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ARTICLE

Cannabinoids and an anti-inflammatory diet for the treatment of neuropathic pain after spinal cord injury (The CATNP Study): study protocol for a randomized controlled trial

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Abstract

Study design Multicenter, randomized, double-blind, placebo controlled, clinical trial.

Objective The objective of this paper is to evaluate the effectiveness of cannabinoids and an anti-inflammatory diet, alone and in combination, for the management of neuropathic pain (NP) after spinal cord injury (SCI).

Setting Two Canadian SCI rehabilitation centers.

Methods A sample of 144 individuals with SCI will receive either an anti-inflammatory diet, cannabinoids or a placebo for 6 weeks. Following this, a combined effect of these treatments will be evaluated for a further 6 weeks. The primary outcome measure will be the change in NP as assessed by the numeric rating scale (NRS). Secondary outcomes will include changes in inflammation, mood, sleep, spasticity, cost-effectiveness, and function.

Conclusion This study will assess the efficacy of an anti-inflammatory diet and cannabinoids (individually and in combination) for the treatment of NP following SCI. Results may reveal a cost-effective, side-effect free intervention strategy which could be utilized for the long-term management of NP following SCI.

Introduction

Background and rationale

Neuropathic pain (NP) is a common and highly debilitating complication following spinal cord injury (SCI) that significantly decreases quality of life. Unfortunately, current treatment options such as antidepressants, gabapentin, and NMDA receptor antagonists have proven only moderately effective [1–3] and are further limited by adverse-effect profiles [3]. Those with SCI have identified a need for additional treatment options, particularly those that are not medications [4]. As such, it is critical to explore alternative treatment strategies that are better tolerated [5–7] and can be implemented long term.

The recent legalization of cannabis in Canada has led to greater access and an increased use of cannabinoids for the treatment of NP following SCI [8]. Although cannabinoids have shown promise in the management of central NP after multiple sclerosis (MS) [9, 10] and have been trialed for a variety of complications following SCI [11], direct evidence related to the effective management of NP in SCI is limited. Accordingly, the CanPainSCI Clinical Practice Guidelines concluded that the evidence is insufficient to develop a

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specific recommendation regarding cannabinoids in the treatment of NP after SCI [12]. In addition, relevant side effects for those with SCI have not been well documented. Studies which evaluate the effectiveness and side effects of cannabinoids in the SCI population are urgently needed.

Anti-inflammatory diets represent a second promising alternative treatment for NP following SCI. A recent RCT compared a 12-week anti-inflammatory dietary intervention to a non-dieting control condition in individuals with SCI and demonstrated that the diet was sufficient to significantly reduce chronic inflammation after only 4 weeks, which, in turn, reduced symptoms of NP [13]. This study reported no adverse events (AE) and a high degree of participant compliance to the diet. These findings are encouraging and may suggest that dietary alterations could represent a safe and sustainable option for the management of neuropathic pain symptoms. This study was, however, performed in a relatively small sample of individuals with SCI, using a combined food and supplement approach which may not be feasible for long-term adherence. This study also lacked a placebo control.

Both cannabinoids and anti-inflammatory diets are novel treatment strategies that may prove beneficial for managing NP following SCI while also being better tolerated than traditional medications. The combined use of these two treatments may also provide greater benefit than a singular treatment given the differing modes of action. For example, while cannabinoids may alter neurotransmitter/neuropeptide release and modulate neuron excitability by acting on receptors, ion channels, and enzymes [14], certain dietary nutrients such as omega-3 fatty acids may alter substrate availability thereby influencing the production of products capable of influencing nociceptor sensitivity [15]. It will be critical to assess the efficacy and safety of these intervention strategies while using a larger sample and accounting for potential placebo effects. Novel evidence supporting the use of cannabinoids and/or further evidence in support of the use of anti-inflammatory diets will be important to justify the widespread adoption of such interventions for NP after SCI. This protocol follows the Standard Protocol Items: Recommendations for Interventional Trials checklist (see Supplementary Information).

Objectives/hypothesis

The overall purpose of this study is to evaluate the effectiveness of cannabinoids and an anti-inflammatory diet, alone and in combination, for the management of NP after SCI. Thus, treatments will first be compared to each other and to placebo, and then due to the potential additive and/or synergistic effect of these treatments (particularly given the anti-inflammatory properties of cannabinoids and an anti-inflammatory diet), combination treatment will also be evaluated. Specifically, the primary objective is to evaluate the effectiveness of cannabinoids and an anti-inflammatory diet both alone and in combination for the treatment of NP after SCI. A secondary objective is to assess the change in inflammation, mood, sleep, spasticity, cost-effectiveness, and function.

