Cover page

Official Title of Study: Impact of Cannabis on Pain and Inflammation Among Patients with Rheumatoid or Psoriatic Arthritis

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RESEARCH PROTOCOL

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Project Title: **Impact of Acute Cannabis Administration on Pain Symptomology and Inflammatory Markers among Patients with Rheumatoid or Psoriatic Arthritis**

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Authority: **This study has been approved by the Brown University Institutional Review Board**

A. RATIONALE AND OVERVIEW

Approximately 25 million adults in the United States report experiencing daily chronic pain [1]. The majority of these patients use pharmacotherapies, including opioids, to alleviate negative physiological and psychological symptoms associated with pain. However, while analgesic pharmacotherapy has efficacy in pain treatment, some classes of medications (e.g., opioids) have significant abuse liability. Moreover, patients frequently report ongoing experience of chronic pain symptoms despite these treatments. For some conditions, patients have sought alternative therapies, including cannabis, to alleviate negative symptoms. Between 45% and 80% of those who use cannabis for medicinal purposes do so for pain management [2,3]. Self-report surveys on use of cannabis for medical purposes suggest that it improves pain, sleep, and negative mood, with modest side effects [4,5]. Indeed, randomized controlled trials (RCTs) indicate that cannabis may be an effective pharmacotherapy for certain chronic pain diagnoses, including multiple sclerosis [6,7], neuropathic pain [8], and cancer-related pain [9]. However, there is a dearth of well-controlled research on use of cannabis to treat symptoms associated with inflammatory conditions such as rheumatoid arthritis (RA) or Psoriatic Arthritis (PA). RA is a chronic inflammatory disease that affects approximately 1.3 million Americans, which is increasing as the US population ages [10]. RA is characterized by joint destruction, stiffness, swelling and pain, leading to loss of function [11]. In addition, key cytokines, or pro-inflammatory secreted proteins, are involved in joint injury associated with RA [12]; specifically, TNF-α and IL-1. Pre-clinical studies indicate that cannabinoids demonstrate promising anti-arthritic properties in both human cells from RA patients and animal models of RA [13]. Preclinical research has shown that cannabinoids are strong anti-inflammatory ligands and function via induction of apoptosis, inhibition of cell proliferation, and suppression of cytokine production [14]. Only one clinical study has investigated the effect of a cannabis plant derivative comprised of an equal ratio of two cannabinoids (i.e., Δ^9-tetrahydrocannabinol [THC] and cannabidiol [CBD]), in oromucosal form, on pain related to RA, and reported promising results [15]. Therefore, more research in this area is critical. Whole plant cannabis may be more effective than synthetic and partial formulations to treat chronic pain conditions, purportedly due to its composition of hundreds of distinct cannabinoids that work in synergy to alleviate symptoms [16]. In addition to THC, which has been shown to reduce several types of chronic pain, CBD may be particularly effective in reducing negative symptomology in RA patients due to its anti-inflammatory properties [13,17].

B.1. SPECIFIC AIMS

This proposal will investigate the impact of whole plant cannabis on pain, affect, and inflammation among RA patients (n = 66). We will administer two cannabis formulations via vaporization (placebo and medium THC [3.6%]/medium CBD [5.4%]) across two experimental sessions using a counter-balanced, double-blind, crossover design. THC doses in the medium potency range will be tested in combination with CBD in the

medium potency range. With respect to inflammation outcomes, prior studies have demonstrated efficacy of cannabis with a 1:1 ratio of THC:CBD. Therefore, we hypothesize that cannabis in the medium THC potency range in combination with medium potency CBD will decrease inflammatory biomarkers relative to placebo.

Aim 1. To determine whether cannabis acutely reduces pain and negative affect as compared to placebo.

a. We hypothesize that, relative to placebo, cannabis (medium THC/medium CBD will decrease subjective reports of pain.
b. We hypothesize that, relative to placebo, cannabis (medium THC/medium CBD) will decrease subjective reports of negative affect.
c. We hypothesize that blood THC and CBD levels will be negatively correlated with subjective reports of pain and negative affect.

