The Benefit of Mindfulness-Based Intervention Using A Wearable Wellness Brain Sensing Device in the Treatment of Post Covid Symptoms

NCT05199233

07 Nov 2024

General Study Information

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Study Title: The Benefit of Mindfulness-Based Intervention Using A Wearable Wellness Brain Sensing Device (Muse-S™) in the Treatment of Post Covid Symptoms

As of 07 Nov 2024

Research Question and Aims

Hypothesis:
Post acute sequelae of SARS-CoV-2 infection (PASC), also known as "long haul covid" or Post-COVID Syndrome, is a significant cause of morbidity and disability in patients who have had COVID-19 with an estimated 10-30% of patients developing PASC with symptoms lingering for months and even years. These symptoms occur in a typical pattern, often including fatigue with post-exertional malaise, dyspnea, widespread pain, subjective cognitive dysfunction (often referred to as "brain fog"), and orthostatic intolerance and remain persistent. These can manifest in the post-covid patient as difficulty breathing or shortness of breath, tiredness or fatigue, difficulty thinking or concentrating, cough, chest and/or stomach pain, headache, palpitations, joint and/or muscle pain, parasthesias, diarrhea, increased anxiety and stress, as well as sleep problems.

We postulate that using a novel biofeedback-assisted meditation device (Muse-S™) daily can enhance calm state brain activity and parasympathetic nervous system activity in post-covid patients. We hypothesize that greater amount of time the patient uses this tool will directly correlate with improvements in stress, resilience, and overall quality of life.

Aims, purpose, or objectives:
In this study 60 patients diagnosed with Post-Covid Syndrome (PASC) at Mayo Clinic Rochester will be enrolled in this study.

Primary:
1. To study the feasibility of using a wearable brain-sensing wellness device (Muse-S™) to potentially reduce stress and anxiety during Post-Covid, which is characterized with increased stress and anxiety.
2. To assess the association between usage of the wearable brain-sensing wellness device (Muse-S™), and quality of life (QOL), subjective stress, anxiety, cognition, - through self-assessment surveys.

Exploratory:
1. To collect data at month 6 (3 months post end of treatment) on continued use of Muse-S™ past the treatment phase, as a proxy for lifestyle changes.

The primary outcome will be the adherence to the Muse-S™ by summarizing the frequency of use and duration of use each time it was accessed.
The secondary outcomes will include:

- change in quality of life (QOL), stress, anxiety, and cognition, score over time

Background:

According to the CDC, new or ongoing symptoms of long COVID may include difficulty breathing or shortness of breath, tiredness or fatigue, difficulty thinking or concentrating, cough, chest and/or stomach pain, headache, heart palpitations, joint and/or muscle pain, pins and needles, diarrhea, sleep problems; all of which can increase anxiety and stress in the post-covid patient.

Integrative Medicine has introduced many mind-body therapies for addressing mental stress. The top stress relievers recommended by Mayo Clinic include: getting active, eating a healthy diet, avoiding unhealthy habits, meditation, laughing more, connecting with others, asserting yourself, practicing yoga, getting enough sleep, keeping a journal, exploring music and being creative, seeking counseling[2]. Among all of these potential options, meditation is the easiest to incorporate in a current lifestyle yet most difficult to undertake without proper training and guidance at the beginning. Muse-S™ is a clinical grade, headband-style wireless EEG system designed to interact with a mobile device (a smartphone or tablet) (https://choosemuse.com). In combination with the Muse-S™ APP running on iOS or Android smartphones, Muse-S™ converts EEG signals measured over the frontal and temporal cerebral cortices into measures of brain state. At the same time Muse-S™ can also guide the user through the meditation steps. Calibrated to an individual user, Muse-S™ distinguishes between active and calm brain states to provide real-time performance feedback, and helps users realize the benefits of mindfulness practice in an engaging and accessible manner. Muse-S™ also has a PPG sensor that tracks heartrate during meditation sessions as well. This has been tested in a prior study by some of the current study team (SP and ITC), with patients undergoing breast cancer surgery[3] and is currently being test in patients with fibromyalgia who concurrently experience pain (ITC and RG) and in healthcare providers who are under stress (ITC).