It is hypothesized that both the anti-inflammatory diet and cannabinoids will individually improve symptoms of NP. It is also hypothesized that the combined effect of cannabinoids and an anti-inflammatory diet will produce the greatest improvement in outcomes.

Methods

Study design

This is a 12-week, multicenter, randomized, double-blind placebo-controlled study evaluating the effect of an anti-inflammatory diet ± cannabinoids (tetrahydrocannabinol/cannabidiol (THC/CBD) and cannabidiol (CBD) only) on NP in adult participants (see Fig. 1 for study timeline). Following a 2-week titration period, participants ($n = 144$) will first be randomized into one of four groups for a 4-week active treatment period: (1) placebo diet + placebo capsules ($n = 36$), (2) placebo diet + THC/CBD capsules ($n = 36$), (3) placebo diet + CBD capsules ($n = 36$), (4) anti-inflammatory diet + placebo capsules ($n = 36$). Following this period participants will then be randomized into three groups to assess the combined influence of the anti-inflammatory diet and cannabinoids: (1) placebo diet + placebo capsules ($n = 36$), (2) anti-inflammatory diet + THC/CBD capsules ($n = 54$), (3) anti-inflammatory diet + CBD capsules ($n = 54$). Data will be obtained through in-person study visits.

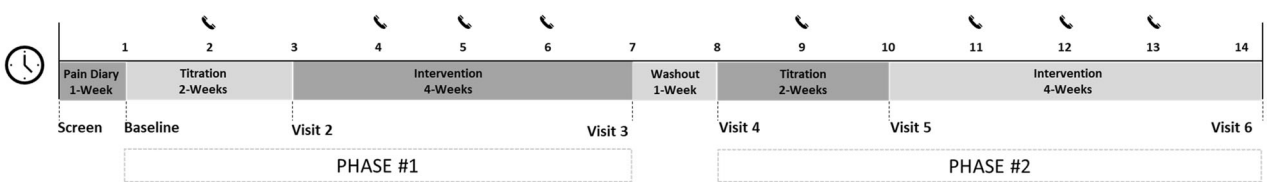

Fig. 1 Timeline. Study timeline of phase 1 and phase 2. Telephone icons represent participant contact via telephone for weeks when in person visits are not scheduled.

Participants

Recruitment/consent procedure

Two sites will participate in the study. If recruitment appears to be challenging within year 1, additional sites may be added starting in year 2. As in any study, retention of participants will be a key issue. Participants will be recruited from the practices of four SCI physiatrists at Parkwood Institute, and from members attending the Power Cord exercise center at the Brock-Niagara Centre for Health and Well-being. Given that the total number of individuals with SCI that attended the Power Cord exercise center and the Parkwood SCI Outpatient Department in 2019 was 30 and 425, respectively, and the estimated prevalence of NP after SCI is over 50%, it is expected that it will be feasible to recruit the desired 144 participants for the study. Participants will be prescreened for NP and then approached by a member of their circle of care so that they may provide permission for a study team member to approach them about the study. In order to enhance participant retention, the study team will contact participants via telephone on all weeks during which in-person visits are not scheduled (weeks 2, 4–6, 9, 11–13) for follow-up on study medication titration, diet compliance, and possible side effects. The participants will also be contacted prior to their next study visit in order to ensure they are prepared for their visit.

Inclusion/exclusion criteria

To be an eligible participant, all inclusion criteria must be answered "yes". This includes: (1) signed informed consent obtained prior to any study-related activities, (2) BMI 18–40, (3) an SCI for at least 12-month duration, non-progressive for at least 6 months, (4) At- and/or below-level NP > 3/10 in severity on the numeric rating scale (NRS) (below-level NP will be defined as pain > 1 dermatomal level below the neurologic level of injury). Participants will need an average > 3/10 pain over the past 7 days on screening, and to complete a daily diary for the week prior to randomization in the morning with an average pain severity of >3/10 on at least four diary entries, (5) ongoing constant pain for at least 3 months, or relapsing/remitting pain for at least 6 months, (6) dosing of other pain medications (NSAIDs, opioids, non-opioid analgesics, antiepileptic drugs, antidepressants) should be stable for at least 1 month prior to study entry, and (7) any cannabinoids, or cannabinoid medications (e.g., nabilone) will need to be stopped at least 1 month prior to screening for and inclusion in the study.