Aim 2. To determine whether cannabis acutely reduces markers of inflammation (IL-1α, IL-1β, IL-6 and TNF-α) as compared to placebo.

a. We hypothesize that, relative to placebo, cannabis (medium THC/medium CBD) will decrease blood markers of inflammation.
b. We hypothesize that inflammation marker levels will be positively correlated with subjective reports of pain and negative affect, and negatively correlated with blood THC and CBD levels.

B.2. SAMPLE DESCRIPTION AND RECRUITMENT

Human subject involvement is necessary to complete this research proposal (n = 66). This proposal will require patients with rheumatoid arthritis (RA) or psoriatic arthritis (PA) to participate in laboratory cannabis administration sessions. Patients will be initially screened by phone or at the clinic, followed by a rigorous medical and diagnostic screening at intake. We describe recruitment procedures, inclusion criteria for participation, rationale for the proposed population, and retention strategies below.

Participants will be recruited from rheumatology clinics in Rhode Island (Brown University Physician outpatient clinic and the Chapman Street Outpatient Clinic of Rhode Island Hospital) and Massachusetts via initial contact by providers involved in the patient's care, flyers, advertisements, mailings, and referral. Potential subjects will be screened via phone, online screener, or at the clinic. Eligible subjects will be scheduled to meet briefly via videocall to provide consent, and then will be scheduled for an initial baseline laboratory visit. Participants may be asked to fill out a HIPAA Authorization Form to facilitate confirmation of RA/PA diagnosis. We will include subjects with a range of baseline pain levels to capitalize on variability, and baseline VAS pain score will be used as a covariate in all analyses. Participants will be enrolled in the study using the following inclusion criteria:

Inclusion Criteria:

a) current RA or PA diagnosis with active arthritis not adequately controlled by standard medication (i.e., self-report pain levels at or above 30/100 on a visual analog scale (VAS) pre-study enrollment)
b) if taking prescribed steroid, non-steroidal anti-inflammatory (NSAID), and/or disease-modifying anti-rheumatic drugs (DMARDS; e.g., tumor necrosis factor inhibitors), must be stable use for at least 1 month prior to enrollment (all must be maintained throughout the study)
c) English-speaking or Spanish-speaking
d) negative urine toxicology screen for cannabis and other drugs (opiates with prescription allowed; may not be used the morning of the study)
e) negative pregnancy test
f) not nursing
g) use of highly effective birth control during the study for both males and females
h) prior history of vaping or smoking cannabis with similar to that being used in the current investigation (i.e. cannabis use via smoking or vaping at least once in lifetime)

Exclusion Criteria:

i) greater than zero breath alcohol concentration
j) presence of a DSM-5 diagnosis of psychosis or panic disorder as assessed by the Mini International Neuropsychiatric Interview (MINI) and not suicidal [past month ideation or intent]
k) self-report of serious adverse reaction to cannabis in the past year
l) smoking more than 20 tobacco cigarettes per day
m) body mass index below 18.0 or above 33.0 kg/m^2 range confirmed during medical exam (as extreme BMIs can influence drug blood levels and BMIs in the obese range are considered cardiovascular risk factors)
n) all current asthma conditions (i.e., active symptomatic asthma within the last week) or current or past history of asthma triggered by smoking or vaping
o) current diagnosis of dementia or Parkinson's disease
p) scores below 23 on the Folstein Mini-Mental Status Exam
q) current diagnosis of moderate to severe traumatic brain injury
r) current diagnosis of epilepsy
s) individuals who are immunocompromised (i.e., post-organ transplant, those with an immune deficiency disorder such as HIV, individuals taking immunosuppressant steroids such as continuous prednisone use, and those with lupus)
t) past kidney disease (e.g., glomerular nephritis, polycystic kidney disease) and/or presence of elevated creatinine (levels above 2.0)
u) cardiac disease confirmed via clinically significant abnormal findings on an EKG (e.g., arrhythmia, conduction abnormalities, ischemia, or evidence of past myocardial infarction), as well as diagnoses of congestive heart failure or cardiomyopathy
v) abnormal vital signs (heart rate will be required to be below 50 or above 110 BPM; blood pressure above 160/100 or below 90/60; blood oxygen levels below 90%)
w) taking any medications on our List of Exclusionary Medications
x) presence of any severe cardiovascular, renal, or hepatic disorder
y) below 18 or above 65 years of age
z) use of cannabis in the past 1 month before commencement of study participation and throughout the study as confirmed via urine toxicology screening
aa) below minimum self-reported pain level of 30/100 on a visual analog scale (VAS) pre-study enrollment via telephone and at baseline due to potential variability in pain level