Study Design and Methods

Methods:

All study participants will receive the Muse S™ Headband system at study entry and will be asked to utilize it at least 4 times per week for a minimum of 10 minutes each time over a period of 3 months (12 weeks). They will be followed for a period of 6 months (3 months of treatment and 3 months post treatment) according to the schedule below.

	Consent /screen /baseline	**Treatment Phase**				**Follow up Phase**
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**
Visit Type	**Face to Face**	**Phone**	**Phone/ Email**	**Phone/ Email**	**Face to Face/ Phone/ Email**	**Face to Face/ Phone/ Email**
Visit Days	**0**	**2**	**30**	**60**	**90**	**180**
Consent/Screening/ Enrollment						
Informed Consent	X					
Inclusion/Exclusion	X					
Demographic and History Form	X					
Safety Data						
Depression	X		X	X	X	X
Adverse Events [1]			X	X	X	X
Concomitant Medication [2]	X		X	X	X	X
Intervention						
Instructions for Muse-S™ & Fitbit® Tracker	X					
Muse-S™ use	X		X	X	X	
Fitbit® Tracker		X			X	X
Outcome						
CBS Cognitive Tests	X				X	X
Anxiety	X		X	X	X	X
Cognition Function	X		X	X	X	X
Emotional Distress	X		X	X	X	X
Quality of Life	X		X	X	X	X
Resilience	X		X	X	X	X
Self-Efficacy	X		X	X	X	X
Sleep	X		X	X	X	X
Stress Scale	X		X	X	X	X
Satisfaction Survey						X
End of Study Forms						X

1 = For visit 5 & 6 only serious adverse events will be newly collected; **2** = For visit 5 & 6, only newly added concomitant medications will be collected

Study Visit Windows:
Each visit will have a window from the midpoint of the prior visit to the midpoint of the latter visit.
Data Collection:

Subjects will have the options of completing study surveys/questionnaires online via email link to REDCap prior to study visit. If not completed by the time the study visit takes place, the coordinator can provide the iPad digital version of the survey/questionnaire to the subject for the in-person visits or can interview the patient via phone for the telephone visits. If a subject misses a visit, the study staff will connect with the subject to collect what study data is appropriate through a simple virtual connection (email redcap surveys or telephone interview of surveys). Data Collection in this study will utilize REDCap[4]. All other data collection will be entered directly into a password protected system.

Assessments:

Safety:

- Depression: The PHQ-2[5,6] is a validated and frequently used self-report measure of depressive symptoms comprising of 2 questions, which were derived from the PHQ-9[7,8].

Outcomes:

- Demographics Form: This form collected demographic and other lifestyle history of the research subject.
- Quality of Life: Will be measured using the *Linear Analogue Self-Assessment (LASA)*[9-11]. This is a six-item measure of quality of life (QOL), in which QOL is conceptualized as a multidimensional construct with five domains (physical, functional, emotional, spiritual, and social). This data will be collected at screen (prior to any treatment), day 30, day 60, day 90 end of treatment, and day 180 end of study (3 months post last treatment).
- Anxiety: *State-Trait Anxiety Inventory (STAI-Y1)*[12-16] This 20-item self-report measure indicates the intensity of feelings of anxiety; it distinguishes between state anxiety (a temporary condition experienced in specific situations) and trait anxiety (a general tendency to perceive situations as threatening). It uses a 4-point visual analog scale, and the participant indicates how they feel in the moment (1 = not at all to 4 = very much so).
- Stress: Will be evaluated through the *Perceived Stress Scale (PSS)*[17,18]. The PSS is a 10-item Likert scale that measures global life stress by assessing the degree to which experiences are appraised as uncontrollable or unpredictable. Scores can range from 0 to 40, with higher scores indicating greater perceived stress. Reliability is reported as 0.85, with Cronbach alphas ranging from 0.75-0.86.
- Resilience: Will be evaluated through the *Connor-Davison Resilience Scale 10 (CD-RS10)*[19]. This is a 10-item, Likert scale, validated scoring system. The CD-RS10 is a reliable means of assessing resilience and is most often used in medical and/or disaster studies[20].