In addition, to be an eligible participant, all exclusion criteria must be answered "no". This includes: (1) history of psychotic disorder, (2) history of convulsive disorders, (3) history of substance abuse, (4) experienced myocardial infarction or clinically significant cardiac dysfunction within the last 12 months, (5) significantly impaired hepatic function (alanine aminotransferase (ALT) > 5 × upper limit of normal (ULN) or total bilirubin (TBL) > 2 × ULN) or the ALT or aspartate aminotransferase > 3 × ULN and TBL > 2 × ULN (or international normalized ratio > 1.5), (6) female patients of child bearing potential and male patients whose partner is of child bearing potential, unless willing to ensure that they or their partner use effective contraception, during the study and for 3 months thereafter, (7) female patient who is pregnant, lactating, or planning pregnancy during the course of the study and for 3 months thereafter, (8) current suicidal ideation, (9) intolerance to cannabinoids, (10) unwilling or unable to adopt a specified diet for a period of 12 weeks, (11) traumatic SCI superimposed on prior congenital stenosis, (12) those unwilling or unable to stop PRN medications for pain during the study, (13) presence of other neurologic conditions, medical conditions, or pain that could confound the assessment of NP after SCI, (14) any other significant disease or disorder which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, may influence the result of the study, or affect the patient's ability to participate in the study, (15) following a physical examination, the patient has any abnormalities that in the opinion of the investigator would prevent the patient from safe participation in the study.

Allocation/randomization of participants

The research coordinator will undertake enrollment of participants into the study. The pharmacy will undertake the randomization of participants using a stratification approach based on baseline pain severity from NRS scores and will dispense the appropriate product (cannabinoid or placebo) to the study coordinator. Randomization will be completed via a coded (groups 1, 2, 3, or 4) block randomization scheme (block size: ten participants) to sequentially allocate participants to groups in order of enrollment. A key to the randomization code will be held by an investigator (EL) who was not directly involved with subject recruitment, the intervention, or testing. Participants, as well as investigators who were responsible for recruiting, aiding in the intervention, and/or testing participants, will be blind to the individual group assignments.

Blinding

All packages will use the same label, minus the code to match each study product (cannabinoid or placebo). Which code belongs to the cannabinoid and which belongs to placebo will only be known to the pharmacy. With respect

to diet, participants will be given a meal plan and recipes by the study dietitian. Whether the participants are on the anti-inflammatory diet or placebo diet will only be known to the dietitian. Regarding the placebo diet, the dietitian will assist in developing a diet that is isocaloric to the anti-inflammatory diet and healthy (for the sake of the participants' well-being, and to blind participants), while allowing many foods that are (counterintuitively) pro-inflammatory. Occasional "cheat" foods are built into the anti-inflammatory diet; the placebo diet will also incorporate these "cheats" but with more pro-inflammatory options. There are many counter-intuitive restrictions in the anti-inflammatory diet that we will be using. Therefore, even fairly astute and educated participants may have trouble discerning which diet they are consuming (anti-inflammatory or placebo). If a few participants realize which diet they are consuming, the placebo effect will be managed by correlating putative changes in perceived NP with changes in pro and anti-inflammatory blood markers. In the event that a participant becomes unwell the study team will employ procedures that can unblind treatments if required urgently.

Interventions

Cannabinoid and placebo capsules

Cannabinoids will be taken orally in the form of a THC/CBD capsule and a high CBD capsule. The THC/CBD capsule will come in a 1:1 ratio, whereas the high CBD capsule will come in a 1:20 ratio. Cannabinoids will be administered using a 2–3-week titration period followed by a 4-week treatment period. During the titration period, participants in the cannabinoid group will be asked to self-titrate the number of THC/CBD or high CBD capsules taken based on a fixed schedule, to a maximum of 16 capsules/day. The anti-inflammatory and placebo groups will titrate placebo capsules in the same fashion. The study coordinator will instruct participants on the titration schedule and provide enough capsules for a 3-week titration period. At the end of the titration period, participants will inform the study coordinator of any complications during the titration period, and the final number of daily capsules achieved. The number of capsules required to complete the 4-week treatment period, based on the daily capsule requirement at the end of the titration period, will then be provided by the study coordinator. The titration schedule will require participants to take one capsule for the first 2 days, followed by two capsules on the 3rd day. The participant may then increase the dose every 2–3 days, with a maximum daily increase of no more than 50% of the previous dose. During the titration period, if a 50% pain reduction is achieved, the participant will note the dose required to achieve this reduction. The participant will continue on this dose for 2 weeks to ensure durability of the effects before entering the active phase. If the results are not durable at that dose, a higher dose may be trialed to achieve greater pain reduction. If the higher dose is not tolerated, or the maximum dose is achieved without additional improvement, the lowest tolerated dose where maximal benefit is achieved will be used. Once the effects are able to be maintained for 2 weeks, the participant will enter the 4-week active phase. Depending on the amount of capsules being taken daily, the participant may divide the dose and take it 2–3 times daily. Participants will log daily capsules taken during the titration and treatment periods. Capsule counts at the end of the titration and treatment periods will be done to ensure compliance. Any unused capsules following the titration period will be taken back and redistributed for the active phase. Any unused capsules following the end of the study will be sent to the pharmacy for disposal.

