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Low-dose naltrexone for post-COVID fatigue syndrome: a study protocol for a double-blind, randomised trial in British Columbia

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ABSTRACT

Introduction A significant proportion of individuals suffering from post COVID-19 condition (PCC, also known as long COVID) can present with persistent, disabling fatigue similar to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and post-viral fatigue syndromes. There remains no clear pharmacological therapy for patients with this subtype of PCC, which can be referred to as post-COVID fatigue syndrome (PCFS). A low dose of the opioid antagonist naltrexone (ie, low-dose naltrexone (LDN)) has emerged as an off-label treatment for treating fatigue and other symptoms in PCC. However, only small, non-controlled studies have assessed LDN in PCC, so randomised trials are urgently required.

Methods and analysis A prospective, randomised, double-blind, parallel arm, placebo-controlled phase II trial will be performed to assess the efficacy of LDN for improving fatigue in PCFS. The trial will be decentralised and open to eligible individuals throughout the Canadian province of British Columbia (BC). Participants will be recruited through the province-wide Post-COVID-19 Interdisciplinary Clinical Care Network (PC-ICCN) and research volunteer platform (REACH BC). Eligible participants will be 19–69 years old, have had a confirmed or physician-suspected SARS-CoV-2 infection at least 3 months prior and meet clinical criteria for PCFS adapted from the Institute of Medicine ME/CFS criteria. Individuals who are taking opioid medications, have a history of ME/CFS prior to COVID-19 or history of significant liver disease will be excluded. Participants will be randomised to an LDN intervention arm (n=80) or placebo arm (n=80). Participants in each arm will be prescribed identical capsules starting at 1 mg daily and follow a prespecified schedule for up-titration to 4.5 mg daily or the maximum tolerated dose. The trial will be conducted over 16 weeks, with assessments at baseline, 6, 12 and 16 weeks. The primary outcome will be fatigue severity at 16 weeks evaluated by the Fatigue Severity Scale. Secondary outcomes will include pain Visual Analogue Scale score, overall symptom severity as measured by the Patient Phenotyping Questionnaire Short Form, 7-day step count and health-related quality of life measured by the EuroQol 5-Dimension questionnaire.

Ethics and dissemination The trial has been authorised by Health Canada and approved by The University of British Columbia/Children's and Women's Health Centre of British Columbia Research Ethics Board. On completion, findings will be disseminated to patients, caregivers and clinicians through engagement activities within existing PCC and ME/CFS networks. Results will be published in academic journals and presented at conferences.

Trial registration number NCT05430152.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The trial will be decentralised and will recruit participants from throughout the geographically large and ethnically diverse Canadian province of British Columbia (BC); this will permit the inclusion of patients from communities that do not typically have access to investigational treatments and patients who may be too symptomatic to attend in-person assessments.
⇒ In addition to evaluating fatigue severity as the primary outcome, the study will capture several secondary outcome measures known to be important to post COVID-19 condition patients, including pain, overall symptom burden, health-related quality of life and activity levels (as measured by step count).
⇒ The study does not have a restriction on how long a participant may have had their symptoms since COVID-19; this may limit the treatment effect if low-dose naltrexone efficacy is greater earlier in the disease course.
⇒ As in-person evaluation is optional, this limits the ability to assess potentially important objective outcomes in some participants.

INTRODUCTION

Background and rationale

Approximately 15–20% of adults with a confirmed or suspected SARS-CoV-2 infection experience long-term symptoms lasting over 3 months.[1–4] The presence of new or persistent symptoms following acute COVID-19 disease is now referred to as post COVID-19 condition (PCC) or 'long COVID'.[5–11] Among the hundreds of symptoms reported by people

with PCC, fatigue is one of the most common and may have the greatest impact on functioning.[5 12–20] Given that millions of individuals may be currently affected by PCC worldwide, it has become a priority to investigate the potential treatments in randomised controlled trials (RCTs).[5 21 22]

However, it has been challenging to identify candidate treatments for PCC as it is a heterogeneous illness, and the underlying pathobiology is poorly understood. It is suspected that different groups of people with PCC may have distinct underlying disease processes, such that the ideal pharmacological therapy may not be the same for all.[5 21] Increasingly, studies have suggested that PCC may not represent a single disease but rather a collection of different conditions or subtypes.[15 23 24]

For example, clinical experience and patient-centred studies have indicated that a proportion of people with PCC present with a symptom profile indistinguishable from myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).[25–30] ME/CFS is characterised by persistent disabling fatigue accompanied by other symptoms including non-restorative sleep and post-exertional malaise.[31–33] While the precise pathogenesis of ME/CFS also remains unresolved, it usually follows acute infections.[34] When provoked by a viral infection, ME/CFS is often referred to as a post-viral fatigue syndrome (PVFS).[34–37] It is believed that some PCC patients have developed a PVFS from SARS-CoV-2, and we will refer to this subset of PCC patients as having 'post-COVID fatigue syndrome' (PCFS).[35–38]

