serotonin [41] as well
137 as several types of transient receptor potential channels (TRP), such as TRPV1 [42], and
138 by modulating the binding affinity of certain G protein-coupled receptors [43]. Several in
139 vitro and animal model studies have demonstrated CBD's anti-inflammatory effect, notably
140 by reducing pro-inflammatory cytokines such as TNF- α , IL-1 β and IL-6, in addition to
141 inhibiting microglial activation [32, 42, 44-51]. CBD has also shown analgesic potential in
142 studies using neuropathic and inflammatory pain models. These human and animal studies
143 suggest a reduction in pain, hyperalgesia, and allodynia following treatment with CBD [35,

144 52-59]. CBD is alleged to possess anxiolytic and anti-depressant properties, as shown in
145 several animal and human studies [60-66]. In addition, a well-controlled preliminary
146 animal study showed that CBD, but not THC, enhanced the biomechanical properties of
147 healing mid-femoral fractures in rats, supporting a beneficial effect of CBD on bone
148 healing [67].

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150 Epidemiological studies have suggested a reduction in opioid use for pain coinciding with
151 an increased use of medical cannabis [30], a trend also documented in Canada [68]. While
152 the interaction between CBD and opioids is not yet fully understood, studies have shown
153 that CBD acts as an allosteric modulator of the mu- and delta-opioid receptors [69]. CBD
154 was also shown to potentially enhance the analgesic effects of endogenous and exogenous
155 opioids. In one study, the use of CBD as a co-analgesic treatment for patients with chronic
156 pain resulted in a reduction in opioid consumption and improvements in overall quality of
157 life [70].

158
159 Providing effective pain management for patients with fractures is not only a fundamental
160 right but also offers numerous benefits. It reduces stress, shortens hospitalization time,
161 decreases associated healthcare costs and lowers the risk of developing chronic pain [1].
162 Preventing chronic pain is easier than reversing the sensitization processes that cause it
163 [71], making acute pain control a priority. Given its excellent safety profile [33, 35]
164 coupled with its downregulating effects on microglial and inflammatory activity, the
165 primary neuroinflammatory and pain mechanism, CBD represents an appealing
166 neuroprotective agent for pain-susceptible orthopedic trauma patients.

167

168 **Study objectives**

169 The primary objective of this study is to evaluate the effects of CBD treatment on self-
170 reported pain in patients following a long bone fracture injury. The second objective is to
171 assess the effect of the CBD treatment on inflammation and patient well-being.
172 Additionally, secondary analyses will look at the possible associations between pain
173 mediators (such as opioids, sex, and mild traumatic brain injury (mTBI)) and response to
174 CBD treatment. The aim is to better identify the effects of these pain mediators on treatment
175 response and the impact of CBD treatment on opioid uptake.

176

177 **Methods**

178 **Study design**

179 This is a randomized, placebo controlled, triple-blind 1-month clinical trial evaluating the
180 effects of two doses (low and moderate) of CBD compared to a placebo on pain and
181 inflammation after a long bone fracture.

182

183 **Participants**

184 A total of 225 participants aged 18 to 70 will be recruited within one week after their long
185 bone fracture injury and consultation to the Hôpital du Sacré-Coeur de Montréal (HSCM),
186 one of the largest Level 1 trauma centres in Canada with approximately 3,500 orthopedic
187 patients treated annually. The planned age range, targeting a population representative of
188 individuals who frequently experience traumatic fractures, was chosen as it allows for a
189 more homogenous evaluation of fracture healing and pain recovery. Including participants

over 70 introduces additional challenges, such as increased comorbidities, chronic diseases, bone fragility, polymedication and increased complications, which could slow the healing process, influence pain perception and complicate result interpretation.

Inclusion criteria

Subjects meeting the following criteria are eligible for the trial:

- Patients with a long bone fracture of the lower limb (tibia, fibula, femur, metatarsals, and phalanges) or the upper limb (humerus, radius, ulna, metacarpals, and phalanges) treated to Hôpital du Sacré-Coeur de Montréal (HSCM) within one week of the accident
- Participants is between 18 and 70 years of age
- Patients with or without surgical procedures

Exclusion criteria

Patients presenting any of the following characteristics are not eligible for the trial:

- Moderate/severe traumatic brain injury (TBI)
- Diagnosis of any of the following mental disorders as defined by the DSM-5: schizophrenia, intellectual disability, bipolar disorder, major depression, a diagnosed and untreated sleep disorders
- History of alcohol or opioid misuse/abuse, as defined by the DSM-5
- Evidence of severe renal (stage 4 or 5) or hepatic impairment (Child B or C)

- 211 - Pregnant or lactating women, women of childbearing potential who are not using
- 212 medically accepted forms of contraception (e.g., condoms, oral contraceptive or
- 213 intrauterine device), or women who are actively planning on becoming pregnant
- 214 - History of adverse reactions to cannabis
- 215 - Patients taking warfarin, sildenafil, valproate or under opioids treatment prior to the
- 216 injury
- 217 - Patients experiencing on average mild-to-absent pain in the last 24h preceding
- 218 recruitment (as per a score <30 on a 0-100mm Visual Analogue Scale (VAS))
- 219 - Transport business drivers and heavy machinery operators
- 220 - A diagnosis of chronic pain, bone pathology (e.g., osteoporosis) or chronic
- 221 inflammatory disease (e.g., rheumatoid arthritis, arthritis, psoriasis)
- 222 - Not having French or English as a spoken language
- 223 - A weighted MoCA score of less than 24
- 224 - Regular cannabis use more than 5 times a week

225

226 Recruitment

227 Recruitment will begin in January 2025 and end in January 2027. Potential participants will

228 be screened daily by the research team and collaborators. Potentially eligible patients will

229 be approached by a research team member and provided with a consent form. Once the

230 research team has addressed any remaining questions and obtained a signed consent form,

231 the participant will be randomized. See figure 1 for an overview of the study timeline.