B.3. RECRUITMENT METHODS

We plan to recruit RA patients primarily from the Brown University Physician outpatient clinic and the Chapman Street Outpatient Clinic of Rhode Island Hospital. Approximately 9,000 patients with various rheumatic conditions and approximately >3,000 with rheumatoid arthritis visit these clinics annually. With the facilitation of our collaborators (please see letter of support), participants will be recruited via initial contact by providers involved in the patient's care, flyers, advertisements, mailings, and referral. Potential subjects will be screened via phone.

Primarily, we will receive referrals from our collaborators at the Brown University Physician outpatient clinic. In addition, we will use internet advertisements on social media sites and flyers at local treatment clinics. The study PI and research assistant (both having completed all required CITI certifications) will be contacted by our collaborators in the instance of referrals, and by other interested patients with rheumatic disease (rheumatoid and psoriatic arthritis). Potential participants will be screened in person at the clinic, or via telephone or online screener. Potential participants will primarily be referred by our collaborators. Patients that meet eligibility criteria, are not well-controlled on current medications, and are deemed to potentially benefit from incorporating cannabis into their treatment regimen will be enrolled in the study.

While use of cannabis to treat chronic pain associated with various conditions (e.g., inflammatory rheumatic diseases) is approved in Rhode Island and many other states, there is limited research in this area and it is not

the standard of care for such diseases. Of note, the cannabis that will be administered in the current investigation will be an adjunct to current approved treatment regimen.

At baseline session conclusion, eligible participants will be scheduled for two 5-hour experimental CB administration sessions and randomized to either placebo or medium THC/medium CBD dose for Experimental Session 1 and will receive the other dose at the following session (Experimental Session 2). The study PI will randomize participants to the dose conditions but will not run experimental sessions. In order to maintain double-blind conditions, CB will be prepared by a pre-designated staff member with DEA clearance. Participants and other study staff working directly with participants will be blind to dose. To control for expectancy effects[18,19], participants will be told they will vaporize CB varying in THC in the low to moderate potency range. CB appearance is identical across dose.

Compensation/Reimbursement: Participants will be compensated $50 for the baseline session, $100 for each of two cannabis administration sessions, and will receive an additional $50 bonus for completion of all experimental sessions for a maximum total of $300. Ineligible subjects will be paid $10 and excluded from participation. Due to experimental sessions involving cannabis administration, participants will be transported home following each experimental session via taxi, Uber, or other rideshare service.

B.4. METHODOLOGY

Synopsis. This study will be the first to investigate the effect of vaporized CB on pain, affect, and markers of inflammation among patients with RA. This research will be conducted over two Aims. Aim 1: To determine whether CB acutely reduces RA-associated pain and negative affect as compared to placebo. Aim 2: To determine whether CB acutely reduces markers of inflammation (IL-1α, IL-1β, IL-6 and TNF-α) as compared to placebo. Using a randomized, placebo-controlled, crossover design, participants (n = 66) will vaporize CB (placebo and medium THC/medium CBD) over two experimental sessions. Blood will be collected during each session (pre-vaporization, 10 min post-vaporization, 60 min post vaporization). Self-reported pain and affect will be assessed at the same time points.