A low dose of the medication naltrexone is a potential treatment for PCFS.[39 40] Naltrexone is an opiate antagonist that is approved for treatment for alcohol and opiate use disorders.[41] For these indications, it is typically prescribed at 25–50 mg.[42] At lower doses (≤5 mg), it has been used off-label for chronic pain, multiple sclerosis, Crohn's disease, recurrent depression, fibromyalgia (FM) and ME/CFS.[43–57] Although evidence supporting the use of low-dose naltrexone (LDN) in ME/CFS has been limited to case series and chart reviews,[46 54] it has been investigated in clinical trials for related conditions such as FM.[50 51 54 57] In these and other studies, LDN has been shown to be safe with a limited side-effect profile.[49 51–53 57]

Based on its hypothesised mechanism of action, it is plausible that LDN could be efficacious for ME/CFS and PCFS. LDN increases circulation of the endogenously produced opiate-like molecule beta-endorphin, which is reduced in ME/CFS.[58 59] Furthermore, LDN has been found to antagonise toll-like receptors on neuroglia and peripheral blood mononuclear cells, resulting in reduced production of inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor (TNF).[60–63] Increased IL-6 and TNF signalling have been implicated in PCC,[64] and studies have implicated increased neuroinflammation in ME/CFS and PCC pathogenesis.[5 65–68]

There is ongoing public interest in investigating LDN for PCC. Media outlets including *Rolling Stone, National Geographic, Reuters* and *The New York Times Magazine* have all touted LDN as a potential PCC treatment, citing the anecdotal experiences of people with PCC and physicians.[69–76] However, published evidence for LDN in the post-COVID-19 context remains limited. In a single-centre study, 52 patients treated with LDN had, on average, overall improvement in activities of daily living, energy levels, pain, concentration and sleep disturbance.[40] In a retrospective study, 37 of 59 (62.7%) patients treated with LDN reported improvement in at least one symptom.[77]

RCTs are required to determine whether LDN is an effective treatment for post-COVID-19 symptoms. Since there is no widely accepted pharmacological treatment for PCFS, the ideal comparator group is a placebo. Accordingly, we have designed a double-blinded placebo-controlled trial of daily LDN versus placebo for the treatment of fatigue severity in PCFS.

Objectives

Study objectives are outlined in table 1. The primary objective is to determine whether LDN can reduce fatigue severity associated with PCFS, as measured by the Fatigue Severity Scale (FSS). The secondary objectives are to determine whether it can reduce pain, reduce symptom severity, improve health-related quality of life (HRQOL) and increase activity levels. We have developed additional exploratory objectives that examine other patient-reported outcome measures (PROMs), laboratory outcomes and physical measurements.

Trial design

The development of this trial protocol followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[78] This trial is designed as a randomised, controlled, double-blind prospective trial with two parallel groups and a primary end point of fatigue severity at 16 weeks. The intervention group will receive LDN capsules dosed at 1.0 mg to 4.5 mg daily and the control group will receive placebo capsules. Randomisation will be stratified by sex and performed as permuted block randomisation with a 1:1 allocation. The trial will be conducted in British Columbia (BC), Canada.

METHODS AND ANALYSIS

Study setting

The trial will involve a collaboration between BC's Post-COVID-19 Interdisciplinary Clinical Care Network (PC-ICCN) and the Complex Chronic Diseases Program (CCDP) at BC Children's and Women's Hospital and Health Centre (C&W) located in Vancouver. The PC-ICCN was founded as a learning health system for post-COVID-19 care and research in BC.[79–82] The network previously comprised of five physical Post-COVID Recovery Clinics (PCRCs) but has now consolidated to a single virtual programme. Adults throughout BC may be referred to this programme by their primary care provider (PCP) if they have had

Table 1 Summary of study objectives and associated outcomes

Primary objective	Primary outcome
To determine if LDN, administered at 1–4.5 mg/day to individuals with PCFS, reduces fatigue severity.	FSS score at 16 weeks.

Secondary objectives		Secondary outcomes
To determine if LDN, administered at 1–4.5 mg/day to individuals with PCFS:	Reduces pain.	Pain VAS score at 16 weeks.
	Improves severity of symptoms associated with PCFS.	PQSymp-12 score at 16 weeks.
	Increases activity levels.	Average number of steps over 7 days at 16 weeks.
	Improves self-reported quality of life.	EQ-5D-5L health utility score at 16 weeks.