Anti-inflammatory and placebo diet

Those on the anti-inflammatory diet will be given a meal plan and recipes to be followed at home after consultation with the study dietitian. In order to ensure participant blinding for the upcoming study, specific examples of foods to be included in the anti-inflammatory and placebo diets are not stated here. In brief, this meal plan will eliminate foods that have been established as pro-inflammatory as well as foods that are commonly associated with even mild intolerances and those that negatively impact cardiovascular health. In their place, the meal plan will consist of foods with established anti-inflammatory properties [13]. Participants will also be given a list of foods that they are allowed on the anti-inflammatory diet, and a list of foods to avoid so that they can make informed substitutions to the meals and ingredients that they are given. They will also be asked to keep a log of their daily food intake so that compliance to the diet can be measured.

When on the placebo diet, participants will also be given a meal plan and recipes by the study dietitian. The dietitian will assist in developing a diet that is isocaloric to the anti-inflammatory diet and healthy (for the sake of the participants' well-being, and to blind participants), while allowing many foods that are (counterintuitively) pro-inflammatory.

Outcomes

Primary outcome measure

Neuropathic pain NP will be assessed via four questionnaires including the NRS [16], the NP Questionnaire (NPQ) [17], the International SCI Pain Basic Dataset

Table 1 Schedule of events.

		Phase No. 1			Phase No. 2			
	Screening	Baseline (week 1)	Visit 2 (week 3)	Visit 3 (week 7)	Visit 4 (week 8)	Visit 5 (week 10)	Visit 6 (week 14)	Telephone visit (weeks 2, 4–6, 9, 11–13)
Procedures								
Informed consent	X							
Medical history	X							
Randomization		X			X			
Administer investigational product		X	X		X	X		
Concurrent meds	X	X	X	X	X	X	X	
Blood samples		X		X	X		X	
IP count			X	X		X	X	
Adverse event evaluation			X	X	X	X	X	X
Study CRFs								
Patient Global Impression of Change (PGIC)				X	X		X	
EQ-5D		X		X	X		X	
iPCQ		X		X	X		X	
Spinal Cord Injury Basic Pain Dataset V 2.0		X		X	X		X	
NPQ		X		X	X		X	
Leeds Sleep Evaluation Questionnaire		X		X	X		X	
POMS		X		X	X		X	
SCI-Spasticity Evaluation Tool (SCI-SET)		X		X	X		X	
Product use questionnaire			X	X	X	X	X	X
Pain Diary	X							
CES-D		X		X	X		X	
Food log		X		X	X		X	
Food expenditure		X		X	X		X	

Schedule of procedures and CRF's to complete throughout study.

(ISCIPBDS) V 2.0 [18], and the Patient Global Impression of Change (PGIC) [19]. All questionnaires will be completed at baseline (prior to beginning product titration), at visit 3 (following the 4-week active intervention period of phase 1), at visit 4 (following the washout period and prior to beginning to the titration schedule of phase 2), and visit 6 (following the 4-week active intervention period of phase 2) (see Table 1 for schedule of events). Assessors who administer questionnaires will follow the same script for each questionnaire to ensure consistency (see Supplementary Information for shell tables).

The primary assessment of NP will be performed via the NRS. The NRS is a simple 11-point scale ranging from 0 to 10, whereby 0 indicates no pain at all, and 10 indicates the worst imaginable pain. The NRS will be performed based on the instruction from McCaffery et al. (1989) [20] whereby participants will be asked to "Please indicate the intensity of current, best, and worst pain levels over the past 24 hours on a scale of 0 (no pain) to 10 (worst pain imaginable)". The average of the three ratings will be used to represent the patient's level of pain over the previous 24 h [21].

The NPQ consists of 32 items pertaining to three unique categories including sensory items, affective items, and sensitivity items. Sensory items are those related to the specific type and severity of pain felt (e.g., degree of burning, stabbing, and throbbing), affective items refer to those related to how the pain affects the participant in daily life (e.g., how irritating is your usual pain?) and sensitivity items relate to how various stimuli may act to increase pain (e.g., increased pain due to heat). Participants will be asked

to rate their pain numerically on a scale from 0 to 100, whereby 0 indicates the complete absence of pain and 100 indicates the worst pain imaginable. Scores for each of the three individual items as well as the average of the three items will be used in the statistical analysis.