232

233 Assignment of interventions

Participants will undergo concealed randomization to avoid selection bias. The study pharmacist will randomly assign participants to one of the three treatment groups (low or moderate CBD or placebo) using a 1:1:1 ratio through block randomization with randomly selected block sizes (9 and 12), stratified by sex, age (i.e., participants aged 45 and under, and those over 45) and type of fracture (i.e., lower and upper limb). Block randomization with randomly selected block sizes (9 and 12) was chosen to minimize selection bias and maintain the blinding of investigators and other project members by ensuring the unpredictability of block assignments. Given that there are three groups, a block size of 9 results in a distribution of 3 patients per group, whereas a block size of 12 allocates 4 patients in each group. The randomization procedure will be performed a priori by an independent biostatistician. Identical tablets for CBD and placebo will ensure blinding of clinicians, researchers, patients, families, and biostatistician to avoid unequal co-interventions, ascertainment bias, and analytic bias. The study pharmacist will be aware of allocation but will have no clinical or interpretive role. Assignments will be kept in sequentially numbered, sealed envelopes to ensure adequate allocation concealment. In the event of a serious adverse event or reaction, the allocation list can be retrieved.

250

251 **Intervention**

Patients in the treatment group will receive either a low dose (25 mg per tablet) or a moderate dose (50 mg per tablet) of CBD self-administered orally as a tablet twice daily with a meal for one month. Patients in the placebo group will receive an identical amount of a matching placebo administered with a meal twice daily for one month.

256

257 *Investigational product*

258 CBD tablets, along with matching placebos, will be supplied by EmpowerPharm (Toronto,
259 Canada). The pharmacokinetic profile of the CBD product has already been established,
260 and efforts to register the product with Health Canada have begun.

261

262 *Dose justification*

263 A wide range of CBD doses ranging from <1 to 50mg/kg has been used in various
264 conditions [72, 73]. The low dose (25 mg) selected for our study is based on initial and
265 ongoing studies of CBD in chronic pain which used a mean dose of 22.5mg and 20mg per
266 day [65]. This is also approximately the mean dose of CBD administered in a successful
267 trial of Sativex (THC/CBD) for neuropathic pain [74]. Moreover, a higher but relatively
268 moderate dose of CBD (50 mg) will be evaluated to assess dose-response effect. CBD
269 doses in this range have shown no statistical difference in intoxication scores in healthy
270 volunteers [75] and doses of up to 800 mg per day for a minimum of 4 weeks showed an
271 excellent safety and tolerability profile [76, 77]. Participants will be advised to ingest the
272 treatment at mealtime, as studies have shown an increased bioavailability of CBD in
273 subjects after eating [78, 79]. To achieve our primary goal of mitigating acute pain, a one-
274 month treatment period has been selected, aligning with the typical evolution of acute pain
275 post-fracture [6].

276

277 **Study procedure**

278 Upon enrollment in the study, research staff will provide study instructions, collect baseline
279 data (e.g., demographics and clinical characteristics), administer questionnaires and

cognitive tests, and collect blood samples for quantification of pro-inflammatory cytokines. Patients will report their pain intensity at baseline, and then three times a week throughout the entire one-month treatment duration. Participants will be instructed to complete a daily medication diary for one month to monitor the administration of study product, as well as opioid, drugs, or other analgesic medication use. This data will be collected via questionnaires sent by e-mail or SMS message from the RedCap secure database. At 24h following treatment completion (one-month follow-up) and at the 3-month follow-up, participants will be evaluated at the research laboratory to collect measures of pain intensity and related outcomes including opioids intake, inflammation, cognition, orthopedic function and indicators of overall well-being. Participants will have to abstain from CBD consumption from the end of treatment until the last follow-up visit. See Table 1 for a detailed schedule of assessments.

Table 1. Schedule of assessment

Domain	Mesure	Screening	Baseline	During Treatment	1-month follow-up	3-month follow-up
Eligibility	Demographic questionnaire	X	X			
	Consent form	X				
	Medical history	X				
	MoCA	X				
	Medication	X	X	X	X	X
Primary outcome	Visual Analog Scale	X	X	X	X	X
Secondary outcomes	Brief Pain Inventory short form (BPI-sf)				X	X
	Blood sample - Inflammation markers		X		X	X
	Cognition		X		X	X

	Rivermead TBI symptoms				X	X
	Short Musculoskeletal Function Assessment (SMFA)				X	X
	Short Form Health Survey				X	X
	Pittsburgh Sleep Quality Index (PSQI)				X	X
	Beck's Depression Inventory-II		X		X	X
	Beck's Anxiety Inventory		X		X	X
Other	Pain Catastrophizing Scale (PCS)		X			
	Treatment Expectation Questionnaire (TEX-Q)		X			
	PTSD Checklist for DSM-5 (PCL-5)		X		X	
	Treatment assignment hypothesis				X	
	Opioid consumption	X	X	X	X	X
	Adverse events			X	X	

Primary outcome

The main outcome is the difference between groups in the mean pain intensity score at one-month follow-up, as measured by the visual analog scale (VAS) [80]. Pain intensity on the VAS will be gathered 24h following treatment completion. The VAS is a 100mm line with anchor words ranging from “no pain” to “worst imaginable pain”. Participants will indicate the intensity of their pain at that moment by placing a mark along the line.

Secondary outcomes

At 1 and 3-month follow-ups, persistent pain, opioid consumption, inflammation markers, quality of life, sleep quality, depression, anxiety, cognition, mTBI symptom resolution, and orthopaedic function outcomes will be collected. In addition, at baseline, participants will be asked to indicate their level of treatment expectation using the Treatment Expectation Questionnaire (TEX-Q-F) [81], a fifteen-question questionnaire, considering the potential modulation of therapeutic effects by patients' expectations of treatment [82, 83]. After treatment completion, participants will also be asked to indicate whether they felt they had received active treatment or placebo.

Measures

Demographic and clinical characteristics

The following information will be collected at baseline to characterize participants: age, sex, height, weight, percentage of adipose tissue using an impedance meter scale, occupation, education level, ethnicity, language spoken, pre-morbid medical history (including psychological health history), pre-morbid substance use (e.g., alcohol, drugs, cigarettes, medications), recreational cannabis use, history of brain trauma, injury type and severity, mechanism of injury.

