

Homeopathic Treatment of Post-acute COVID-19 Syndrome - A Pilot Randomized Controlled Trial

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## Background

Post-acute COVID-19 Syndrome, or Long Covid, is being seen increasingly as a serious public health problem. While the high mortality rate and impact on the health care system of acute Covid-19 illness is profound, the long-term effects of the illness, even in those with mild disease, is just now being recognized. It is estimated that 10 to 30 percent of people diagnosed with COVID-19 experience prolonged illness beyond three weeks (Greenhalgh, Aug 2020) and roughly 1.5 percent are affected for 3 months or more (Sleat, 2020). A recent study reported that two-thirds of patients with mild to moderate COVID-19 had persistent symptoms two months after symptom onset. (Carvalho-Schneider, 2020) Considering that more than 100 million people have been infected with COVID-19 worldwide, this syndrome undoubtedly affects millions, many of them in the US.

The exact cause of Long Covid is not known but is thought by some to be due to a dysfunctional immune-inflammatory response that can affect even people who were never hospitalized. (Greenhalgh, Nov 2020). Many of the symptoms are similar to those of chronic fatigue/myalgic encephalomyelitis, including fatigue, post-exertional malaise, and brain fog. Treatment for Long Covid is mostly supportive, since there are no known conventional therapies for the syndrome at this time.

The clinical manifestations of Long Covid are varied and each patient can have a constellation of different symptoms. In an international online survey of nearly 3,800 respondents self-diagnosed with Long Covid, the most frequently reported symptoms were fatigue (98.3 percent), post-exertional malaise (89.0 percent) and cognitive dysfunction (88.0 percent). Other common symptoms included sleep difficulties (78.6 percent), emotional and mood changes (88.3 percent), headaches (77 percent), and musculo-skeletal complaints (93.9 percent). (Davis, 2020) Sixty-five percent of respondents reported symptoms persisting for more than six months.

Homeopathy was first developed in Germany by Samuel Hahnemann in the late 18th century. It is based on the principle of similars, whereby highly dilute preparations of substances that have been found to cause symptoms in healthy volunteers are used to treat patients who have similar symptoms when ill. Homeopathic medicines are prepared according to standardized methods as specified by the Homeopathic Pharmacopoeia of the United States (HPUS), which was mandated by Congress to regulate the manufacture of homeopathic medicines as part of the Food, Drug, and Cosmetics Act of 1939. Most homeopathic products are derived from plant, animal, or mineral sources and because of the highly dilute nature of the preparations, are without toxic side effects. The mechanism of action of homeopathy is not well understood, but is thought to be due to enhancement of the immune response

and other auto-regulatory systems of the body. (Bell, 2015)

*Classical homeopathy*, used widely by medical practitioners for acute and chronic illnesses, involves a 60-90 minute initial consultation during which a wide collection of physical, general, and mental-emotional symptoms are elicited from the patient. An individualized homeopathic medicine is prescribed, matching the specific signs and symptoms in that patient with those known to be associated with a particular medicine in the homeopathic literature. Using this individualized approach, two or more people with the same diagnosis may be given different medicines, depending on symptoms.

Previous clinical studies have shown classical homeopathy to be superior to placebo in treating a wide variety of illnesses (Mathie, 2014), including chronic diseases with symptoms similar to long COVID, such as fibromyalgia (Bell, 2004) and chronic fatigue syndrome (Weatherley-Jones, 2002). Because homeopathy is a system that treats the whole person, taking into account physical, emotional, and mental symptoms, it is likely to be of particular value to people suffering from the myriad symptoms associated with Post-acute COVID-19 Syndrome.

### Hypothesis/Purpose

Our ultimate goal is to determine whether an individually prescribed homeopathic medicine has an effect greater than a placebo and is a viable treatment option to improve fatigue and quality of life for patients suffering from the symptoms of Post-acute COVID-19 Syndrome. We hope to achieve this goal by conducting a clinical trial that is scientifically rigorous and clinically relevant. Because such a trial would be costly, we first need to do a pilot study that demonstrates our ability to conduct a full-scale trial successfully. Expected results of this pilot study will be to obtain sufficient experience and preliminary feasibility data to justify a larger clinical trial of this hypothesis.

