

Pain Relief with Integrative Medicine (PRIME)?: Feasibility Trial of Acupuncture for Long
COVID

Study Protocol

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Background and Significance

Since the COVID-19 pandemic began in 2020, more than 102 million U.S. citizens (31% of the population) have had documented COVID-19 and 1.1 million have died.^{1,2} A substantial number of people with COVID-19 have experienced persistent debilitating symptoms months or years after the initial infection, referred to as post-acute sequelae of COVID-19 (PASC), or “Long COVID.”^{3,4} Estimates of the percentage of persons with COVID who have Long COVID (LC) range from 10% to 60% throughout the first year post-infection depending on the study design and populations studied.^{5,6} The high prevalence of LC is a significant public health concern and presents a major challenge for clinicians and their patients.

Although the pathophysiology of LC is thought to involve a prolonged, dysfunctional hyperimmune response,^{7,8} it remains a complex, poorly understood medical challenge for which broadly effective treatments are lacking.⁹ Over 200 symptoms have been attributed to PASC, including many pain-related symptoms.^{10–12} Pain is reported by almost half of all patients, but is often not well recognized or attributed to LC.¹³ However, studies have found that the onset of new pain symptoms and exacerbation of pre-existing pain conditions have been consistently reported in patients following their COVID-19 illness and should be considered in a LC work-up.^{14,15} The onset and trajectory of symptoms vary. For example, pain in joints, back, neck, bones, and ears are more common at one year than at two months post-infection.⁹ The high prevalence of LC is negatively impacting the quality of life, daily function, and ability to work, and has placed enormous demands on the healthcare system.¹⁰ As a result, clinicians are often frustrated that they have little to offer these patients to relieve their pain. There is a need for research that identifies effective treatment strategies for patients with LC pain.

This initial study determined the feasibility of successfully conducting a subsequent fully-powered pragmatic randomized trial evaluating the effectiveness of Traditional Chinese Medicine acupuncture for persistent pain problems experienced by persons with LC. We restricted this study to patients who had moderate to severe pain after COVID infection because pain is a relatively neglected area of LC research and pain negatively impacts other symptoms often reported by patients with LC, such as sleep, cognition, and fatigue. We chose to study acupuncture because it has been found safe and effective for various types of chronic pain,^{16,17} but its effectiveness for LC pain is unknown.¹⁸

Acupuncture is a physical treatment that aims to correct imbalances in the body (including inflammation and pain) within a Chinese Medicine paradigm. It focuses on treating the whole patient rather than a single symptom or disease, and therefore seems particularly well suited for a complex condition like LC that affects multiple body systems.^{19,20} As there is no evidence that acupuncture is safer or more effective than usual care for LC, the trial retained clinical equipoise.

Innovation

National organizations and leaders have called out the need for more federally-funded RCTs studying interventions for LC.²¹ This trial has the potential to lead to the identification of effective treatments for the tens of millions of patients with LC pain in the U.S., thereby providing clinicians tools to more effectively respond to their patients' suffering. Patients with LC usually exhibit a range of symptoms affecting several body systems, thus treatments that address the whole person's health might provide an efficient way to help these patients. Our study engaged patients, clinicians, and clinic staff in a user-centered fashion to ensure these important perspectives were considered and included in all aspects of the study.

Approach

The goal of this preliminary study was to test methods and procedures to be used in a fully-powered trial to evaluate treatment effectiveness.²² Specifically, we tested the feasibility of conducting a 2-arm randomized clinical trial for evaluating the effectiveness of acupuncture for pain in patients with LC. Before launching the feasibility trial, three patients with LC pain were asked to serve on a patient advisory board (PAB). This board collaborated with the research team and an expert advisory board to review treatment protocols, survey instruments, patient-related outcome (PRO) measures, and project implementation strategies.

We randomized participants to receive acupuncture or continued usual care (Aim 1). Data pertaining to study feasibility, patient experience, and patient-reported outcomes (PROs) for pain, quality of life, mental health, and function were collected (Aims 1 and 2). Based on our feasibility study results, a manual of operations containing the finalized study protocol and analysis plan is being developed (Aim 3).