Exploratory objectives		Exploratory outcomes
To determine if LDN, administered at 1–4.5 mg/day to individuals with PCFS:	Reduces inflammatory marker values in peripheral blood.	IL-6, IFNγ and CRP values at 16 weeks. Cytokine profile values using Human Cytokine Proinflammatory Focused 15-plex Discovery Assay Array at 16 weeks.
	Improves disease severity associated with PCFS.[124]	CK level at 16 weeks.
	Improves rT3 as an indirect marker of disease severity.[125]	rT3 in conjunction with TSH, free T3 and free T4 at 16 weeks.
	Improves AM blood cortisol and improves ACTH.	AM blood cortisol level at 16 weeks. ACTH level at 16 weeks.
	Reduces fatigue VAS score.	Fatigue VAS score at 16 weeks.
	Improves sleep.	SQ-2 at 16 weeks. Sleep VAS score at 16 weeks.
	Improves depression symptoms.	PHQ-9 score at 16 weeks.
	Improves anxiety symptoms.	GAD-7 score at 16 weeks.
	Improves self-reported health.	Self-reported health VAS score at 16 weeks.
	Improves functional status.	Post-COVID-19 Functional Status Scale at 16 weeks.
	Reduces prevalence markers of POTS or postural hypotension.*	Prevalence of POTS or postural hypotension symptoms based on serial blood pressure and heart rate measurements at 16 weeks.
	Improves clinical endurance/strength parameters in subjects with PCFS.*	Hand grip strength at 16 weeks.[126] Sit and stand test results at 16 weeks.

*Optional in-person visits.
ACTH, adrenocorticotropic hormone; CK, creatine kinase; CRP, C reactive protein; EQ-5D-5L, EuroQol 5 Dimension 5-level; FSS, Fatigue Severity Scale; GAD-7, General Anxiety Disorder-7; IFN, interferon; IL-6, interleukin-6; LDN, low-dose naltrexone; PCFS, post-COVID fatigue syndrome; PHQ-9, Patient Health Questionnaire-9; POTS, postural orthostatic tachycardia syndrome; PQSymp-12, Patient Phenotyping Questionnaire Short Form-12; rT3, reverse triiodothyronine; SQ-2, Sleep Questionnaire-2; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; VAS, Visual Analogue Scale.

COVID-19 and meet the criteria for PCC. The CCDP is an interdisciplinary programme that supports patients with ME/CFS and related conditions.[83]

Eligible participants will be recruited from throughout BC. Participants will have virtual or in-person study visits, may have their study product and pedometer delivered to them, complete questionnaires electronically and have blood tests done at their local laboratories. The collection of exploratory data during in-person visits will be optional.

Eligibility criteria

Inclusion and exclusion criteria are listed in table 2. To be included, participants must be aged 19–69 years, have significant fatigue and related symptoms that started after a SARS-CoV-2 infection and meet the criteria we have developed for PCFS. These criteria are adapted from the Institute of Medicine (IOM) ME/CFS standard clinical criteria,[33] but with a duration of symptoms of 3 months rather than 6 months to be consistent with PCC definitions (box 1).[11] Diagnosis for eligibility purposes will be determined from clinical assessment by a study physician and supported by laboratory data and responses to the screening and baseline questionnaires. If there is clinical uncertainty regarding the diagnosis, the case will be discussed with a second physician. Participants who do not have a documented positive PCR test will be eligible if they are determined by a physician through medical history to have had a positive rapid antigen test (RAT)

Table 2 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Male and female patients aged 19 to less than 70 years. 2. Case of SARS-CoV-2 over 3 months previously, confirmed by a positive test result or clinical confirmation by a physician. 3. Meet the clinical diagnostic criteria for PCFS (box 1). 4. Agree to maintain any other regular medications at current doses for the duration of the trial (except for essential need of new medication or dose change, as prescribed by a physician). 5. Agree to use effective contraception for the trial duration, as appropriate (if female). 6. The participant resides within the delivery area for the drug as determined by FedEx Clinical Trial Services.	1. Pregnant, planning to become pregnant or breast feeding. 2. Use of opioid medications within last 15 days, as reported by the patient or during the trial. 3. A positive urine test for opioids (only for the first 16 participants; see below). 4. History of alcohol, opioid or other substance misuse. 5. Participation in another interventional clinical trial in the last 30 days or planned during the trial period. 6. Confirmed ME/CFS or FM existing prior to SARS-CoV-2 infection. 7. Allergy to naltrexone or medication components. 8. Acute hepatitis, liver failure or severe kidney failure. 9. Current or recent use of naltrexone within 30 days.