Pain

At 1- and 3-month follow-up, persistent pain will be assessed using the Brief Pain Inventory short form (BPI-sf) [84], a 9-item self-report questionnaire assessing for the presence, intensity, and location(s) of pain, as well as perceived efficacy of pain relief treatment, and pain interference with activities of daily living. In addition, pain will be

assessed using the VAS at several time points for comparison: baseline, three times per week during treatment, 24h after the end of treatment and at the 3-month follow-up. Pain catastrophizing will also be assessed during the initial visit using the Pain Catastrophizing Scale [85], a 13-item questionnaire evaluated on Likert scales, given the significant contribution of psychological factors in the experience of pain.

Opioid usage

Participants will continue their usual pain care regimen throughout the study. Opioid usage and analgesic will be recorded in a daily medication diary for the initial month and through the number of prescription refills for months two and three. Self-reported opioid use in a diary has been shown to be an accurate assessment of the quantity of opioids consumed [86].

Inflammation

Blood levels of pro-inflammatory cytokines including interleukins (IL-6, IL-10, IL-1 β) and TNF- α will be collected at baseline and at the 1 and 3-month follow-up sessions. To assess cytokine levels, blood samples will be separated in buffy coat, serum and plasma, and stored at -80 °C in polypropylene tubes on average 1-2h after the blood draw. EDTA plasma will be tested with cutting-edge ultra-sensitive Quanterix ImmunoAssay Analyzer Simoa HD-X to quantify biomarkers using the Cor-Plex-Cytokine-10-Plex assay panel as per manufacturer recommendation. Simoa is a leader in the quantification of plasma biomarkers with markedly lower detection threshold than traditional ELISA [87].

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349 *Cognition*

350 At baseline, 1 and 3-months follow-ups, neuropsychological tests highly sensitive to pain,
351 and that do not require the use of the fractured limb, will be administered: a task assessing
352 information processing speed (Symbol Search from the WAIS-IV Battery), two memory
353 tests (California Verbal Learning Test and Digit Span from the WAIS-IV battery), two
354 executive function tests (D-KEFS Color-Word and Verbal Fluency), and an attention test
355 (Elevator counting with distraction and Elevator counting without distraction from the Test
356 of Everyday Attention battery) (see Lezac et al., 1995 for test descriptions).

357

358 *Mild TBI symptoms resolution*

359 Patients who sustained a concomitant mTBI with their fracture will be included in the
360 study. Additional measures will be documented to control for this variable. At 1 and 3-
361 months follow-up, information on mTBI symptoms resolution will be collected for patients
362 diagnosed with a mTBI concomitant to the fracture using the Rivermead Post-Concussion
363 Questionnaire [88].

364

365 *Orthopaedic function*

366 At 1 and 3-months follow-ups, the Short Musculoskeletal Function Assessment (SMFA)
367 Questionnaire [89] will be administered. The SMFA includes 34 questions that evaluate
368 patient's function, and 12 questions related to how bothered patients are by their symptoms.

369

370 *Well-being*

At 1 and 3-months follow-ups, various important domains of well-being significantly modulated by pain will be measured including: quality of life using the Short Form (36) Health Survey [90], a 36-item self-report questionnaire for measuring quality of life across 9 domains; sleep quality and quantity using the Pittsburgh Sleep Quality Index (PSQI) [91], a self-report questionnaire that assesses sleep quality and quantity over the past 4 weeks. Additionally, at baseline, 1 and 3-months follow-ups depression and anxiety symptoms will be assessed using the Beck's Depression Inventory-II (BDI-II) [92] and the Beck's Anxiety Inventory (BAI) (86). The BDI-II is a 21-item multiple-choice self-report questionnaire for measuring depression symptoms. The BAI is a 21-question multiple-choice self-report inventory used for measuring the severity of anxiety. Finally, symptoms of post-traumatic stress disorder will be assessed at the first visit and at 1-month follow-up using the PTSD Checklist for DSM-5 (PCL-5) questionnaire [93].

Data management

Data collected will be transcribed from the source documents into the electronic Case Report Form (eCRF) on the REDCap database hosted at CIUSSS du Nord-de-l'Île-de-Montréal [94] and quality controlled by a second qualified staff member. Data will be stored on a secure network with regular backups. An external, independent clinical monitor will conduct regular monitoring visits according to the monitoring plan, during which they will review and verify source data, informed consent forms, medical records, laboratory results, case report forms, medication dispensing logs and protocol deviations.

Statistical analyses

394 *Sample size estimation*

395 A 30% relative pain intensity reduction on the VAS (expected response of 50% or more in
396 the CBD group and expected 20% in the placebo group) has been used extensively to reflect
397 clinically significant pain relief in clinical trials. Based on a Fisher's exact test, a sample
398 size of 225 participants (3 groups of 75) will be required to reach a power of 80% to detect
399 a statistically significant difference in the proportion of patients who reaches 30% pain
400 reduction between the CBD groups and placebo at 1-month post-injury, assuming a dropout
401 rate of 20% and a significance level of 5%. These parameters are taken from a successful
402 randomised, placebo-controlled clinical trial using Sativex© in treating 125 neuropathic
403 pain patients [74].

404 Moreover, considering that the placebo group may ingest more opiates and that the
405 anticipated inter-group effect at one month may be reduced to 20%, a total sample size of
406 225 subjects could be required to achieve 80% power, assuming a drop-out rate of 20%
407 and a significance level of 5%.

409 *Primary outcome*

410 The primary outcome will be analyzed using an ANCOVA, with mTBI and orthopedic
411 surgery as covariables and treatment (low and moderate CBD vs. placebo) as factor in the
412 mean VAS pain score at the 1-month follow-up.

414 *Secondary outcomes*

415 For the secondary outcomes, a Kaplan Meier survival analysis with the log-rank test on
416 VAS pain data collected during treatment will be used to assess CBD treatment success

rate relative to placebo at achieving 50% pain intensity reduction during treatment duration. The proportion of patients no longer experiencing significant pain symptoms at the 3-month follow-up (i.e., patients who did not convert to chronic pain) will be compared, as defined as VAS pain ≤ 30 between treatment with a chi-squared test. A mixed model for repeated measures with covariables mTBI and orthopedic surgery and treatment as factor will be used to assess between-group treatment effects on total opioids use at both 1 and 3-month follow-ups. The same approach will be used to assess between-group treatment effects at both 1- and 3-month follow-ups on secondary outcomes measures listed above.

