Vagus Nerve Stimulation as Treatment for Long Covid
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PROTOCOL for Vagus Nerve Stimulation as a Treatment of Long Covid

A surprisingly large number of patients who have survived COVID infection remain ill with a syndrome commonly called Long Covid. A report from this institution[1] reported that the most common symptoms following the acute infection were fatigue, brain fog and headache. Our own work confirmed our hypothesis that many of these patients were so severely ill that they fulfilled case criteria for chronic fatigue syndrome [Mancini et al and Natelson, in press]. There is no current treatment and so physicians in practice have little they can offer such patients. Importantly, a recent paper used vagus nerve stimulation [VNS] via electrodes attached to the left tragus and reported improvement in a number of symptoms of Long Covid[2]. Since cervical VNS is known to downregulate immune function and is currently being tested as a treatment for rheumatoid arthritis, the researchers had hypothesized that improvement might be due to immune downregulation[3]; however there was no evidence of immune dysregulation prior to treatment and thus the hypothesis could not be tested. Although the mechanism for improvement remains unknown, the important thing was that auricular VNS did improve the health status of patients with Long Covid – a condition for which alternative therapies do not exist.

Dr. Natelson has extensive experience with using VNS to treat medically unexplained symptoms. In the first study, the only way to chronically stimulate the vagus was via an implanted stimulator surgically inserted around the left cervical vagus[4]. The study was done on 13 women with fibromyalgia – a pain syndrome associated with substantial fatigue. That study was important for two reasons: First implanted subjects were able to tolerate stimulation usually in most cases without problems and second, five of the patients no longer fulfilled criteria for fibromyalgia at the end of the study – an outcome never reported in any previous drug study. A major problem with this study was its expense – the cost for surgery and device exceeded $25,000.

Unfortunately, efforts to get NIH funding for a blinded follow up study were unsuccessful. Therefore, Dr. Natelson applied for and got funding to use VNS to try to reduce the widespread pain reported by many Gulf War veterans using transcutaneous VNS to the left vagus. Unfortunately, the results of that study were negative[5]. We believe the reason for this lack of effect was that the amount of stimulation in the tVNS study was only 12 min while that for the implanted VNS study was 144 min. Fortunately, the device used in the study on Long Covid clipped to the tragus of the ear and allowed stimulation for 35 min a day over the 10 days of study. We believe the difference in outcome between our own Gulf Vet study and this one on Long Covid has to do with amount of stimulation delivered and the fact that auricular VNS targets afferent fibers only while cervical VNS activates both afferent and efferent fibers. We propose using the same device used in the Long Covid study here. Importantly the transcutaneous device that stimulates the auricular branch of the vagus has been designated non-significant risk (NSR) by the FDA [This designation was given in the process of US regulatory work by the manufacturer]. Therefore this proposed trial will not require any interaction with FDA.

This will be an investigator-initiated pilot study seeking evaluable data on 15 subjects; we are asking the IRB permission to enroll up to 18 subjects in case of drop out. If the outcome is positive, Dr. Natelson will immediately use the results to write an RO1 to do a blinded trial of VNS in Long Covid.

ResearchMatch will be used as a method for identifying and contacting potential subjects. The study specific announcement is included with this submission.

Inclusion Criteria

- Patient had a history compatible with COVID-19 infection at least 6 months previous to today.
- Patient was not admitted to an ICU and did not require oxygen supplementation if hospitalized
- Patient did not have organ pathology during COVID-19 such as pneumonia.
- Patient has been cleared by primary care provider or specialist as having no medical explanation for their symptoms and signs and has had a recent normal ECG (within 4 months).
- Patient continues ill and identifies his/her major problem as being one with fatigue, brain fog or widespread pain. To be included in the study, the patient must have at least one of the following: fatigue sufficient to produce a substantial decrease in activity at work, home, social or school life over the past month where substantial is 3 or higher on a 0 to 5 scale [0, none; 1, mild; 2, moderate; 3, substantial; 4, severe; 5, very severe]; brain fog producing at least a substantial burden over the past month; four quadrant pain producing at least a substantial burden over the past month.
- Sexually active women will be asked to take at home pregnancy tests if willing to participate in this trial. Pregnancy tests will be reimbursed and patients will communicate with the coordinator the results as well as show proof. We will not be testing menopausal woman or women without a sexual partner.
- Patient is 18 to 72 [upper age limit to exclude older patients who may have cover disease producing their symptoms].