FM, fibromyalgia; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; PCFS, post-COVID-19 fatigue syndrome.

or compatible symptoms. Individuals will be excluded if they have a history of ME/CFS prior to SARS-CoV-2 infection, have significant liver disease, have taken naltrexone within 30 days or have taken opioids within 15 days.

Interventions

Eligible participants will be randomised at a ratio of 1:1 (n=80 each) into either an active treatment group with LDN or a placebo. The treatment duration is 16 weeks. The LDN and placebo will be compounded by Macdonald's Prescriptions Labs (Vancouver, BC) and dispensed at the C&W Pharmacy where the blinding will occur.

Macdonald's Prescriptions Labs will compound the required doses of LDN from Naltrexone Hydrochloride USP supplied by MEDISCA in empty gelatin CONI-SNAP capsules.[84] The compounded LDN capsules will be filled with CELLULOSE, NF/EP (Microcrystalline) (Flocel 101).[85] Placebo capsules will look identical to the compounded LDN capsules and filled with the same diluent and food colouring. We will complete batch testing of the LDN and placebo compounds (online supplemental appendix 1).

The dose-titration schedule from 1 mg to 4.5 mg is outlined in table 3. The drug will be dispensed to participants by certified courier, temperature-controlled shipping, in-person pick-up or delivered by staff. Participants will be able to adjust treatment doses by reverting to the previous well-tolerated dose if they experience persistent but minor side effects following any increase in dose. If a participant has reverted to a previous dose, that dosage will be maintained for the remainder of the study period. Changes in doses will be documented by the participant by completing a daily dosing diary, completed for the first 4 weeks and 7 days after any change in dose.

By allowing participants to reduce doses if experiencing any potential side effects, we expect low rates

Box 1 Study diagnostic criteria of post-COVID fatigue syndrome

Diagnosis requires that the patient have the following three symptoms after a SARS-CoV-2 infection:
⇒ A substantial reduction or impairment in the ability to engage in pre-illness levels of activity (occupational, educational, social or personal life) that:
  ⇒ lasts for more than 3 months.
  ⇒ is accompanied by fatigue that is:
    ⇒ often profound,
    ⇒ of new onset (not life-long),
    ⇒ not the result of ongoing or unusual excessive exertion,
    ⇒ not substantially alleviated by rest.
⇒ Post-exertional malaise.
⇒ Unrefreshing sleep.
At least one of the two manifestations must be present:
⇒ Cognitive impairment.
⇒ Orthostatic intolerance.
AND
Absence of other diseases or conditions that explain symptoms, based on differential diagnosis.

Table 3 Product supply timeline and titration schedule

Week(s)	Supply	Dose	Capsules
1	First	1 mg/day	1 mg capsule
2	First	2 mg/day	Two 1 mg capsule
3	First	3 mg/day	Three 1 mg capsules
4–6	First	4.5 mg/day	Three 1 mg capsules, plus one 1.5 mg capsule
7–16	Second	4.5 mg/day*	One 4.5 mg capsule*

There will be two dispensing time points when participants will be supplied with the study product. The first supply will be for weeks 1–6 and the second supply will be for weeks 7–16 of the study. For the first supply, participants will receive 1 mg and 1.5 mg capsules of the study product (low-dose naltrexone or placebo). They will be asked to up-titrate the dosage as tolerated and keep a diary of their dosage. In the second dispensing period, they will be supplied with capsules of their maximum tolerated dose.
*Or maximum tolerated dosage (ie, one 1 mg capsule, one 2 mg capsule or one 3 mg capsule).

of medication use interruption. In addition to diaries, participants may also have visits or contact with the study team where adherence can be discussed. Furthermore, there are treatment compliance questions asked with each series of questionnaires. The participants will be asked to return the unused study drug, empty containers and study drug diary sheet(s).

Participants will be asked to maintain any other regular medications at their current doses for the duration of the trial unless there is an essential need for a new medication or dose change. Participants can withdraw from the study at any time without giving reasons. Withdrawal criteria are described in online supplemental box S1.

Outcome measures

The primary outcome measure is fatigue severity, as measured by the FSS. The FSS is a 9-item PROM scored from 9 (least fatigue) to 63 (most fatigue).[86] A score of >36 is consistent with clinically significant fatigue.[87 88] The FSS has been validated in multiple diseases and has been used in randomised trials for ME/CFS.[87 89–91] The FSS received the highest level of recommendation of any subjective fatigue measure for ME/CFS by the National Institute of Neurological Disorders and Stroke Common Data Elements (NINDS CDE) Project and was a recommended measure by the Post-COVID-19 Core Outcome Set (PC-COS) initiative.[17 18 92–95] We have previously investigated the FSS in patients with PCC in BC and demonstrated that the instrument has strong acceptability, internal consistency and construct validity in this population.[17]