Overview:

The study for which we assessed feasibility was a pragmatic 2-arm randomized clinical trial for evaluating the effectiveness of acupuncture compared to usual care for improved pain and associated morbidity. As the overall goal of this feasibility study was to ascertain the acceptability of the protocol, several criteria for assessing feasibility were pre-specified. We implemented the study in two phases. ***Phase 1 was an initial pilot test phase and Phase 2 was the formal feasibility assessment phase.*** In Phase 1, we randomized 20 patients (10 to each treatment arm) to allow us to identify any significant problems with our initial study materials and procedures and to make any necessary modifications. During this time, we determined our acupuncture protocol was too rigid and worked with our acupuncturists and NCCIH staff to make the protocol more flexible. In Phase 2 we randomized 60 patients (30 to each treatment arm) for our primary assessment of study feasibility.

Recruitment and Sample: We recruited patients from the UW Medicine Long COVID Clinic with self-reported pain scores of four or greater (representing moderate to severe pain) on a 0 to 10 scale.^{23–25}

We recruited these patients through two methods. The first method was through direct contact by the study team. The Long COVID Clinic intake form is administered to all patients in the Long COVID Clinic and allowed patients to “opt in” for future contact for research opportunities. We selected from opt-in patients, individuals 18 years of age or older to be contacted directly by the study team through email invitations that describe the study and explain the inclusion and exclusion criteria. The second method was through a referral from the Long COVID Clinic. We provided the Long COVID Clinic clinicians with EPIC “smart-phrases” that included information about the study and how to contact the study team. During clinic visits, the clinicians were asked to use this smart phrase for any patients with pain or who may be interested in research. This method allowed us to invite potentially eligible participants who did not initially indicate interest in research on their intake form but whose clinicians believed they might benefit from acupuncture.

Screening, Consent, Enrollment: Interested patients were directed to an online survey site where they were given more information about the study and able to complete a screening questionnaire. Due to the absence of a well-defined and universally accepted definition for LC, we opted to utilize the definition agreed upon by the national PASC Collaborative and used by the UW Long COVID Clinic that loosely follows CDC and WHO criteria. Our inclusion criteria included having a documented COVID diagnosis/positive test, or presumed COVID based on high-risk exposure, and new symptoms not attributable to another condition for >3 months post COVID diagnosis. Other criteria included age, pain intensity, no previous acupuncture treatment for LC, ability to travel to acupuncture appointments, and no contraindications for acupuncture.

Those eligible were then asked to provide informed consent, complete a short demographic survey, and the baseline survey. Once completed, they were considered enrolled. The research manager confirmed their enrollment details and randomized the participant. To ensure equal allocation of the 80 study participants to the treatment arms, randomization was done by permuted block randomization stratifying by reported gender to ensure the two treatment arms were balanced.

Intervention arms:

Acupuncture: Participants randomized to acupuncture were asked to attend eight individual weekly treatments at a UW Medicine Primary Care clinic.

Each visit began with a brief intake assessment, followed by treatment with needles inserted at selected body and ear acupoints while the patient lay supine. After needle removal, the acupuncturist applied Pyonex press tags (shallow needles) to specific points for up to five days to extend treatment stimulation between sessions.

The treatment protocol followed TCM principles and was designed to address pain and related symptoms within a whole person framework. Needling targeted pre-specified core

points and, when appropriate, additional points tailored to individual pain symptom presentations, reflecting real-world clinical practice while remaining within protocol-defined boundaries. Acupuncturists attempted to achieve De Qi (a characteristic sensation commonly sought during acupuncture), and needles remained in place for 20-30 minutes.

Core points included bilateral LI4 and ST36, plus unilateral Ear Shenmen. Acupuncturists could add up to seven additional points (maximum of 12 needles) from a predefined list in the acupuncture protocol for symptom-specific treatment, such as brain fog, fatigue, and post-exertional malaise (PEM). Needle sizes were 0.18 x 30 mm for body points and 0.16 x 15 mm for all ear and/or body points. After needle removal, up to 10 Seirin Pyonex press TACK needle(s) Orange (0.3 mm) were applied to the body or ear points and retained for up to five days. Patients were instructed to remove the tags earlier if uncomfortable and were asked to report retention duration at the next visit.