### Technical Objectives

Our objectives for the study are to: 1) identify efficient means of recruiting subjects, 2) test and refine our initial study design and treatment protocol, 3) evaluate the instruments for assessing treatment outcomes, 4) estimate sample sizes that will be required in the full-scale trial, 5) determine which homeopathic medicines are most often prescribed for this syndrome, and 6) determine whether there is a measurable effect size difference or positive trend in reduction of symptoms in patients treated with homeopathy.

### Methods

Overview: In this double-blind pilot study, 66 patients who have tested positive for COVID-19 and

who have had unexplained fatigue for at least 60 days, as well as at least one other symptom of Post-acute COVID-19 syndrome will be randomized to one of two treatment arms: classical homeopathy or placebo. Treatment will be provided by trained homeopathic practitioners, who will see the patients at 4 week intervals over the course of 12 weeks. Fatigue scores and general health status as measured by the SF-36 will be measured at entry to the study and at 4 week intervals for 12 weeks. The MYMOP score of specific symptoms will be administered at entry to the study and at the end of 12 weeks.

Recruitment: Subjects will be recruited from advertisements on Facebook. We hope to enroll 15-20 patients per month during the 4 month enrollment period. We will use an online survey to screen potential subjects to determine eligibility. Those who are eligible will be scheduled for a telephone screening appointment, during which eligibility will be confirmed and informed consent will be obtained using a consent form approved by the Southwest College of Naturopathic Medicine Human Subjects Committee. Baseline questionnaire data will be collected, including the Fatigue Assessment scale (FAS), the SF-36 quality of life survey, and the Measure Yourself Medical Outcomes Profile (MYMOP).

Eligibility: Patients entered into the study will be ages 18-64 and have a confirmed diagnosis of COVID-19 by previous PCR testing. They will also have a history of persistent, unexplained fatigue for at least 60 days since diagnosis of COVID-19, one other symptom consistent with the syndrome, and a FAS score of 22 or above. Subjects must also have adequate cognitive function to be able to give informed consent and be technologically competent to complete online forms and perform video calls. They must also be willing to fill out regular questionnaires and to use homeopathic medications.

Exclusions: Patients taking steroids, immunosuppressives, or opioid analgesics or who have opioid or other substance dependence and/or are undergoing treatment for substance abuse will be excluded from the study. Patients who were treated in an Intensive Care Unit for Covid-19 and those with concurrent health problems such as active cancers, clinically significant kidney, heart, or hepatic impairment will be excluded. Those diagnosed prior to COVID-19 infection with chronic fatigue syndrome, fibromyalgia, Lyme disease, or chronic psychiatric or neurological illness will also be excluded. Also excluded will be women with suspected or confirmed pregnancy and those who are breastfeeding, those who are enrolled in another trial. Those who are currently being treated by a homeopathic practitioner will also be excluded as well as those who have started a new medication or treatment for Post-acute Covid-19 within the past two months.

Treatment: At the initial visit via video conferencing, a licensed homeopathic practitioner (MD, DO, ND, PA, NP) will conduct a thorough homeopathic evaluation and determine the specific homeopathic medication that seems best suited for each subject. Homeopathic practitioners will have a

minimum of five years in practice and be members of a professional homeopathic organization. Because of the individualized nature of classical homeopathic treatment, the usual paradigm of a clinical trial whereby all patients receive the same medicine cannot be followed. Instead, the method of classical homeopathic treatment as practiced in the real world will be evaluated, with one specific medicine prescribed for each patient at the initial visit. Medicines prescribed must be listed in the Homeopathic Pharmacopoeia of the United States (HPUS). The homeopathic dosage and repetition of doses will be chosen by each practitioner based on the clinical characteristics of the subject. Practitioners will be able to change the homeopathic medicine as needed during the course of the trial, in the same way they would in their usual practice.