Secondary PROMs will include pain severity as measured by the pain Visual Analogue Scale (VAS); total symptom score on the Patient Phenotyping Questionnaire Short Form (PQSymp-12) and HRQOL captured by the EQ-5D-5L instrument. Pain is a common symptom in PCC, and studies have suggested that LDN may be an effective analgesic.[5 16 43 49 52 53 55] The pain VAS is a single-item tool that has been shown to have strong psychometric properties among patients with chronic pain.[96] The PQSymp-12 is a 12-item questionnaire that covers seven clusters of symptoms derived from the Canadian Consensus Criteria for ME/CFS; it has been recommended as a core assessment measure for ME/CFS by the European Network on ME/CFS (EUROMENE)[97] and is included in the UK ME/CFS biobank.[98] The EQ-5D-5L is a generic HRQOL instrument that was recommended by PC-COS.[95] By applying Canadian preference weights, responses to the EQ-5D will be used to derive a health utility (HU) score from 0 (dead) to 1 (perfect health).[99]

An additional secondary outcome is the average step count. We will ask participants to wear a pedometer and document daily step counts for 7 days prior to starting the study drug and again in week 16. All participants will use the same brand and type of pedometer (OZO Fitness CS1 Easy Walk Pedometer). Step counts have been used previously in randomised trials to measure a change in activity levels among patients with ME/CFS.[91 100–102]

There will be several exploratory outcomes (online supplemental table S1), including PROMs (fatigue VAS, sleep, depression symptoms, anxiety symptoms, self-reported health and functional status), laboratory based (inflammatory markers, CK, thyroid profile, AM cortisol and ACTH level) and based on physical measurements (grip strength, sit and stand test, and orthostatic changes in vitals). Physical measurements will be limited to participants who choose to attend in-person visits.

MRI study

As a sub-study of the RCT, 25 participants of each study arm are planned to have brain MRI scans at baseline prior to the intervention/placebo and at 16 weeks. A multimodal functional and spectroscopy (fMRI/MRS) protocol piloted in an ME/CFS study (REB# H20-01804, unpublished) will be employed (online supplemental figure S1). MRI findings will be linked to the primary and other outcome measures.

Participant timeline

The participant timeline is detailed in figure 1 and table 4.

Sample size

The sample size was calculated based on the primary hypothesis of reduction in fatigue severity with treatment. To detect a 4.7-point difference (effect size (d)=0.5) in the Fatigue Severity Scale (FSS) (9–63) between arms, we estimate a sample size of 64 participants per arm assuming 80% power, 5% significance and a pooled SD of 9.4 (estimated from the CCDP Data Registry).[83] To account for possible loss to follow-up of 20%, we estimate a final sample size of 80 per arm, for a total target sample size of 160 participants. We chose this method for sample size estimation (as opposed to the use of a minimal clinically important difference (MCID)) because we believed this to be a realistic treatment effect and there were no published MCID values available for the FSS in ME/CFS or PCC.[103 104] In a sensitivity analysis, we calculated sample size using a published MCID for systemic lupus erythematosus and this yielded a similar estimate (online supplemental appendix 2).[105]

Recruitment and screening

New PC-ICCN patients will be contacted regarding study participation, and the PC-ICCN directory will be used to identify other candidate PCC patients to contact. Additionally, the trial will be accessible to individuals through REACH BC, a provincial online platform that facilitates connections between research studies and participants. All potential participants will be asked to complete an online pre-screening questionnaire, and those potentially eligible will meet with research staff to provide consent. Consented participants will complete baseline questionnaires and be assessed by a physician to confirm eligibility. Baseline laboratory studies for all participants will be done prior to initiation of the study drug and abnormal results will be reviewed by a study physician.