Analyses will be performed on an intention-to-treat (ITT) dataset. The ITT dataset will include all participants randomized in the analysis, whether or not they have completed treatment in order to limit bias and reflect results under real treatment conditions.

Missing data will be reported and justified in the results. The multiple imputation method, which has been recognized in clinical studies involving experimental treatment, will be applied. Additionally, a sensitivity analysis will be performed to assess the impact of missing data on the results.

Discontinuation

Participants may withdraw from this research project at any time without giving reasons. Discontinuation of treatment does not imply withdrawal from the trial. The following reasons will be considered as grounds for patient withdrawal from the trial: withdrawal of consent by the participant, failure to pass the selection phase, meeting an exclusion

440 criterion, failure to participate in follow-up, termination of the trial by the investigator,
441 major protocol deviation incompatible with trial participation, an adverse event or any
442 other condition which, in the opinion of the investigator, would expose the participant to
443 undue risk by continuing the treatment trial, any condition that the investigator considers
444 medically necessary to withdraw the patient from the trial.

446 **Adherence**

447 During the baseline visit, a research team member will conduct an information session to
448 discuss the significance of adhering to the guidelines related to doses, timing of drug
449 administration, the procedure to be followed in case of a missed dose, and the importance
450 of reporting any adverse event. Automatic SMS reminders will be sent to ensure
451 completion of the digital VAS and medication diary. A high protocol adherence is expected
452 given that cannabidiol has limited adverse side effects, and the administration is oral and
453 non-invasive. A 10% loss to follow-up is expected based on a 3-month trial with the same
454 patient characteristics[95]. For adherence purposes, patients will be instructed to return all
455 treatment bottles, empty or not, to be monitored by the pharmacy staff. Each participant
456 will receive financial compensation for costs incurred during their participation in this
457 research study. Participants who withdraw or are withdrawn from the project prior to its
458 completion will receive an amount proportional to the length of their participation.

460 **Safety and serious adverse events**

461 Risks of adverse effects are considered low given the demonstrated excellent safety profile
462 of CBD [33, 35]. Somnolence, fatigue, drowsiness, gastro-intestinal issue, and decreased

appetite are the most probable adverse events associated with CBD in adult patients [34]. Participants will be instructed to advise the research team of any adverse events which will be thoroughly monitored and documented. Access to on-duty emergency physicians at HSCM will be provided during the entire treatment duration.

Patient and public involvement

Neither patients nor the public were involved in the development, design and conduct of this study.

Confidentiality

All data collected in our databases will be stored following a de-identification process. Participants will be identified by a unique identification code, and nominal data will be protected separately. Uncoded data will only be accessible to the principal investigator. No identifying data will be disclosed in any scientific communication or publication.

Ethics and dissemination

Ethical approval has been granted by the CIUSSS du Nord-de-l'Île-de-Montréal ethics board (#2025-2105 issued August 2024) and Health Canada (License, #LIC-NKA1EX2TUA-202-3 issued on March 26, 2024, and No Objection Letter, HC6-024-c275232 issued on May 30, 2024). This study adheres with the Declaration of Helsinki. The results will be published in a peer-reviewed journal and presented at local, national, and international conferences.

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3 486 **Author Contributions**

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5 487 DB, DW, FB, CA, GL, AP, DR, LDB conceived the study. DB and AAD will ensure
6
7 488 coordination, recruitment and conduct of the protocol. DB and LDB wrote the manuscript.
8
9
10 489 All authors contributed to the revisions of the manuscript. LDB is guarantor.
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14
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18
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20
21 494 recherche du Québec-Santé (BF2-341229). CBD and placebo will be manufactured by
22
23 495 EmpowerPharm (Ontario, Canada). The study's design, management, analysis, and
24
25 496 reporting are entirely independent of the CBD manufacturers.
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31 498 **Competing interests:** None declared.
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35 500 **Figure 1. Study Schema. CBD, cannabidiol; mTBI, mild traumatic brain injury.**
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43 505 **References**

- 44
45 506 [1] Ahmadi A, Bazargan-Hejazi S, Heidari Zadie Z, Euasobhon P, Ketumarn P,
46 507 Karbasfrushan A, et al. Pain management in trauma: A review study. J Inj Violence Res.
47 508 2016;8(2):89-98.
48
49 509 [2] Urquhart DM, Williamson OD, Gabbe BJ, Cicuttini FM, Cameron PA, Richardson
50 510 MD, et al. Outcomes of patients with orthopaedic trauma admitted to level 1 trauma
51 511 centres. ANZ J Surg. 2006;76(7):600-6.
52
53 512 [3] Wu A-M, Bisignano C, James SL, Abady GG, Abedi A, Abu-Gharbieh E, et al. Global,
54 513 regional, and national burden of bone fractures in 204 countries and territories, 1990–