Sleep Quality:
(*ASCQ-Me® v2.0 Sleep Impact - Short Form*[21]) is an effective instrument used to measure the impact sleep has on overall health in adults. The ASCQ-Me Sleep Impact SF is equivalent to the PROMIS Sleep Disturbance and Sleep-Related Impairment Surveys except the scoring is reversed.[21] The PROMIS surveys indicate greater symptom burden as the score goes higher and the ASCQ-ME survey indicates better health as the score goes up. The Sleep Impact Scale consists of 5-item, likert scale, validated, scoring system.[22] The 5 questions focus on experiences in the prior 7 days.

Self-efficacy (*Short Form 4a – 4 items*)[23]: This PROMIS Self-efficacy Scale defines self-efficacy as confidence in one's ability to successfully perform specific tasks or behaviors. It assesses confidence in one's ability to successfully perform specific tasks or behaviors related to one's health in a variety of situations. Each item on the measure is rated on a 5-point scale (1=I am not at all confident; 2=I am a little confident; 3=I am somewhat confident; 4=I am quite confident; 5=I am very confident)

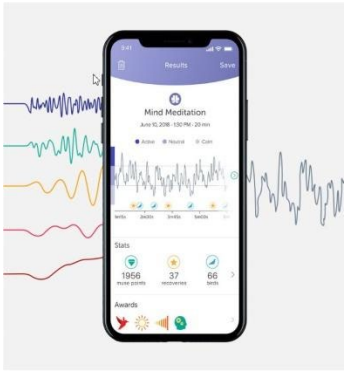
- Emotional Distress: Adapted from the Emotional Distress-short form 7a (7 items)[23]. The PROMIS Anxiety item banks assess self-reported fear (fearfulness, panic), anxious misery (worry, dread), hyperarousal (tension, nervousness, restlessness), and somatic symptoms related to arousal (racing heart, dizziness). Anxiety is best differentiated by symptoms that reflect autonomic arousal and experience of threat. Only one behavioral avoidance item is included in the adult item bank; therefore, behavioral fear avoidance is not fully evaluated. The anxiety measures are universal rather than disease specific. The original adult short form (7a), which is being used in this study was constructed by the domain team with a focus on representing the range of the trait and also representing the content of the item bank. Domain experts reviewed short forms to give input on the relevance of each item. Psychometric properties and clinical input were both used and likely varied in importance across domains. Each item on the measure is rated on a 5-point scale (1=never; 2=rarely; 3=sometimes; 4=often; and 5=always) with a range in score from 7 to 35 with higher scores indicating greater severity of anxiety. The original form instructed participants to think about the past seven days, but for purposes of this study, we will reword the question to focus on the current time ('now').
- Cognitive Function (*short form 6a - 6 items*)[23]: The PROMIS Cognitive Function and Cognitive Function Abilities Subset item banks assess patient-perceived cognitive deficits. Facets include mental acuity, concentration, verbal and nonverbal memory, verbal fluency, and perceived changes in these cognitive functions. The extent to which cognitive impairments interfere with daily functioning, whether other people observe cognitive impairments, and the impact of cognitive dysfunction on quality of life are also assessed.
- Cognitive Testing: *The Cambridge Brain Science* (CBS) web-based tests were developed in the laboratory of Dr. Adrian Owen, Canada Excellence Research Chair in Cognitive Neuroscience and Imaging (owenlab.org), over the course of his 25-year career. The tests are self-administered, do not require supervision, and effectively assess aspects of cognition including reasoning, memory, attention and verbal ability. Over 300 scientific studies have been run to date using the CBS tests, yielding numerous publications in leading academic journals[24-27]. The tests have been validated in studies of patients, brain imaging studies of healthy volunteers and in several large-scale public studies involving tens of thousands of volunteers. They have proven to be efficient and sensitive measures of cognitive performance and can be used to consistently monitor participants and patients due to the unlimited versions of problem sets within each task. The 12 tasks (*see CBS Task Overview.pdf) can be customized to use specific tasks if a shortened assessment is required for research. A custom 3-task assessment would take approximately 10 minutes and for the purposes of this study, we would recommend the use of the following tasks:
  1) **Double Trouble –** 90 seconds (*measure of Response Inhibition*) - Version of the Stroop task. It is a "double" version in which there can be up to two incongruities (the top word and the bottom words), so is a little more difficult than other versions and has been sensitive to a range of interventions known to improve attention, response inhibition, or cognition in general. Response times and accuracy can be separately calculated for each difficulty level (congruent /incongruent / double incongruent), in addition to an overall score.
  2) **Feature Match –** 90 seconds (*measure of Attention*) - Version of a "spot the difference" game. It uses areas of the brain involved in tuning attention and requires both fast response time and accuracy to get a good score.
  3) **Monkey Ladder**- *(measure of Memory)*- Sets of numbered squares are displayed on a screen at random locations. After a set time the numbers disappear leaving blank squares. The participant must respond by clicking the squares in ascending numerical sequence. Difficulty is increased or