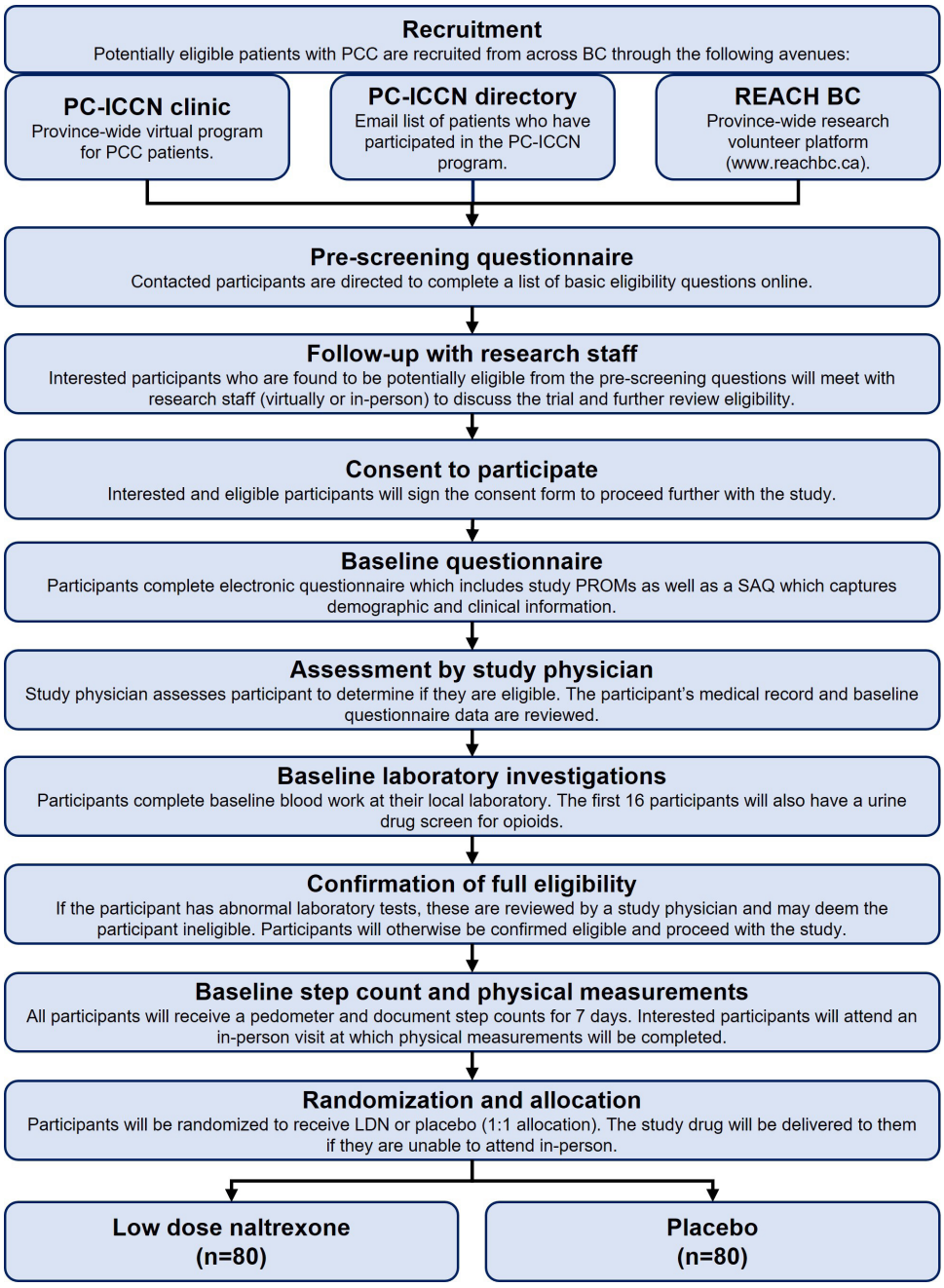

Figure 1 Flowchart of initial study procedures. This flowchart outlines the process for study recruitment, eligibility assessment and baseline assessments. A full study timeline is outlined in table 4. BC, British Columbia; LDN, low-dose naltrexone; PCC, post-COVID-19 condition; PC-ICCN, Post-COVID-19 Interdisciplinary Clinical Care Network; SAQ, Short Answer Questionnaire.

Allocation

Participants will be randomised into either the LDN treatment group or the placebo at a ratio of 1:1 (n=80 each), as per a computer-generated randomisation schedule stratified by sex and using permuted blocks varying between two, four and six participants. A statistician who is not part of the study team will generate a randomisation sequence and corresponding randomisation codes. The randomisation codes will be used to maintain the blinding and will be uploaded to REDCap. The randomisation sequence will be provided to the unblinded CWH Research Pharmacy. After confirmation of eligibility, research staff will randomise participants by REDCap, which will provide the randomisation code. CWH Pharmacy staff will then dispense the study drug based on the randomisation allocation sequence.