- 2019: a systematic analysis from the Global Burden of Disease Study 2019. *The Lancet Healthy Longevity*. 2021;2(9):e580-e92.
- [4] Alves CJ, Neto E, Sousa DM, Leitão L, Vasconcelos DM, Ribeiro-Silva M, et al. Fracture pain-Traveling unknown pathways. *Bone*. 2016;85:107-14.
- [5] Claes L, Recknagel S, Ignatius A. Fracture healing under healthy and inflammatory conditions. *Nat Rev Rheumatol*. 2012;8(3):133-43.
- [6] Einhorn TA, Gerstenfeld LC. Fracture healing: mechanisms and interventions. *Nat Rev Rheumatol*. 2015;11(1):45-54.
- [7] Marsell R, Einhorn TA. The biology of fracture healing. *Injury*. 2011;42(6):551-5.
- [8] Loi F, Córdova LA, Pajarinen J, Lin TH, Yao Z, Goodman SB. Inflammation, fracture and bone repair. *Bone*. 2016;86:119-30.
- [9] Huang X, Hussain B, Chang J. Peripheral inflammation and blood-brain barrier disruption: effects and mechanisms. *CNS Neurosci Ther*. 2021;27(1):36-47.
- [10] Fine PG. Long-term consequences of chronic pain: mounting evidence for pain as a neurological disease and parallels with other chronic disease states. *Pain Med*. 2011;12(7):996-1004.
- [11] Nampiaparampil DE. Prevalence of chronic pain after traumatic brain injury: a systematic review. *Jama*. 2008;300(6):711-9.
- [12] Castillo RC, MacKenzie EJ, Wegener ST, Bosse MJ. Prevalence of chronic pain seven years following limb threatening lower extremity trauma. *Pain*. 2006;124(3):321-9.
- [13] McDonald SJ, Sharkey JM, Sun M, Kaukas LM, Shultz SR, Turner RJ, et al. Beyond the Brain: Peripheral Interactions after Traumatic Brain Injury. *J Neurotrauma*. 2020;37(5):770-81.
- [14] Walker WC. Pain pathoetiology after TBI: neural and nonneural mechanisms. *The Journal of head trauma rehabilitation*. 2004;19(1):72-81.
- [15] Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. *Br J Anaesth*. 2013;111(1):52-8.
- [16] Molitoris KH, Balu AR, Huang M, Baht GS. The impact of age and sex on the inflammatory response during bone fracture healing. *JBMR Plus*. 2024;8(5).
- [17] Soleymanha M, Mobayen M, Asadi K, Adeli A, Haghparast-Ghadim-Limudahi Z. Survey of 2582 cases of acute orthopedic trauma. *Trauma Mon*. 2014;19(4):e16215.
- [18] Sluys KP, Shults J, Richmond TS. Health related quality of life and return to work after minor extremity injuries: A longitudinal study comparing upper versus lower extremity injuries. *Injury*. 2016;47(4):824-31.
- [19] Archer KR, Castillo RC, Wegener ST, Abraham CM, Obremskey WT. Pain and satisfaction in hospitalized trauma patients: The importance of self-efficacy and psychological distress. *Journal of Trauma and Acute Care Surgery*. 2012;72(4):1068-77.
- [20] Mehta SP, MacDermid JC, Richardson J, MacIntyre NJ, Grewal R. Baseline pain intensity is a predictor of chronic pain in individuals with distal radius fracture. *J Orthop Sports Phys Ther*. 2015;45(2):119-27.
- [21] Powelson EB, Mills B, Henderson-Drager W, Boyd M, Vavilala MS, Curatolo M. Predicting chronic pain after major traumatic injury. *Scand J Pain*. 2019;19(3):453-64.

1
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17
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42
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44
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50
51
52
53
54
55
56
57
58
59
60

[22] Majuta LA, Longo G, Fealk MN, McCaffrey G, Mantyh PW. Orthopedic surgery and bone fracture pain are both significantly attenuated by sustained blockade of nerve growth factor. *Pain*. 2015;156(1):157-65.

[23] Atchison JW, Herndon CM, Rusie E. NSAIDs for musculoskeletal pain management:current perspectives and novel strategies to improve safety. *J Manag Care Pharm*. 2013;19(9 Suppl A):S3-19.

[24] Maruyama M, Rhee C, Utsunomiya T, Zhang N, Ueno M, Yao Z, et al. Modulation of the Inflammatory Response and Bone Healing. *Front Endocrinol (Lausanne)*. 2020;11:386.

[25] Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. *Biochem Pharmacol*. 2020;180:114147.

[26] Lembke A, Humphreys K, Newmark J. Weighing the Risks and Benefits of Chronic Opioid Therapy. *Am Fam Physician*. 2016;93(12):982-90.

[27] Raphael-Mizrahi B, Gabet Y. The Cannabinoids Effect on Bone Formation and Bone Healing. *Curr Osteoporos Rep*. 2020;18(5):433-8.

[28] Buchheit T, Zura R, Wang Z, Mehta S, Della Rocca GJ, Steen RG. Opioid exposure is associated with nonunion risk in a traumatically injured population: An inception cohort study. *Injury*. 2018;49(7):1266-71.

[29] RMHIDTA. The Legalization of Marijuana in Colorado: The Impact: Volume 6, September 2019. *Mo Med*. 2019;116(6):450.

[30] Hill KP, Palastro MD, Johnson B, Ditre JW. Cannabis and Pain: A Clinical Review. *Cannabis Cannabinoid Res*. 2017;2(1):96-104.

[31] Khan SP, Pickens TA, Berlau DJ. Perspectives on cannabis as a substitute for opioid analgesics. *Pain Manag*. 2019;9(2):191-203.

[32] Burstein S. Cannabidiol (CBD) and its analogs: a review of their effects on inflammation. *Bioorg Med Chem*. 2015;23(7):1377-85.

[33] Gray RA, Heal DJ, Maguire DR, Gerak LR, Javors MA, Smith S, et al. Preclinical Assessment of the Abuse Potential of Purified Botanical Cannabidiol: Self-Administration, Drug Discrimination, and Physical Dependence. *J Pharmacol Exp Ther*. 2022;382(1):54-65.

[34] Micallef J, Batisse A, Revol B. [Pharmacology of cannabidiol: Red flags, consequences and risks in humans]. *Therapie*. 2022;77(5):585-90.

[35] Alaia MJ, Hurley ET, Vasavada K, Markus DH, Britton B, Gonzalez-Lomas G, et al. Buccally Absorbed Cannabidiol Shows Significantly Superior Pain Control and Improved Satisfaction Immediately After Arthroscopic Rotator Cuff Repair: A Placebo-Controlled, Double-Blinded, Randomized Trial. *Am J Sports Med*. 2022;50(11):3056-63.

[36] Calapai F, Cardia L, Sorbara EE, Navarra M, Gangemi S, Calapai G, et al. Cannabinoids, Blood–Brain Barrier, and Brain Disposition. *Pharmaceutics*. 2020;12(3):265.

[37] Atsmon J, Heffetz D, Deutsch L, Deutsch F, Sacks H. Single-Dose Pharmacokinetics of Oral Cannabidiol Following Administration of PTL101: A New Formulation Based on Gelatin Matrix Pellets Technology. *Clin Pharmacol Drug Dev*. 2018;7(7):751-8.