decreased by one number depending on if the participant was correct in the previous trial. After three errors the task ends. Outcome is measured by maximum level completed and the average score of the number of successfully completed tasks divided by the number of successfully completed problems.

- Satisfaction with the program: This questionnaire is adapted from *Was it Worth it Questionnaire (WIWI)*[28] to measure study and Muse-S™ satisfaction. It will be administered to the participants after completing the intervention at the end of the study, probing their satisfaction with the research study. These data could be used to assess the feasibility of the intervention by asking the patient if the entire research experience was worth it for them.

Adherence to Intervention:

- Adherence to the Muse-S™ & *Fitbit*® *Tracker* will be assessed by de-identified data available within the cloud, provided by InteraXon and Fitbit® dashboard. InteraXon only has information per subject through subject ID (as was provided by Mayo Clinic site), so when the cloud data is provided to Mayo, it will be linked to each subject through their study ID. Fitbit® has information that the subject will give at time of downloading application. For each a de-identifiable email address will be used. Study team members will review the data from each application report and contact subjects that data is not being collected on.



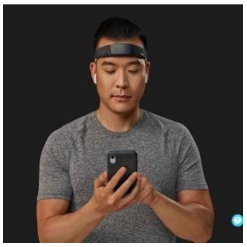
Intervention:

- The Muse-S™ Headband system: The Muse-S™ Headband system is a brain sensing headband that measures brain activity by detecting electrical impulses created by the brain. The Muse-S™ Headband system uses a series of focus attention training methods to train the brain. Each focus attention session can vary in length, with the ideal being a minimum of 10 minutes, and has been shown to reduce stress, anxiety, and improve focus and productivity. The Muse-S™ Headband system has seven sensors with four channels of EEG data for an accurate, high-quality experience. The battery life is approximately five hours and uses an industry-standard micro-USB charger. Sixty Muse-S™ Headband systems will be provided by the manufacturer at no cost in support of this study.

Use of Muse-S™ Headband systems will be demonstrated to each participant prior to their first mindfulness practice session, which will be completed during the baseline visit with the study coordinator. The study coordinator will present the participant with detailed instructions on how to begin each session. The frequency of the sessions thereafter will be at the participant's discretion according to the study's requirements (daily practice). Mindfulness training will follow the protocol in the Muse-S™ APP, which follows a standard breathing exercise with EEG brain state feedback through the mobile device, as designed by a panel of experienced mindfulness practitioners. In short, the Muse-S™ functions like a *FitBit*® like device for the brain.

The study participants can access 3 different types of meditation while using the Muse-S™ Headband system. They are as follows:

- **Mind Meditation** uses the Muse-S™ headband to track the user's brain activity during meditation and translates the brain's activity into guiding sounds. This is a classic focused attention on the breath meditation, where you get real time feedback on your brain. Users get real time feedback to know when they are in focused attention and when their mind is wandering and are cued to return to a state of focused attention (meditation state). Users also see data from their brain after the meditation. Real time feedback during Mind Meditation is the Muse-S™ signature meditation and teaches the fundamentals of a meditation practice in remaining in a calm focused attention state and being able to move your mind away from distracting thoughts. This teaches them the skill to notice their minds and learn to direct themselves out of their discursive mind and onto a neutral object like their breath, while giving them neurofeedback to guide them when they are "doing it right" and reinforce the learning. It is recommended that Muse Mind be done daily for a minimum of 5 minutes per day. Users can do more if they choose.
- **Guided Meditation -** These are different breathing exercises where different breathing techniques, such as box breathing, 6-4 breathing, etc., are taught to help the individual regulate their breath. The participant is given real time feedback to keep them breathing along in time with the guide.