The ISCIPBDS asks participants about nociceptive and NP experienced over the previous 7 days. Participants are asked how this pain interfered with day-to-day activities, overall mood, and sleep on a scale from 0 to 10. Participants are also asked how many different pain problems they experienced and to describe the worst, second worst, and third worst pain problems if applicable. The three items related to day-to-day activities, overall mood, and sleep will be used in the current analysis.

The PGIC is a single-item, self-report measure which reflects a patient's belief about the efficacy of treatment. Patients rate their overall improvement in NP on a seven-point scale with ratings of "very much improved", "much improved", "minimally improved", "no change", "minimally worse", "much worse", or "very much worse".

Secondary outcome measures

Similar to the primary outcome measures, all secondary outcomes measures will be completed at baseline (prior to beginning product titration), at visit 3 (following the 4-week active intervention period of phase 1), at visit 4 (following the washout period and prior to beginning to the titration schedule of phase 2), and visit 6 (following the 4-week active intervention period of phase 2).

Inflammation Blood samples (20 ml) will be drawn by a certified phlebotomist. Blood samples will be analyzed for pro-inflammatory markers, including C-reactive protein (CRP), interleukin-2 (IL-2), IL-6, interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and prostaglandin E2. In addition, samples will be analyzed for the anti-inflammatory markers IL-4, IL-10, and IL-1RA.

Mood Mood will be assessed via the Center for Epidemiological Studies Depression Scale (CES-D) [22] and the Profile of Mood States (POMS) questionnaire [23]. The CES-D will be used to assess the presence of depressive symptomatology. The CES-D is a 20-item questionnaire which asks participants to rate how often they have experienced items over the previous 7 days. Ratings are made on a four-point scale (0–3) including "rarely or none of the time" (<1 day), "some or a little of the time" (1–2 days), "occasionally or a moderate amount of the time" (3–4 days), or "most or all of the time" (5–7 days). Scores are summed to create a final score ranging from 0 to 60, whereby higher scores indicate the presence of more symptomatology. A score of 16 points or greater is considered depressed.

The POMS questionnaire will be used to assess current mood. The POMS is a self-administered, 65-item questionnaire, whereby participants are assessed on six separate subscales including: tension, depression, anger, vigor, fatigue, and confusion. Items within each subscale are rated on a five-point Likert scale, whereby 0 indicates "not at all", and 4 indicates "extremely". Items from within each subscale will be totaled to provide a measure of that subitem. Scores will also be totaled to provide an overall measure of affect that is labeled total mood disturbances.

Sleep The Leeds Sleep Evaluation Questionnaire (LSEQ) [24] will be used to assess aspects of sleep and early morning behavior. The LSEQ includes ten self-rated questions related to falling asleep, quality of sleep, waking following sleep, and behavior following wakening. Questions are scored on a 100 mm visual analog scale. Mean scores for each of the four dimensions are calculated.

Spasticity The SCI-Spasticity Evaluation Tool (SCI-SET) [25] will be used to assess the impact of spasticity on daily life. The SCI-SET is a self-reported, 35-item questionnaire that requires participants to recall the previous 7-day period when rating spasticity on a scale from −3 (extremely problematic) to +3 (extremely helpful). A total score is calculated by summing all applicable responses and dividing the sum by the number of applicable items.

Function The five level EuroQol five-dimension scale [26] will be used for measuring generic health status. This questionnaire evaluates generic quality of life with one question for each of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five response levels: no problems (Level 1); slight; moderate; severe; and extreme problems (Level 5). The instrument also includes a visual analogue scale (EQ-VAS) that provides a single global rating of self-perceived health and is scored on a 0–100 mm scale representing "the worst…" and "the best health you can imagine", respectively. Following the instructions provided by the EQ5D3L and the previous longitudinal cohort study by Golicki et al. (2015) [27], we will dichotomize each of the five items into level 1—"no problems", level 2—"moderate problems", and level 3—"extreme problems" and assess changes in the distribution of responses.

The iMTA Productivity Cost Questionnaire (iPCQ) [28] will be used to assess how NP affects one's ability to work and perform regular activities. This questionnaire examines the productivity loss due to absence from paid work, the decrease in productivity while engaging in paid work, and

the reduction in unpaid work resulting from an underlying condition.