[38] Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet*. 2003;42(4):327-60.

- [39] Hosseini A, McLachlan AJ, Lickliter JD. A phase I trial of the safety, tolerability and pharmacokinetics of cannabidiol administered as single-dose oil solution and single and multiple doses of a sublingual wafer in healthy volunteers. *Br J Clin Pharmacol*. 2021;87(4):2070-7.
- [40] Moazen-Zadeh E, Chisholm A, Bachi K, Hurd YL. Pharmacokinetics of Cannabidiol: A systematic review and meta-regression analysis. *medRxiv*. 2023.
- [41] Russo EB, Burnett A, Hall B, Parker KK. Agonistic Properties of Cannabidiol at 5-HT1a Receptors. *Neurochemical Research*. 2005;30(8):1037-43.
- [42] Costa B, Colleoni M, Conti S, Parolaro D, Franke C, Trovato AE, et al. Oral anti-inflammatory activity of cannabidiol, a non-psychoactive constituent of cannabis, in acute carrageenan-induced inflammation in the rat paw. *Naunyn Schmiedeberg's Arch Pharmacol*. 2004;369(3):294-9.
- [43] Laun AS, Shrader SH, Brown KJ, Song ZH. GPR3, GPR6, and GPR12 as novel molecular targets: their biological functions and interaction with cannabidiol. *Acta Pharmacol Sin*. 2019;40(3):300-8.
- [44] Kuret T, Kreft ME, Romih R, Veranič P. Cannabidiol as a Promising Therapeutic Option in IC/BPS: In Vitro Evaluation of Its Protective Effects against Inflammation and Oxidative Stress. *Int J Mol Sci*. 2023;24(5).
- [45] Kongkadee K, Wisuitiprot W, Ingkaninan K, Waranuch N. Anti-inflammation and gingival wound healing activities of *Cannabis sativa* L. subsp. *sativa* (hemp) extract and cannabidiol: An in vitro study. *Arch Oral Biol*. 2022;140:105464.
- [46] Yndart Arias A, Kolishetti N, Vashist A, Madepalli L, Llaguno L, Nair M. Anti-inflammatory effects of CBD in human microglial cell line infected with HIV-1. *Sci Rep*. 2023;13(1):7376.
- [47] Li H, Kong W, Chambers CR, Yu D, Ganea D, Tuma RF, et al. The non-psychoactive phytocannabinoid cannabidiol (CBD) attenuates pro-inflammatory mediators, T cell infiltration, and thermal sensitivity following spinal cord injury in mice. *Cell Immunol*. 2018;329:1-9.
- [48] Kozela E, Juknat A, Vogel Z. Modulation of Astrocyte Activity by Cannabidiol, a Nonpsychoactive Cannabinoid. *Int J Mol Sci*. 2017;18(8).
- [49] Kozela E, Lev N, Kaushansky N, Eilam R, Rimmerman N, Levy R, et al. Cannabidiol inhibits pathogenic T cells, decreases spinal microglial activation and ameliorates multiple sclerosis-like disease in C57BL/6 mice. *Br J Pharmacol*. 2011;163(7):1507-19.
- [50] Giacoppo S, Galuppo M, Pollastro F, Grassi G, Bramanti P, Mazzon E. A new formulation of cannabidiol in cream shows therapeutic effects in a mouse model of experimental autoimmune encephalomyelitis. *Daru*. 2015;23:48.
- [51] Dopkins N, Miranda K, Wilson K, Holloman BL, Nagarkatti P, Nagarkatti M. Effects of Orally Administered Cannabidiol on Neuroinflammation and Intestinal Inflammation in the Attenuation of Experimental Autoimmune Encephalomyelitis. *J Neuroimmune Pharmacol*. 2022;17(1-2):15-32.
- [52] Britch SC, Craft RM. Cannabidiol and Delta-9-Tetrahydrocannabinol Interactions in Male and Female Rats With Persistent Inflammatory Pain. *J Pain*. 2023;24(1):98-111.

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2
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42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

[53] Costa B, Trovato AE, Comelli F, Giagnoni G, Colleoni M. The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. *Eur J Pharmacol.* 2007;556(1-3):75-83.

[54] Aguiar DD, da Costa Oliveira C, Fonseca FCS, de Almeida DL, Campos Pereira WV, Guimarães FS, et al. Peripherally injected cannabidiol reduces neuropathic pain in mice: Role of the 5-HT(1A) and TRPV1 receptors. *Biochem Biophys Res Commun.* 2023;660:58-64.

[55] Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clin Rehabil.* 2003;17(1):21-9.

[56] Wanasuntronwong A, Kaewsrising S, Rotpenpian N, Arayapisit T, Pavasant P, Suprongsinchai W. Efficacy and mechanism of the antinociceptive effects of cannabidiol on acute orofacial nociception induced by Complete Freund's Adjuvant in male *Mus musculus* mice. *Arch Oral Biol.* 2022;144:105570.

[57] Urits I, Gress K, Charipova K, Habib K, Lee D, Lee C, et al. Use of cannabidiol (CBD) for the treatment of chronic pain. *Best Pract Res Clin Anaesthesiol.* 2020;34(3):463-77.

[58] Gulbransen G, Xu W, Arroll B. Cannabidiol prescription in clinical practice: an audit on the first 400 patients in New Zealand. *BJGP Open.* 2020;4(1).

[59] Verrico CD, Wesson S, Konduri V, Hofferek CJ, Vazquez-Perez J, Blair E, et al. A randomized, double-blind, placebo-controlled study of daily cannabidiol for the treatment of canine osteoarthritis pain. *Pain.* 2020;161(9):2191-202.

[60] Guimarães FS, Chiaretti TM, Graeff FG, Zuardi AW. Antianxiety effect of cannabidiol in the elevated plus-maze. *Psychopharmacology (Berl).* 1990;100(4):558-9.

[61] de Mello Schier AR, de Oliveira Ribeiro NP, Coutinho DS, Machado S, Arias-Carrión O, Crippa JA, et al. Antidepressant-like and anxiolytic-like effects of cannabidiol: a chemical compound of *Cannabis sativa*. *CNS Neurol Disord Drug Targets.* 2014;13(6):953-60.