Blinding

All participants will be blinded to their treatment regimen. The placebo and intervention capsules will appear identical, and the C&W Pharmacy will distribute the study drug to study staff in identical containers. Participants, their healthcare providers and all study staff

Table 4 Participant timeline and schedule of study procedures

Timepoint	Screening and baseline	Week 1	Weeks 4–5	Week 6	Week 12	Week 16
ENROLMENT:						
Eligibility screening by research staff and study physician	X					
Informed consent	X					
Allocation	X					
INTERVENTIONS:						
Study drug (LDN or placebo)	X	X	X	X	X	X
Study drug diary (daily for first 4 weeks and for 7 days after any change in dose)	X	X	X			
VISITS:						
Adverse effects check		X	X	X*	X*	X
Monitor study drug use		X	X	X*	X*	X
ASSESSMENTS:						
Questionnaires†	X			X	X	X
Laboratory investigations	X					X
Pedometer (number of steps per day)	X					X
Hand grip (muscle strength)‡	X					X
Blood pressure and heart rate‡	X					X
Sit and stand test‡	X					X

This table outlines the schedule of study procedures. See figure 1 for timeline of recruitment, eligibility screening and baseline assessments.
*Occurs as part of questionnaires if optional visit does not occur.
†Short answer questionnaire for demographic and clinical information is done at baseline only.
‡Only for those agreeing to have in-person visits.
LDN, low dose naltrexone.

including research assistants, coordinators, statisticians, trial physicians and investigators will be blind to allocation. Unblinding will only occur when knowledge of the actual treatment is essential for further management of the patient or investigation of serious adverse events (SAEs). If unblinding is deemed necessary by the DSMB or investigator, the C&W Pharmacy will be contacted for release of treatment allocation.

Data collection and management

We will use the secure REDCap platform for the storage of study data.[106 107] Participants will complete questionnaires electronically, with the links provided to the participant via email. Data from other sources will be entered manually and will include study physician assessments, laboratory results, dose diary information, step counts, physical assessment measures and adverse events (AEs). REDCap field validation tools will be used where possible to optimise data accuracy (eg, dates that are out of range and data that are missing). No new data will be collected from participants who withdraw, except for reason for withdrawal and details regarding AEs and SAEs.

Biological specimens

Leftover plasma will be stored at −80°C at the BC Children's Hospital Biobank for up to 10 years to allow for additional sample testing related to this protocol that may be identified from the results of this study.

Monitoring and oversight

A Trial Steering Committee (TSC) will be formed with patient partners, investigators and other research team members. Additionally, we have formed a Data Safety and Monitoring Board (DSMB) that is comprised of peer researchers with expertise in clinical trials and ethics and independent from the study team. Lastly, an independent study monitor from the CWH Quality Assurance Office has been hired to verify participant rights and well-being, data collection and compliance with regulatory requirements. Roles of the TSC, DSMB and study monitor are outlined in online supplemental box 2.

Statistical methods

Primary and secondary outcomes will be analysed by intention-to-treat. The primary outcome (FSS score at 16 weeks) will be analysed using a linear mixed effects model adjusting for baseline level, sex (stratification factor) and other relevant prognostic factors identified *a priori*. The model will include interaction between treatment arm and time, treatment arm and baseline level and include all post-randomisation timepoints at which the FSS is captured. To assess the FSS at 16 weeks, we will calculate

an estimated marginal mean difference between arms with a corresponding 95% CI, with statistical significance set at 0.05. Similar contrasts at each interim time point will be provided. Effect modification by baseline FSS level will be demonstrated graphically. Participants who are lost to follow-up will be compared descriptively with those who remain in the trial. If selection bias occurs, we will consider inverse probability weights for censored individuals.

For secondary and exploratory outcomes, questionnaire, laboratory and physical measure data will be analysed similarly with generalised linear models, adjusting for baseline level and other relevant prognostic factors and using link function based on the variable type from questionnaires (eg, logit for binary outcomes).

Effect modification by baseline factors will be considered by the inclusion of interaction terms with treatment arm in the above models. Possible effect modifiers include baseline fatigue severity, sex, gender, age, severity of and time of acute SARS-CoV-2 infection, pre-existing co-morbidities, COVID-19 vaccination, final dose and side effects. The significance of effect modification will be based on the likelihood ratio test comparing models with and without the interaction term.

Dose-response analyses will involve a comparison of various dosing levels as a covariate versus control in the primary linear model. Secondary analysis will look only at dose comparisons within the intervention arm. Dose will be included in these models as a non-linear effect via restricted cubic splines.

We will conduct a per-protocol analysis to assess the expected effect of adhering to the trial protocol using G-methods, which allow for adjustment for post-randomisation confounding.[108]

All analyses of primary and secondary outcomes will be pre-specified in detail in a Statistical Analysis Plan and signed off on by all investigators prior to data analysis.

Harms

Protocols to address particular AEs and SAEs are described in online supplemental appendix 3. We will implement REDCap alerts for AEs noted through the questionnaires. Additionally, participants will be asked if they have had any AEs at each study visit. All AEs will be assessed by a study physician. All SAEs will be reported to the DSMB. SAEs will be reported to the Research Ethics Board (REB) and Health Canada (HC) as per local regulations. For mild AEs, the patient may be reassured to continue taking the medication as per protocol. Previous studies and our clinical experience have suggested that LDN is generally well tolerated, and mild AEs will often ease with treatment continuation.[40 48 49 51–53]

Inspections and auditing

The trial will be subject to inspections or audits by HC, REB and the Canadian Institutes for Health Research.