Baseline Session: Following online/phone screening, potential subjects will meet remotely with research staff for a videocall to complete the study consent forms and discuss any questions. Participants will then attend an in-person baseline screening session at the laboratory to confirm eligibility and complete a physical exam. They will be asked to refrain from alcohol for 24 hours and caffeine for 2 hours prior to experimental sessions. Subjects will complete an alcohol breathanalysis for breath alcohol concentration (BrAC), and urine drug screen and pregnancy test (females). Subjects with a positive BrAC will be rescheduled. Tobacco smokers will be permitted to smoke a cigarette following the CO test to prevent nicotine withdrawal. Subjects will be administered a medical screening questionnaire to rule out history of adverse reaction to CB, and the MINI to make diagnostic exclusions of suicidality and key DSM-5 diagnoses (psychosis, panic disorder).

Eligible subjects will complete baseline measures and a physical exam conducted by physician or nurse practitioner to determine medical clearance prior to the CB administration sessions. The physical exam will include assessment of heart rate, blood pressure, and blood oxygen levels. Vital signs will be assessed again at the beginning of each experimental session. During the physical exam, a medical history will be obtained, blood will be drawn, and an EKG will be performed. To assess severe renal disease, the nurse practitioner will ask about any past kidney disease (e.g., glomerular nephritis, polycystic kidney disease), and blood will be tested for presence of elevated creatinine. The physical exam will also include physical function testing pertaining to RA/PA: self-selected gait speed, 5-chair rise test, single leg stance test[20,21].

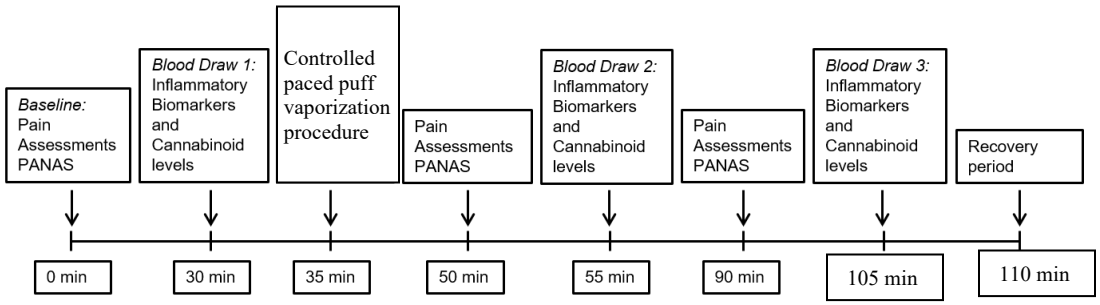
To confirm that participants are not currently experiencing cognitive impairment at the commencement of study participation, they will complete the Folstein Mini-Mental Status Exam (MMSE; Folstein et al., 1975) which includes 30 items to assess cognitive impairment on a scale from 30 (no impairment) to 0.

Psychoactive and pain-relieving effects of CB are acute, thus experimental sessions will be separated by at least

two days. No subjective or behavioral effects will last past CB administration in the laboratory. Urine screens may test positive for CB at session 2 (if active dose was administered at session 1), however, we confirm no recent smoking via CO test, thus urine screens that are positive for THC are irrelevant.