- **Sleep section & Go-to-sleep Meditations -** Muse's sleep section can be used to both help people fall asleep and stay asleep, as well as to track sleep.

  In the sleep section of the app, there are different kinds of experiences that can help participants fall asleep and fall back asleep if they wake in the night referred to as Go-to-sleep intervention. The Sleep Journeys, Guidances, and Soundscapes are different kinds of content that include a mix of visualizations, guided meditations designed for sleep, bedtime stories along with biofeedback that entrains the listener into sleep. Participants choose which type of experience they prefer, and this variation is required as some like voices, some like bedtime stories, some like only ambient sounds.

  All the content is designed to help you fall asleep, and also fall back asleep when you wake up in the night. There is also some new content that is responsive. For instance, as you are falling asleep, it quiets, or if you wear the headband in the night it is able to detect that you've woken up and will gently begin to play again to lull you back to sleep.

  Go-to-sleep Meditations use the headband and are guided meditations that can be combined with an audio sound scape generated from your biosignals (heart rate, brain and movement). Sleep Journeys are designed to help you fall asleep faster. They are intended to be used in bed while you fall asleep to help calm your body and mind and entrain you into sleep. If you fall asleep with the headband on you can wear it through the night if you wish. Some people find Go-to-sleep journeys deeply relaxing and use them during the day as a relaxation tool as well.

All study participants will have access to The Muse-S™ Headband system's customer service team based in Toronto, Canada, by telephone and email for assistance should they experience technical problems with the device.

- Server Data: As the subject completes any Muse-S™ sessions, the information from these sessions will be uploaded to the Muse-S™ iCloud server hosted by Google. Each subject will

be able to see their own data at the end of each session, and data from the previous session stored in the "me" tab in the app. Subject to the study organizers ensuring that the subjects have signed the appropriate consents, study organizers will have access to each subject's data to monitor compliance, performance and outcomes, but will not get access to Journal entry information (if subject chooses to write a Journal entry). These data that the study organizers will have access can include the study-specific identification number, gender, and age of the subject, the session type, the time and duration of each session, EEG data, heart rate (PPG) data, and the performance per session. Interaxon's privacy policy, which can be found at www.choosemuse.com/privacy will apply to Interaxon's use of the subjects' data. In order to maximize protection of the individual's privacy, the study organizers will ensure that the subjects are assigned anonymized email address and names for use in the Muse -S™ application and when contacting the Muse-S™ customer support. To ensure that no health data is shared with Interaxon, the study organizers have agreed to ensure that no health data will be shared. At the end of the study, the data collected in Google iCloud Server associated with study email addresses will be deleted.

- The Muse-S™ steps include: 1) Open the Muse-S™ App on subject device. 2) select meditation type 3) if meditating with the headband, turn on the Muse-S™ headband. It will pair via bluetooth to the app 4) put on headband (if doing a meditation with headband) 5) meditate 6) add any journal or mood entry if desired 7) review results
- Cleaning the Muse-S™: Each patient will be given a brand new, out-of-the-box Muse-S™ Headband system. If cleaning must occur, the entire Muse-S™ including the headset can be wiped down with a standard disinfectant wipe. The band can also be hand-washed gently with soap and water. The module on the band is not waterproof but can be wiped with disinfectant.

Tracking Vitals:

Fitbit Tracker:
Participants will be asked to wear their Fitbit® 24/7 except during a time of recharging. Fitbit® Data will be collected at visits 2, 5 and 6 by the study team and from participants Fitbit® app that has been downloaded on their personal electronic device. The data collected will include Heart Rate, steps, sleep quality, and blood oxygen saturation level (SpO_2).[29] A Fitbit® account will be created by each study participant with the help of the research coordinator to allow us to track study participation. Information collected from the Fitbit® app will be logged into the database. This approach for working with the Fitbit has been successfully used in the past by Mayo investigators.[30]

Subject Retention:
Participants will not be remunerated for participating in this study, but they will be allowed to keep the Muse-S™ Headbands and Fitbit®.