Patient and public involvement

Patient partners will be included as part of the TSC.

Trial dates

This trial started recruitment in January 2024 and aims to complete follow-up by the end of 2024.

ETHICS AND DISSEMINATION

Research ethics approval

This study was approved by the UBC/C&W harmonised REB (#H21-02254); any protocol modifications will be reported to the REB.

Consent or assent

Research staff will have interested participants consent via the secure REDCap electronic consent platform. Participants will receive information regarding the trial electronically and will have the opportunity to discuss the trial specifics and meet with a research team member (virtually or in person) before deciding on participation. The consent form is provided in online supplemental appendix 4.

Access to data

The study principal investigator, co-investigators, clinical research coordinator, research assistants and statistician will have access to the collected data.

Dissemination policy

We will follow the Consolidated Standards of Reporting Trials (CONSORT) guidelines for reporting the results of parallel arm trials.[109] We will submit manuscripts to peer review journals, give presentations at conferences, and media releases will be organised. We will leverage our connections with PCC and ME/CFS networks to share our findings with patients, their caregivers, PCPs and other care providers.

DISCUSSION

This report described the protocol for a 16-week, phase II RCT to investigate the efficacy of LDN for treating fatigue severity in patients with PCFS, an illness we have defined as ME/CFS symptoms persisting at least 3 months following SARS-CoV-2 infection.

Our study will build on prior and ongoing evaluations of LDN. In our review of studies listed on ClinicalTrials.gov, we identified one upcoming trial (NCT05946551) which also investigates LDN in PCC. However, this trial is smaller (expected n=36) and focused on feasibility outcomes. There are no trials listed that investigate LDN in ME/CFS.

A positive outcome in our trial would inspire greater confidence in LDN as a treatment for the millions of patients with PCFS symptoms and could prompt larger, multi-institutional phase III studies. Unlike other candidate PCC treatments such as Paxlovid, stellate ganglion blockade and hyperbaric oxygen,[110–116] LDN is widely

available, relatively inexpensive and generally safe. A negative outcome in this trial would also be a valuable contribution to the literature and would directly impact clinician decisions regarding prescribing LDN. The results of this trial may inform guidelines for PCC.

The trial has limitations. It is limited to English speakers and is based in a single province. We do not have a restriction on how long a participant may have had their symptoms since COVID-19. This may limit the treatment effect if LDN efficacy is greater earlier in the disease course. The decentralised nature of the trial also limits the number of objective outcomes that can be collected from all participants.

However, our decentralised strategy for this trial has several advantages. First, it will allow individuals who live outside Vancouver to participate, including those in communities who may not have access to off-label or investigational treatments.[14] Second, it will permit the inclusion of more symptomatic individuals. Some individuals with PCFS have reported symptom exacerbation from even minimal cognitive and physical exertion,[117] and remote participation may prevent flare-ups experienced from in-person visits. Third, it will encourage participation from patients who may be reluctant to attend in person given the risks of COVID-19 re-infection. Lastly, it will expedite study completion by broadening the pool of eligible applicants and reducing logistical barriers associated with in-person recruitment and enrolment.

This trial has other strengths. By using the provincial PC-ICCN and REACH BC directories, we will be able to efficiently identify and contact hundreds of potential participants by email. Our focus specifically on individuals with the ME/CFS phenotype distinguishes this trial from others for PCC and increases the likelihood that participants will have a similar underlying pathophysiology. Lastly, our trial includes multiple secondary and exploratory outcome measures that may be valuable for further hypothesis generation.

This is one of the first trials in Canada investigating a pharmacological treatment for PCC and will have a direct impact on how this illness is treated. We hope that it will also promote engagement, good faith and optimism among the PCC community—a group that has experienced stigma and has expressed frustration regarding the paucity of interventional studies for their illness.[21 118–122] Furthermore, the trial has implications beyond COVID-19; we expect that the results will have applicability to ME/CFS and other post-infection fatigue syndromes, including those that could emerge from future pandemics.[123]

Confidentiality

Following UBC REB guidelines, all study-related information will be stored in locked facilities at C&W, and all electronic material stored on secure network drives or servers. Participants will be allocated study identification (ID) numbers and a master file linking the study ID and personal information will be saved separately.

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Competing interests HN is a member of the Canadian Guidelines for Post-COVID-19 Condition Guideline Team for Pharmacologic and Nonpharmacologic Clinical Interventions. The other authors have no competing interests to declare.

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