Cost-effectiveness Participants will be asked how much they spent "out-of-pocket" on their diet in the last week. This question will allow for the examination of participant expenditure for the anti-inflammatory and placebo diets. Using this information along with the cost of treatment (THC/CBD capsules and high CBD capsules) and the cost of lost productivity, the incremental cost of the anti-inflammatory diet and the incremental cost of THC/CBD and high CBD treatment will be calculated. Study results for the EQ-5D will be translated to utility values and converted to quality-adjusted life years (QALY). From these data, the incremental cost per QALY will be calculated to estimate the cost-effectiveness of anti-inflammatory diet, THC/CBD and high CBD treatment.

Statistical methods

Sample size calculation

Power calculations were based on previous studies which utilized pregabalin for the treatment of NP [29] as well as prior cannabinoid studies in the MS population [30]. A SD of 2.1 was assumed based on previous pregabalin studies [29]. For the current study, a treatment difference between groups of at least 0.9 on the NRS is expected based on prior data referenced from the previous MS study [30]. If a four-group, two-way analysis of variance (ANOVA) is used, assuming a power of 0.9 and an alpha of 0.05, a total sample size of 126 will be required. If we treat THC/CBD vs. placebo, CBD vs. placebo, and anti-inflammatory diet vs. placebo as independent analyses, assuming a treatment effect of 1.3 (as in a prior study on cannabinoids in MS [30], as well as a study on pregabalin in the SCI population [29]) and a standard deviation of 2.1, 33 participants per group (132 participants total) would be required assuming a power of 0.8 and an alpha of 0.05. A much larger sample size (272 participants) would be required to detect a treatment difference of 0.9 in this instance, which is beyond the scope of the available budget. A larger treatment effect difference between groups (1.3) is justified based on prior studies of cannabinoids and pregabalin [9, 29, 30] and represents a more clinically relevant difference. Using a 10% attrition rate on a sample of 132 people, ~144 participants would need to be recruited. A greater number of participants may be screened for the study but may not necessarily participate due to exclusion criteria found during the in-person screening process. All participants who have taken at least one dose of the study medication (even in the titration period) will be included in the final analysis.

Statistical analysis

Analysis will be performed using a Modified Intention-to-Treat Analysis Dataset (participants who took at least one dose of investigational product and/or have an amount of follow-up outcome data) and an Evaluable or Per-Protocol Analysis Dataset (participants who took at least 80% of investigational product for 80% of the days within the maintenance period, thus their data are likely to represent the effects of treatment). Statistical analyses will be performed using SPSS (IBM SPSS Statistics for Windows, version 23.0; IBM Corp., Armonk, NY).

To answer the primary research question, pertaining to the change in NP scores as assessed by the NRS in response to cannabinoids and an anti-inflammatory diet, both in isolation and in combination, statistical analyses will be performed for phase 1 and phase 2 of the trial (see Fig. 2 for schematic of study design). For phase 1, which will assess the efficacy of each intervention in isolation, the normality of the data will first be tested via the Shapiro–Wilk test. Normally distributed data will be analyzed using a two-way (group × time) repeated measures ANOVA with four levels for group to test for differences in the change in NP between the placebo diet and placebo capsule group (group 1, phase 1), the placebo diet and THC/CBD capsule group (group 2, phase 1), the placebo diet and high CBD capsule group (group 3, phase 1), and the anti-inflammatory diet and placebo capsule group (group 4, phase 1) and two levels for time (baseline and 6 weeks (post-intervention phase 1)). For phase 2, which will assess the efficacy of the interventions in combination, the normality of the data will first be tested

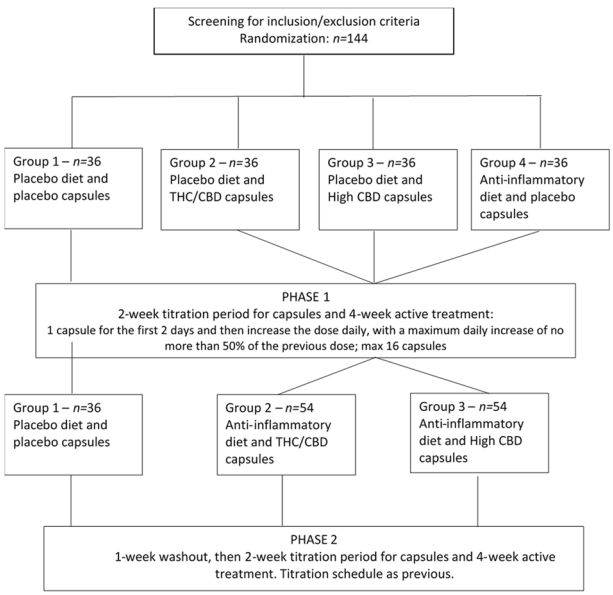

Fig. 2 Schematic of study design. CBD cannabidiol, THC tetrahydrocannabinol.