[62] Resstel LB, Tavares RF, Lisboa SF, Joca SR, Corrêa FM, Guimarães FS. 5-HT1A receptors are involved in the cannabidiol-induced attenuation of behavioural and cardiovascular responses to acute restraint stress in rats. *Br J Pharmacol.* 2009;156(1):181-8.

[63] Zanelati TV, Biojone C, Moreira FA, Guimarães FS, Joca SR. Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT1A receptors. *Br J Pharmacol.* 2010;159(1):122-8.

[64] Bergamaschi MM, Queiroz RH, Chagas MH, de Oliveira DC, De Martinis BS, Kapczinski F, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. *Neuropsychopharmacology.* 2011;36(6):1219-26.

[65] Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmons S, et al. Initial experiences with medicinal extracts of cannabis for chronic pain: Results from 34 'N of 1' studies. *Anaesthesia.* 2004;59(5):440-52.

[66] Shannon S, Lewis N, Lee H, Hughes S. Cannabidiol in Anxiety and Sleep: A Large Case Series. *Perm J.* 2019;23:18-041.

- [67] Kogan NM, Melamed E, Wasserman E, Raphael B, Breuer A, Stok KS, et al. Cannabidiol, a Major Non-Psychotropic Cannabis Constituent Enhances Fracture Healing and Stimulates Lysyl Hydroxylase Activity in Osteoblasts. *J Bone Miner Res*. 2015;30(10):1905-13.
- [68] Lucas P, Baron EP, Jikomes N. Medical cannabis patterns of use and substitution for opioids & other pharmaceutical drugs, alcohol, tobacco, and illicit substances; results from a cross-sectional survey of authorized patients. *Harm Reduct J*. 2019;16(1):9.
- [69] Kathmann M, Flau K, Redmer A, Tränkle C, Schlicker E. Cannabidiol is an allosteric modulator at mu- and delta-opioid receptors. *Naunyn Schmiedebergs Arch Pharmacol*. 2006;372(5):354-61.
- [70] Capano A, Weaver R, Burkman E. Evaluation of the effects of CBD hemp extract on opioid use and quality of life indicators in chronic pain patients: a prospective cohort study. *Postgrad Med*. 2020;132(1):56-61.
- [71] Loggia ML, Chonde DB, Akeju O, Arabasz G, Catana C, Edwards RR, et al. Evidence for brain glial activation in chronic pain patients. *Brain*. 2015;138(Pt 3):604-15.
- [72] Hendricks O, Andersen TE, Christiansen AA, Primdahl J, Hauge EM, Ellingsen T, et al. Efficacy and safety of cannabidiol followed by an open label add-on of tetrahydrocannabinol for the treatment of chronic pain in patients with rheumatoid arthritis or ankylosing spondylitis: protocol for a multicentre, randomised, placebo-controlled study. *BMJ open* [Internet]. 2019 2019/06//; 9(6):[e028197 p.]. Available from: <http://europepmc.org/abstract/MED/31167870>.
- [73] Millar SA, Stone NL, Bellman ZD, Yates AS, England TJ, O'Sullivan SE. A systematic review of cannabidiol dosing in clinical populations. *Br J Clin Pharmacol*. 2019;85(9):1888-900.
- [74] Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain*. 2007;133(1-3):210-20.
- [75] Solowij N, Broyd S, Greenwood L-m, van Hell H, Martellozzo D, Rueb K, et al. A randomised controlled trial of vaporised Δ^9 -tetrahydrocannabinol and cannabidiol alone and in combination in frequent and infrequent cannabis users: acute intoxication effects. *European Archives of Psychiatry and Clinical Neuroscience*. 2019;269(1):17-35.
- [76] Freeman TP, Hindocha C, Baio G, Shaban NDC, Thomas EM, Astbury D, et al. Cannabidiol for the treatment of cannabis use disorder: a phase 2a, double-blind, placebo-controlled, randomised, adaptive Bayesian trial. *Lancet Psychiatry*. 2020;7(10):865-74.
- [77] Mongeau-Pérusse V, Brissette S, Bruneau J, Conrod P, Dubreucq S, Gazil G, et al. Cannabidiol as a treatment for craving and relapse in individuals with cocaine use disorder: a randomized placebo-controlled trial. *Addiction*. 2021;116(9):2431-42.
- [78] Mozaffari K, Willette S, Lucker BF, Kovar SE, Holguin FO, Guzman I. The Effects of Food on Cannabidiol Bioaccessibility. *Molecules*. 2021;26(12).
- [79] Silmore LH, Willmer AR, Capparelli EV, Rosania GR. Food effects on the formulation, dosing, and administration of cannabidiol (CBD) in humans: A systematic review of clinical studies. *Pharmacotherapy*. 2021;41(4):405-20.