Usual Care: All study participants retained access to their usual LC care. Participation in this study did not affect the care that participants randomized to usual care received. Due to the unique presentations of LC, treatments were tailored to each patient.²⁶ In the UW Long COVID Clinic, visits typically addressed nutrition, restorative activity, sleep, and mental health, with medications and/or supplements discussed based on the patient's symptoms and other underlying diagnoses, all while maintaining a biopsychosocial approach to care.²⁶

The appropriate comparator, therefore, was the care patients were currently receiving for their LC-related pain – that is, their current “usual care” – which is consistent with prior NIH-funded pragmatic trials of nonpharmacologic pain interventions²⁷ and aligned with the design of a future pragmatic effectiveness trial in which acupuncture would be offered as an adjunct to real-world LC care.

Data Collection: Data were collected from participants at four time points (Baseline [Week 0], Midpoint [Week 4], Post-Intervention [Week 8], and Final Follow-Up [Week 20]). Surveys were sent electronically via email and completed on a computer or mobile device.

Outcome Measures: We collected data on various validated patient-reported outcome (PRO) measures of pain, function, and quality of life to ensure they would work in a full-scale clinical trial. The primary outcome was asked at all four time-points, secondary outcomes were asked three times as they not asked at the Midpoint (Week 4) timepoint.

- Primary Outcome: Our primary outcome measure was the PEG (Pain, Enjoyment, General Activity) assessment scale. This measure of pain impact is an easily-understood three-question instrument that asks about average pain, enjoyment of life, and general activity in the past week on 0 to 10 scales.²⁸
- Secondary Outcomes:
 - The Pain Catastrophizing Scale (PCS)²⁹ is a 13-item self-report measure of catastrophic thinking related to pain, including subscales of rumination, magnification, and helplessness. PCS is a commonly used measure of pain

experience and catastrophizing and we believe it to be especially relevant to the LC population.

- The PROMIS-29³⁰ measures data across 7 domains (anxiety, sleep, depression, physical function, pain intensity, social roles, and fatigue) to allow for a broad picture of the impact of PASC on participant's health. PROMIS-29 has been used in a variety of studies on the PASC population.^{31,32}
- The PROMIS Cognitive Function³³ scale complements the PROMIS-29 with questions relevant for participants with PASC co-morbidities such as "brain fog."
- The Pain-Related Self-Efficacy Scale

Adverse events were systematically collected through acupuncturists' notes at the end and beginning of each treatment session and through reviews of electronic health records.

Feasibility Measures: Feasibility outcomes were measured in terms of their success in achieving predetermined goals for each of the key components. The following criteria were chosen in accordance with traditional protocols and based on other feasibility studies

- a) *Recruitment:* 1) Timely recruitment of study participants (criterion: complete recruitment of 60 participants within five months); 2) Effectiveness of excluding ineligible participants (criterion: less than 5% found to be ineligible after entry into the study); 3) Participant completion of enrollment process (criterion: 90% of individuals who were screened as eligible were fully enrolled)
- b) *Retention* of participants in their assigned treatments (criterion: 75% of participants attend at least 6 of 8 acupuncture visits)³⁴
- c) *Questionnaire Response Rates:* (criterion: 70% of participants complete baseline, mid-point, and post-treatment questionnaires; 75% complete final questionnaire)
- d) *Intervention fidelity* (criterion: 80% of sessions fully adhere to acupuncture treatment protocol)³⁵
- e) *Participant Adherence* to treatment recommendations (criterion: 50% leave acupuncture needles in place for at least 3 days)

Analysis plan

We used simple descriptive statistics to describe demographic characteristics of those enrolled in the study and to assess the extent to which specific aspects of our study met our pre-specified feasibility criteria. This included the final counts of: recruitment numbers, participants that attended at least 6 acupuncture treatments, participants completing each of the four surveys, numbers of sessions that met intervention fidelity out of all acupuncture sessions, and numbers of sessions participants retained the pyonex press needles for at least 3 days out of all acupuncture sessions where pyonex press needles were used.

Outcome measures were described for each treatment group using means and standard deviations. This study was not designed to detect outcome differences between treatment groups. Although this study is not powered to detect a significant difference, the

preliminary effects will be used to assess the clinical impact this intervention may have and help guide the power analysis for a larger randomized clinical trial assessing the effectiveness of acupuncture on pain-related function and quality of life outcomes.

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