via the Shapiro–Wilk test. Normally distributed data will be analyzed using a two-way (group × time) repeated measures ANOVA with three levels for group to test for differences in the change in NP between the placebo diet and placebo capsule group (group 1, phase 2), the anti-inflammatory diet and THC/CBD capsule group (group 2, phase 2), and the anti-inflammatory diet and high CBD capsule group (group 3, phase 2) and two levels for time (week 8 (phase 2 baseline) and week 14 (post-intervention phase 2)). If significant group × time interactions are found (or main effects for group), then Bonferroni post hoc tests will be used to determine which means are significantly different from one another. If any data prove to be non-normally distributed, nonparametric analyses will be performed via a Mann–Whitney test on the change scores between groups. Statistical significance will be set at $p \leq 0.05$ for all tests.

To address the secondary research questions pertaining the change in inflammation, mood, sleep, spasticity, cost-effectiveness, and function the same statistical approach as performed in the primary objective will be completed. Normality of the data will first be tested via the Shapiro–Wilk test for all outcome measures. Normally distributed data will be analyzed using a two-way (group × time) repeated measures ANOVA using the same grouping and time points for phase 1 and phase 2 as performed in the primary objective. If significant group × time interactions are found (or main effects for group), then Bonferroni post hoc tests will be used to determine which means are significantly different from one another. If any data proves to be non-normally distributed, nonparametric analyses will be performed via a Mann–Whitney test on the change scores between groups. Statistical significance will be set at $p \leq 0.05$ for all tests.

Sub-analysis

Generally, higher NRS scores at baseline are associated with a higher minimal clinically important difference (MCID). Prior studies in chronic pain have stratified assessment of absolute MCID changes depending on baseline pain scores, but stratification methods and criteria are highly variable. We propose stratification and sub-analysis based on baseline pain severity as follows: 4–7/10; and >7/10. This is extracted from a systematic review in acute pain, as a similar categorization is not available in the chronic pain literature. A global rating of change scale will be used to dichotomize results into responder/nonresponder categories and further sub-analysis.

Adverse events and serious adverse events (SAE)

An AE is any untoward medical occurrence in a patient administered a product regardless of its cause. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study product, whether or not considered related to the study product. An AE will be considered an SAE if the reaction or event results in any of the following seriousness criteria: death, a life-threatening experience, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or other medically important condition. All AEs will be recorded on the AE form and reported to the principle investigator. All AEs will be evaluated for duration, intensity, and causal relationship with the study product or other factors. It will be determined whether an AE is classified as an expected AE or unexpected AE based on whether the nature, severity, or frequency of the event is consistent with the risk information previously described for the study product. Participants will be instructed to report any AE they experience. AEs will be assessed at each in-person study visit as well as by telephone each week when no in-person visit is scheduled.

End of study/discontinuation

Participants may withdraw, or the study team may withdraw a participant, at will at any time. Participants are considered to have withdrawn if the participant withdraws consent or is lost to follow-up. Participants will be withdrawn from the study by the study team if one of the following conditions applies: the occurrence of any clinical AE, laboratory abnormality, or other medical condition or situation such that continued participation in the study would not be in the best interest of the participant, the occurrence of a newly developed or not previously recognized exclusion criteria that precludes further study participation, or a safety concern related to trial product is noted.

Data collection, management, and confidentiality

Data collection will be the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator will be responsible for ensuring accuracy, completeness, legibility, and timelines of the data reported. CRFs will be maintained for recording data for each participant enrolled in the study. Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the appropriate CRFs. The data will be kept in a locked cabinet in a locked office for protection, and will undergo internal quality checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. All participants and their data will be identified by a unique study identification number. The study data entry and study management

systems used by clinical sites and by research staff will be secured and password protected. At the end of the study, all study data will be de-identified and archived in a secure database. A data monitoring committee is not required. The PI will safeguard the interest of participants, by reviewing emerging data, assessing the safety and efficacy of trial procedures, and monitoring the overall conduct of a trial. The PI will be communicating any new information to the REB over the course of the trial.

Dissemination

The results of the study will be disseminated via presentations at conferences and publication of peer reviewed articles. Results will be also be made available via clinicaltrials.gov upon study completion and will be shared upon request by contacting the corresponding author.