1
2
3 728 [80] Delgado DA, Lambert BS, Boutris N, McCulloch PC, Robbins AB, Moreno MR, et al.
4 729 Validation of Digital Visual Analog Scale Pain Scoring With a Traditional Paper-based Visual
5 730 Analog Scale in Adults. *JAAOS Global Research & Reviews*. 2018;2(3):e088.
6
7 731 [81] Shedden-Mora MC, Alberts J, Petrie KJ, Laferton JAC, von Blanckenburg P,
8 732 Kohlmann S, et al. The Treatment Expectation Questionnaire (TEX-Q): Validation of a
9 733 generic multidimensional scale measuring patients' treatment expectations. *PLoS One*.
10 734 2023;18(1):e0280472.
11
12 735 [82] Benedetti F, Carlino E, Piedimonte A. Increasing uncertainty in CNS clinical trials:
13 736 the role of placebo, nocebo, and Hawthorne effects. *Lancet Neurol*. 2016;15(7):736-47.
14 737 [83] Spinella TC, Stewart SH, Naugler J, Yakovenko I, Barrett SP. Evaluating cannabidiol
15 738 (CBD) expectancy effects on acute stress and anxiety in healthy adults: a randomized
16 739 crossover study. *Psychopharmacology (Berl)*. 2021;238(7):1965-77.
17
18 740 [84] Jumbo SU, MacDermid JC, Kalu ME, Packham TL, Athwal GS, Faber KJ.
19 741 Measurement Properties of the Brief Pain Inventory-Short Form (BPI-SF) and Revised
20 742 Short McGill Pain Questionnaire Version-2 (SF-MPQ-2) in Pain-related Musculoskeletal
21 743 Conditions: A Systematic Review. *Clin J Pain*. 2021;37(6):454-74.
22
23 744 [85] Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and
24 745 validation. *Psychological Assessment*. 1995;7:524-32.
25 746 [86] Daoust R, Paquet J, Williamson D, Perry JJ, Iseppon M, Castonguay V, et al.
26 747 Accuracy of a self-report prescription opioid use diary for patients discharge from the
27 748 emergency department with acute pain: a multicentre prospective cohort study. *BMJ*
28 749 *Open*. 2022;12(10):e062984.
29
30 750 [87] Li D, Mielke MM. An Update on Blood-Based Markers of Alzheimer's Disease Using
31 751 the SiMoA Platform. *Neurol Ther*. 2019;8(Suppl 2):73-82.
32
33 752 [88] King NS, Crawford S, Wenden FJ, Moss NE, Wade DT. The Rivermead Post
34 753 Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced
35 754 after head injury and its reliability. *J Neurol*. 1995;242(9):587-92.
36 755 [89] Swiontkowski MF, Engelberg R, Martin DP, Agel J. Short musculoskeletal function
37 756 assessment questionnaire: validity, reliability, and responsiveness. *J Bone Joint Surg Am*.
38 757 1999;81(9):1245-60.
39
40 758 [90] Garratt AM, Ruta DA, Abdalla MI, Buckingham JK, Russell IT. The SF36 health
41 759 survey questionnaire: an outcome measure suitable for routine use within the NHS? *Bmj*.
42 760 1993;306(6890):1440-4.
43
44 761 [91] Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep
45 762 Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*.
46 763 1989;28(2):193-213.
47 764 [92] Beck AT, Steer RA, Brown G. Beck depression inventory : manual. . Psychological
48 765 Corporation: San Antonio, TX. 1996.
49
50 766 [93] Ashbaugh AR, Houle-Johnson S, Herbert C, El-Hage W, Brunet A. Psychometric
51 767 Validation of the English and French Versions of the Posttraumatic Stress Disorder
52 768 Checklist for DSM-5 (PCL-5). *PLoS One*. 2016;11(10):e0161645.
53 769 [94] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic
54 770 data capture (REDCap)—A metadata-driven methodology and workflow process for

771 providing translational research informatics support. Journal of Biomedical Informatics.
772 2009;42(2):377-81.
773 [95] Jodoin M, Herrero Babiloni A, Provost C, Blais H, Bellemare A, Desjardins M, et al.
774 10-Day Theta Burst Stimulation Intervention Facilitates the Clinical Rehabilitation of
775 Patients After an Isolated Limb Fracture: A Longitudinal SHAM-Controlled Pilot Study.
776 American Journal of Physical Medicine & Rehabilitation. 2024;103(11):e152-e61.
777

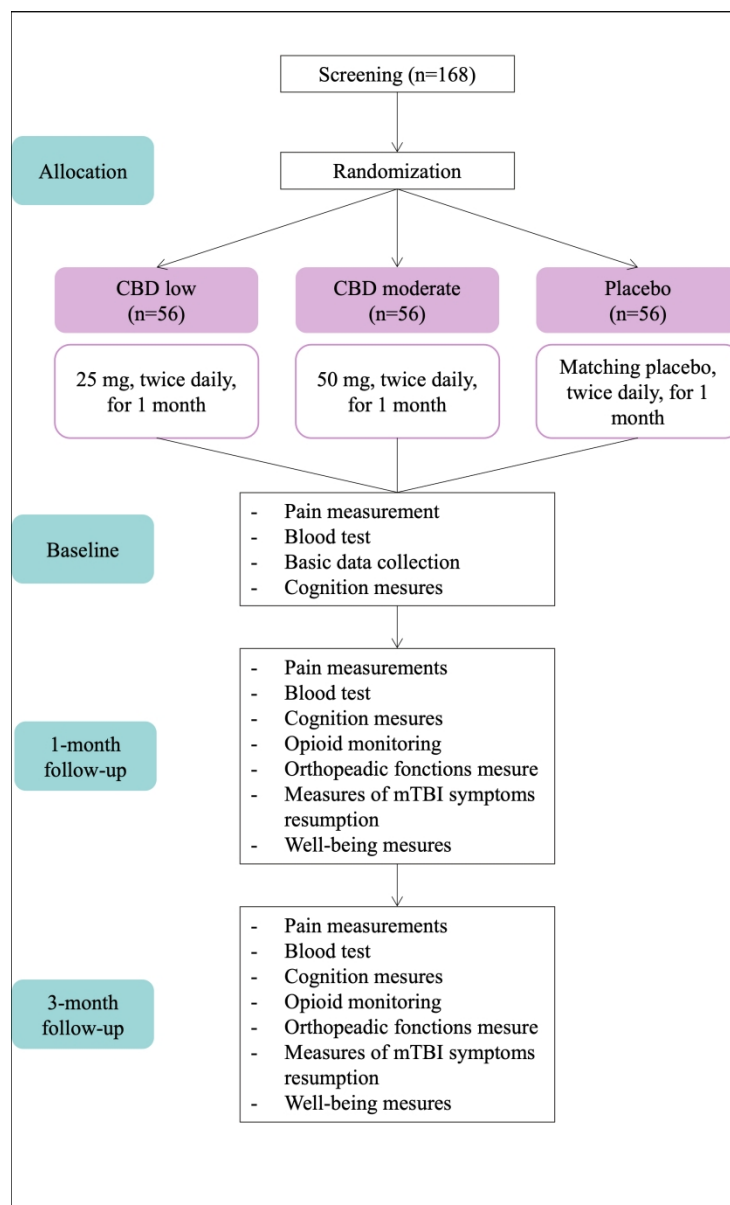


Figure 1 - Study schema

171x281mm (330 x 330 DPI)