The homeopathic prescription will be communicated to a homeopathic pharmacist, who will use a randomization scheme prepared by a third party for the patients to receive either the individualized medicine or a placebo, both of which will be identical in taste, appearance, odor, and packaging. Study medications will be express mailed to subjects' home addresses in packages that do not reveal personal information about the subject, along with dosage instructions. Existing conventional and integrative therapies that the subjects are using at the time of enrollment will be documented and subjects will be asked not to change, add, or remove any treatment unless recommended by their own conventional treating provider(s).

Randomization and blinding: Subjects in the study will be randomly assigned to receive individualized homeopathic treatment or placebo (1 : 1). After the confirmation of eligibility, subjects will be randomized with concealment. Every subject will be assigned with a number and a third party will randomize the subjects to each of the 2 study groups using computer generated random numbers. Randomization will be stratified by age (< or > 50) and duration of Long Covid symptoms (< or > 6 months), in permuted blocks of four or six. Randomization will be known only to the homeopathic pharmacist, who will not break the code until after treatment of each subject is completed. An exception to this will be when a research subject suffers an unexplained severe event. In such a case, the randomization code will be broken and the subject withdrawn from the study.

Follow-up: Subjects will have follow-up visits by video with the homeopathic practitioners at 4, 8, and 12 weeks following the initial consultation. At each of these visits, the patients will be reevaluated, adverse side effects will be inquired about, and the classical homeopathic prescription will be renewed or revised, which will again be filled by the homeopathic pharmacist and mailed to the subjects. Although the specific homeopathic prescription might change, subjects randomized to each group will continue to receive placebo or active medicines throughout the study.

The subjects will also complete online questionnaires at 4, 8 and 12 weeks after the initial visit to

evaluate outcomes. At the end of the 12 week study period, those subjects who received placebo will be given the option to receive a verum homeopathic medicine and an additional follow-up visit after 6 weeks will be scheduled for them.

#### Outcomes:

The primary outcome measurements:

- Fatigue Assessment Score (FAS) at baseline, week 4, week 8 and week 12
- General health status, using the SF-36 at baseline, week 4, week 8 and week 12

Secondary outcome measurements:

- Measure Yourself Medical Outcomes Profile (MYMOP), in which each patient chooses the two most bothersome symptoms to record and follow (at study entry and at the end of 12 weeks)
- The number of subjects who have  $FAS \leq 21$  will be compared at week 4

Analysis: Because this is a pilot study with a small sample size, statistical tests are unlikely to reveal any statistically significant differences. However, the data will be summarized and analyzed as if this were a full-scale trial in an intention to treat analysis by the study statistician.

- Demographic data and baseline features will be compared using independent sample t-test and chi-square test for continuous and categorical variables respectively. (Age, sex, duration of symptoms, co-morbidities)
- Missing values will be handled by single imputation by last observation carried forward to handle missing data at the analytical stage.
- The Fatigue assessment scale (FAS) and the SF-36 (8 domains) from baseline (Day=0) and at 4-, 8-, and 12-week follow up will be analyzed by repeated-measure analysis of variance (treatment x time interaction).
- The Measure Yourself Medical Outcomes Profile (MYMOP) collected at baseline and at week 12 will be analyzed by independent sample t-test if normal or Wilcoxon ran sum test if not.
- The proportion of subjects who 'return to normal' (ie have  $FAS \leq 21$ ) will be compared at week 4 with chi-square test.
- Analyses will be performed using SPSS software, version 26. Two-tailed  $P < 0.05$  will be used to denote statistical significance.
- Evidence of non-significant trends will be noted, and the variability of the FAS will be used for sample size estimation for the full-scale trial.

All modifications to this study will be approved by the Human Subjects Committee. Any adverse

event that occurs temporally related to participation in the study will be documented, whether or not it is considered to be related to the homeopathic medicines. Serious and unexpected adverse experiences will be immediately reported by telephone to the Human Subjects Committee.

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