Study Design:
We will use standardized procedures to ensure uniform instructions and support for all subjects for the recruitment, screening, and study entry.

Recruitment:

Patients with Post-Covid Syndrome will be recruited from the Mayo Clinic Practice. The study staff will inform participants of the study during practice meetings, and if the participants indicate interest, they will connect with research staff and arrange a time to meet to begin the consent process.

Participants will not be reimbursed for their time spent in the study, but all participants will be given the option of keeping the Muse-S™ Headband system as well as the Fitbit® tracker for continued use post study participation.

Consent and Screen:
Study coordinator will meet with the potential participant who has expressed an interest in participating in the study. The study coordinator will begin by introducing the study details, and after determining that the subject has continued interest in study participation, will move on to the study consent. If the subject chooses to consent, the study coordinator will screen the participant for study entry inclusion/exclusion criteria.

Once a subject meets all entry criteria , the post-covid phenotype, as designated by the Post-Covid Clinic staff, will be recorded and the subject will begin study participation. At this point, they will be asked to complete the study surveys/questionnaires. Finally, a POCUS will be performed during this first face to face visit if one has not been completed clinically in the previous 2 weeks.

Please note: Patients must have access to an iOS or Android capable device to take part in this study in order to interact with the Muse-S™ Headband system.

Treatment phase:
During the first three months of study, participants will be asked to complete the online study intervention using the Muse-S™ headband. Participants will be contacted via telephone and online (REDCap) for study visits at day 2, 30 and 60. At day 90, they will be asked to return to the clinic for an in-person visit (telephone and online will be alternatives).

Study Follow-Up Visits:
The study will consist of a 6-month visit post baseline (3-month post end of intervention). Participants will be asked to complete an in-person visit, if possible (telephone and online will be the alternative), which will include a second POCUS exam.

Subject Information

Target accrual: We plan to recruit 80 patients diagnosed with Post-Covid Syndrome at Mayo Clinic with the intent of enrolling 60 to study.

Subject population: A total of 60 patients diagnosed with Post-Covid Syndrome at Mayo Clinic who meet the following study criteria:

Inclusion Criteria:
1. 18 years of age or older at time of consent
2. Identified with Post-Covid Syndrome (PASC) at Mayo Clinic Rochester:

3. Not pregnant by subject self-report at time of consent
4. Have the ability to provide informed consent
5. Have the ability to complete all aspects of this trial
6. Have access to an iPhone, iPad, or Android device
7. Have no contraindicating comorbid health condition which would interfere with the proper use of the Muse-S™ system, as determined by the clinical investigators

Exclusion Criteria:
1. Used an investigational drug within the past 30 days
2. Anyone that is not on a stable dose of medication for anxiety, depression or sleep
3. Currently (within the past 3 weeks) been practicing mindfulness training on a weekly/regular basis
4. Currently (within 3 weeks) has been enrolled in another clinical or research program which intervenes on the patients' QOL, or stress
5. An unstable medical or mental health condition as determined by the physician investigator

Data Analysis

Data Analysis Plan:
Demographic characteristics are described using mean and standard deviations or frequencies and percentages based on the type of variable. For the primary aim of assessing feasibility, descriptive statistics and graphical displays will be presented for data obtained on frequency and duration of use over the 12 weeks of treatment. A linear mixed model with repeated measures for each time point that stress and sleep were taken will be utilized to estimate the association between the number of sessions spent using the Muse-S™ with the stress and sleep level outcome. As secondary outcomes, the results of the LASA, resilience, coping, and cognitive testing will be analyzed using similar mixed models. In all cases, results will be summarized using point estimates and corresponding 95% confidence intervals. Given the number of outcomes assessed, all analyses will be considered exploratory.

Endpoints:
Primary Hypothesis:
a) Post Covid patients enrolled in this study will find the Muse-S™ Headband system easy to use and will use it per protocol.

Secondary Hypotheses:
a) Stress score will be lower and sleep score will be improved when compared to the baseline measures for those who use the Muse-S™ system as directed.
b) As the use of the Muse-S™ system increases, QOL, resilience and coping will improve.

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