Discussion

This study will be the first randomized double-blind placebo-controlled trial to assess the efficacy of cannabinoids and an anti-inflammatory diet for the treatment of NP following SCI. As NP represents a highly prevalent and debilitating condition following SCI, with limited treatment options, this study will provide critical insights regarding the efficacy and safety of these alternative treatment options.

While the mechanisms of NP are not fully understood, it is now well established that NP is not simply a consequence of the initial structural damage to the nociceptor, but also of the environment with which the nociceptor interacts [31]. A number of pro-inflammatory mediators such as IL-1β, IFN-γ, IL-6, and TNF-α (tumor necrosis factor alpha) have been shown to be capable of reducing nociceptive thresholds via both direct [32] and indirect [33] (prostaglandin dependent) mechanisms thereby contributing to symptoms of hyperalgesia. The chronic inflammation commonly observed following SCI [34, 35], may therefore exacerbate symptoms of NP and provide a target for intervention.

Although dietary needs change drastically following SCI, research pertaining to diet in this population is relatively sparse; particularly so with regard to anti-inflammatory dietary interventions. Dietary alterations have the potential to influence concentrations of inflammatory mediators via numerous mechanisms including improvements in metabolic health and body composition, changes in cell membrane composition (e.g., increases in omega-3), improved enzyme regulation, and altered gene transcription [36]. Although very few studies have assessed the efficacy of anti-inflammatory diets on NP following SCI, early findings have been promising. The implementation of a 12-week anti-inflammatory diet was shown to significantly reduce symptoms of NP in a sample of 20 individuals with SCI while reporting no adverse effects. Such results are encouraging, however, as this study was not blinded, and involved a relatively small sample size, future larger scale, placebo-controlled RCTs are warranted.

The pharmacological actions of cannabinoids on NP are not fully understood and likely involve multiple pathways [37]. Cannabinoids have been shown to have an inhibitory effect on pain responses by acting on the cannabinoid receptors CB1 and CB2 [38]. While CB1 receptors are found predominantly in the central nervous system (CNS); CB2 receptors are found mainly on immune cells [39, 40], which suggests that cannabinoids may have an immunoregulatory role as well. Several studies have shown that cannabinoids downregulate cytokine production and upregulate regulatory T cells, thereby suppressing the inflammatory response. Cannabinoids may therefore be capable of influencing NP either via a direct CNS influence, or via a reduction in inflammation. While research related to the use of cannabinoids for NP in SCI is extremely limited, RCTs have been performed in non-SCI populations. A systematic review and meta-analysis including 11 RCTs by Meng et al. [38] concluded that cannabinoids provided a small analgesic effect, in a non-SCI population, with no AEs. These studies were, however, limited by small sample sizes, inclusion of participants with heterogenous characteristics including chronic pain syndromes which may not have been associated with NP, and a high level of heterogeneity regarding cannabinoid type (e.g., CBD, THC, and CBD/THC), dose, and intervention length.

As such, high-quality, large-scale clinical trials that evaluate the efficacy and safety of cannabinoids in an SCI population are urgently needed. Our study will include a large sample size of individuals with SCI ($n = 144$), include only participants who have been screened for NP, and will utilize homogenous assessment tools and interventions. Our study will also have the added advantage of comparing the effects of cannabinoids in the form of both THC/CBD and CBD only. THC has been shown to be associated with psychotropic effects as well as tachycardia, anxiety, dysphoria, sedation, and depression [41]. As CBD is not associated with the same psychotropic effects it will be possible to assess whether CBD alone can produce similar relief of NP symptoms while avoiding the adverse effects associated with THC.

In conclusion, this study will assess the efficacy of an anti-inflammatory diet and cannabinoids (individually and in combination) to treat NP following SCI. If successful, results from this study may reveal a cost-effective, side-effect free intervention strategy which could be utilized for the long-term management of NP following SCI.

Trial status

Recruitment is expected to begin in August 2020 and will continue until 144 participants have been recruited. The study is expected to conclude in January 2022.

Data availability

The data sets used and/or analyzed during the current study are available from the corresponding author on request.

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Author contributions DSD and EL were substantially involved in the conception and design of the study. ARA, DJA, DSD, and EL are participating in the coordination of the study and the acquisition of data. DJA drafted the paper with the assistance of DSD, EL, ARA, and BCFC. DSD, EL, BCFC, and AR critically revised the text. The present publication has been approved by all involved.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The protocol, informed consent form, recruitment materials, and all participant materials will be submitted for ethical approval through the University of Western REB and the Brock University REB prior to participant recruitment. The study will be conducted in full conformity with the ICH E6, Health Canada Food and Drugs Act, and Good Clinical Practice.

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