Experimental CB Administration Sessions (1-2): Information including medications and pain level will be reconfirmed the morning of experimental sessions to maintain study eligibility. At each experimental session, BrAC and carbon monoxide (CO) level will be tested to confirm no recent alcohol or CB use. CO level must be 8ppm or below in order to proceed with the session; levels that are higher than 8ppm may be given some time to decrease to 8ppm (i.e. we will re-test) at the PI's discretion. Cigarette smokers will be given an opportunity for a smoking break after the test if they would like. Subjects will complete urine toxicology screening to confirm no other drug use. Females will be tested for pregnancy at each session. Vital signs will be obtained. Subjects will consume a calorie-controlled breakfast and complete pre-administration measures and questionnaires, an automatically inflating blood pressure (BP) cuff will be secured to continuously record heart rate and BP during the entire experimental session, and blood collection procedures will be implemented (see Figure 1). Participants will complete physical function testing[20,21]. Participants will then vaporize the assigned CB dose and complete post-administration subjective measures of pain, affect, and drug effects. CB vaporization procedures will begin at 11am in order to reduce variability in pain that may occur throughout the day. Subjects will vaporize CB using a Storz & Bickel MIGHTY Vaporizer apparatus. Approximately 250mg CB will be ground to maximize surface area and will be placed in the vaporizer. The vaporizer will be prepared exclusively by study staff or the PI. Using the step-by-step quick-start guide and manual, study staff will prepare the vaporizer and will give it to the participant. The vaporizer device will be used on a dry surface away from paper and other flammable substances. A cued-puff procedure[22] will standardize CB administration. Participants will listen to an audio-recording that will signal them to "get ready" (5 seconds), "inhale" (5 seconds), "hold vapor in lungs" (10 seconds), "exhale," and to wait before repeating the inhalation cycle (40 seconds). A research assistant and the study nurse will continuously monitor the subject during the vaporization session via two-way mirror. In our previous studies which employed the paced-puffing procedure for combustible CB cigarettes with similar THC levels, all participants were able to complete an entire cigarette in 9 puffs in 8 mins on average[18,19]. All participants will be required to complete 9 inhalations according to standardized procedures. Following cannabis administration (peak effects at 20-min post vaporization), participants will complete assessments including pain and affect. Peak THC/CBD levels will be assessed. Pain and affect will continue to be assessed three times over the recovery period at 1-hour intervals.

Figure 1. Schedule of Activities for Experimental Sessions.



Blood Sampling Procedures: We will collect blood at 3 time-points during each experimental session for analysis of inflammatory biomarkers (i.e., IL-1α, IL-1β, IL-6, IL-10, IL-17A, TNF-α, INFɣ, MCP1, BDNF; sCD14); whole blood for future genetic analysis, if the participant consents to that portion; cannabinoid plasma levels (i.e., THC and CBD) pre-CB administration, at the termination of the CB administration procedure (10 mins post-completion of CB administration), and 60 mins post-completion of CB administration. These time-points were selected to characterize the impact of acute CB administration on pain and affect immediately following administration and at a delayed time-point (60-minutes post completion) to assess the duration of analgesia. Individual blood draws will be conducted in an antecubital vein at each pre-designated time point (see Figure 1). Blood samples will be collected in heparinized tubes (0.15 µl heparin) and placed on ice immediately after each blood draw. Within 15 minutes of collection, blood will be centrifuged and plasma will

be transferred to a microtube and stored at -30ºC. Plasma will be analyzed for inflammatory biomarkers and cannabinoid levels using gas chromatography/mass spectrometry (GC-MS) techniques.

Blood samples taken at the baseline/physical exam will be analyzed: i.e. IL-1α, IL-1β, IL-6, IL-10, IL-17A, TNF-α, INFɣ, MCP1, BDNF; sCD14; CRP; cannabinoid plasma levels (i.e., THC and CBD); creatinine, AST, ALT; whole blood for future genetic analysis (if the participant consents to that portion, as it is optional)

Blood samples taken at the experimental sessions will be analyzed: i.e. THC, CBD, IL-1α, IL-1β, IL-6 and TNF-α, sCD14, CRP

Sobriety Assessment: Subjects will remain in the laboratory for 3-hours following CB vaporization (psychotropic effects taper off within 2-3 hours[24]), during which time snacks and water will be provided. Vital signs will be monitored and resumption of normal vital signs will be required for discharge. Subjects will then be evaluated for motor signs of intoxication. To ensure there are no residual cannabis effects 3 hours post-vaporization, participants will complete and pass a field sobriety test (i.e., heel-to-toe walking test, single leg raise balance test)[25]. Following successful completion of the field sobriety test, subjects will be transported home via train, taxi, rideshare, or with a responsible adult to avoid driving following CB use. In the event of a failed test, participants will remain in the laboratory 20 more minutes until repeat testing is completed and passed.