Patients will sign informed consent remotely via RedCap. Patients will already have been seen by a physician who will have ruled out any medical cause for the patient's current symptoms. Patients will complete the Chalder Fatigue Scale [11 questions with four possible answers each]; Short Profile of Mood States [37 words concerning which patients provide input on a 5 point scale ranging from not at all to extremely] and the SF-36, a 36 question vehicle to determine the patient's health related quality of life.

The Parasym - The study team will store and dispense the investigational device with the appropriate guidance. The investigational device will be stored with the Principal Investigator within a locked cabinet in a locked room. Upon receipt of investigational device, inventory the shipment, insuring that information on all packing slips (inside and outside containers) matches exactly the contents of the containers including: Quantity, Lot numbers, Quantity per dispensing package. Insure the device and supplies required for study conduct are within an appropriate expiration date - record receipt. Dispensing of Investigational device - Each time study article is dispensed by the Investigator or other member of the research team, the Study Device Dispensing Log will be completed. All investigation devices dispense will include the following labeling: The investigational device or its immediate package shall bear a label with the following information: the name and place of business of the manufacturer, packer, or distributor the quantity of contents, if appropriate, and the following statement: "CAUTION--Investigational device. Limited by Federal (or United States) law to investigational use." The label or other

labeling shall describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions. Documentation on these forms will include: Date of dispensing, Subject's identifying number and/or initials, Lot number(s), Name or initials of individual dispensing, Date/time study device returned by subject • Subject who returned device identified by number and/or initials. After use by the subject, accept and retain all returned, used study devices and store in a locked cabinet in a locked room only accessible by the study team. If the device is missing, document the reasons.

Disposal Parasym – the study article is prepared for return to supplier or disposed of on-site. File copies of study device packing slips, shipment receipts, accountability records, and disposal instructions appropriately. Note return or disposal on the Dispensing Log. Patients that complete the trial will be able to keep the device, those who opt out of the trial prior to completion will have to return the device. This will be written in the dispensing log.

They will then be mailed a Parasym device and have a zoom session with research personnel to assure appropriate use. Subjects will be instructed to use the device as instructed [i.e., attached to the left tragus] for 35 min each day using a current which is not uncomfortable to use. That is, subjects can adjust the current and will asked to increase it to an intensity that is tolerable to use for the 35 min stimulation period. Patient will be able to control the duration of the stimulus. We will advise the subject to give him/herself at least 35 min of stimulation but that they can increase that duration up to an hour pending how they feel [the study on Long COVID used 35 min but in their other trials, they use 60 min].

Patients will be provided the cell number of a member of the research team and will be told to call if they have any problems or questions about the treatment or the study itself.

Patients will be called at 4 and 6 weeks after starting treatment and will again be asked to provide data on the visual analog scales concerning [1] fatigue; [2] brain fog; [3] widespread pain. They will also be asked to complete the Chalder, POMS, the SF-36 and a 7 point question on self rated current state of health [+3 very much better; 0 no change; -3 very much worse] -- Patient Global Impression of Change (PGIC).

Criteria for primary outcome: Improvement on two of the following with improvement defined as: a 0.6 SD reduction in impaired physical function on the SF-36; reduction in severity of the most troubling symptom endorsed by the patient to 0-2 on the visual analog scale [none, mild or moderate]; no longer a “case” on the Chalder; much improved or very much improved on the PGIC.

Criterion for secondary outcome: Improvement by at least 10 points on the short version of the POMS.

Criteria for successful outcome: At least a third of patients fulfill criteria for primary outcome.

At the conclusion of the study, patients will be able to keep their Parasym VNS device.

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3. Koopman FA, Chavan SS, Miljko S, Grazio S, Sokolovic S, Schuurman PR, et al. Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. *Proc Natl Acad Sci U S A*. 2016;113:8284-8289

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