Discharge Criteria: Participants will be permitted to leave the laboratory three hours following vaporization and only following a 75% reduction in their peak heart rate level during the experimental session. Blood pressure will be required to return to baseline ranges (below 160/100 and above 90/60). To ensure there are no residual cannabis effects 3 hours post vaporization, participants will complete and pass a field sobriety test (i.e., heel-to-toe walking test, single leg raise balance test). In the event of a failed test, participants will remain in the laboratory 20 more minutes until repeat testing is completed and passed.

Drug: Bulk CB (placebo, 3.6% THC/5.4% CBD) will be provided by the NIDA Drug Supply Program. Placebo CB is identical in appearance to active CB however THC and CBD have been extracted. Non-psychoactive plant material remains. Bulk CB will be stored in a freezer until the day before use. At least 12 hours before each session, CB will be thawed by staff and humidified in a closed humidifier with a saturated sodium chloride solution at room temperature (for security and storage aspects, see **Security and Regulatory Aspects for Cannabis**). These doses were selected based on previous chronic pain work suggesting that the pain-relieving effects of CB are experienced at lower THC doses. Previous work found that identical levels of analgesia were produced by both 7% and 3.5% THC concentrations[26]. Thus, THC in the 1-5% range was selected to avoid undesirable effects of CB administration (e.g., acute anxiety) that may occur in some subjects, particularly in individuals without recent exposure to CB. Previous research using similar samples suggests that such adverse effects are acceptable to patients with chronic pain[4,27].

Security and Regulatory Aspects for Cannabis: Cannabis is subject to regulatory control under Schedule I of the Controlled Substances Act and the Psychotropic Convention. Cannabis will be provided by the National Institute on Drug Abuse (NIDA) and will be stored frozen in an airtight container in a locked refrigerator safe located in a cement block room without windows and one door that is locked with code-protected card-key access at 121 South Main Street on the 3rd floor. Only DEA designated individuals will have access to this room (located in the same building and floor as the location of cannabis administration). Thus, cannabis will remain secure at all times. Cannabis will be prepared by a pre-designated staff member with DEA clearance. The staff member will retrieve cannabis prior to a scheduled experimental session, humidify it at room temperature for 24 hours before use (per NIDA's instructions) in the same cement block room, and transfer it directly to the laboratory following the start of the session. Cannabis will be logged and monitored by the DEA; remainders will be incinerated as per compliance with the DEA regulations. Dr. Robert Swift, MD, PhD, Professor at CAAS, holds a Drug Enforcement Administration (DEA) license for Schedule I drugs with a specific approval for cannabis.

Statistical Analysis Plan: The sample size required for the proposed study is based on the primary outcome: pain assessment score. Using the results on SF-MPQ pain at present from Blake and colleagues to inform our parameters, we assume that participants will have a reduction in pain of 0.72 points following active cannabis compared to placebo cannabis with a standard deviation of the mean difference of 2.0715. We calculate the necessary sample size using a 2-period, 2-treatment, crossover design, comparing cannabis to placebo. At a two-sided significance level of 0.05, a design encompassing 66 patients will have power equal to 0.79 to detect this difference with this standard deviation.

The primary aim of this investigation is to assess current self-reported pain level (SF-MPQ) following cannabis administration (THC versus placebo). A one-sided t-test will be conducted to compare pain level following vaporization of each dose.

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