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ORIGINAL ARTICLE

Psychophysiologic Symptom Relief Therapy for Post-Acute Sequelae of Coronavirus Disease 2019

Michael Donnino, MD; Patricia Howard, BS; Shivani Mehta, BA; Jeremy Silverman, BA; Maria J. Cabrera, BA; Jolin B. Yamin, PhD; Lakshman Balaji, MPH; Katherine M. Berg, MD; Stanley Heydrick, PhD; Robert Edwards, PhD; and Anne V. Grossestreuer, PhD, MSc

Abstract

Objective: To determine if psychophysiologic symptom relief therapy (PSRT) will reduce symptom burden in patients suffering from post-acute sequelae of coronavirus disease 2019 (COVID-19) (PASC) who had mild/moderate acute COVID-19 disease without objective evidence of organ injury.

Patients and Methods: Twenty-three adults under the age of 60 years with PASC for at least 12 weeks after COVID-19 infection were enrolled in an interventional cohort study conducted via a virtual platform between May 18, 2021 and August 7, 2022. Participants received PSRT during a 13-week (approximately 44-hour) course. Participants were administered validated questionnaires at baseline and at 4, 8, and 13 weeks. The primary outcome was a change in somatic symptoms from baseline, measured using the Somatic Symptom Scale-8, at 13 weeks.

Results: The median duration of symptoms before joining the study was 267 days (interquartile range: 144, 460). The mean Somatic Symptom Scale-8 score of the cohort decreased from baseline by 8.5 (95% CI: 5.7-11.4), 9.4 (95% CI: 6.9-11.9), and 10.9 (95% CI: 8.3-13.5) at 4, 8, and 13 weeks, respectively (all $P<.001$). Participants also experienced statistically significant improvements across other secondary outcomes including changes in dyspnea, fatigue, and pain (all $P<.001$).

Conclusion: PSRT may effectively decrease symptom burden in patients suffering from PASC without evidence of organ injury. The study was registered on clinicaltrials.gov (NCT 04854772).

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An estimated 4%-35% of people infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) experience prolonged symptomatology long after the acute phase of their infection.[1-3] Although the most common symptoms include chronic pain, fatigue, dyspnea, and "brain fog," an array of other symptoms have also been reported. The World Health Organization has defined such post-acute sequelae of coronavirus disease 2019 (COVID-19) (PASC) as those that are still present 3 months after the onset of symptomatic infection, have persisted for at least 2 months, and are not explained by alternative diagnoses.[4] According to various reports, 2-4 million Americans have been unable to work because of PASC,[5] with $2.6 trillion projected in costs to the economy.[6] PASC can result from identifiable organ injury (ie, that detected by imaging, pulmonary, and cardiac testing, etc.) typically after severe, acute COVID-19 disease. However, a significant number of individuals with PASC report only mild or moderate acute infection and have no clearly identifiable organ injury on the basis of traditional clinical testing.[7]

The etiology for patients with PASC who had mild/moderate COVID-19 disease and no identifiable organ injury remains elusive. There have been a number of reports on the potential etiologies including capillary microclots,[8] gut viral reservoirs,[9] low cortisol levels,[10] mitochondrial dysfunction,[11] endothelial dysfunction,[12] subtle changes on

From the Department of Emergency Medicine (M.D., P.H., S.M., J.S., M.J.C., J.B.Y., L.B., A.V.G.); Division of Pulmonary, Critical Care, and Sleep Medicine (M.D., K.M.B.), Beth Israel Deaconess Medical Center, Boston, MA; New York Institute of Technology College of Osteopathic Medicine, Old Westbury. NY (S.M.); Department of Anesthesiology, Pain Management Center, Brigham and Women's Hospital, Harvard Medical School, Chestnut Hill, MA (R.E.).

cardiac magnetic resonance imaging (MRI),[13] autoimmune reactions,[7] and the presence of a persistent virus/spike protein,[14] but these findings have not been confirmed and/or shown to be the direct cause of the symptoms. In contrast, Sneller et al.[7] examined 186 adults with PASC at least 6 weeks after laboratory-confirmed COVID-19 infection and found no evidence of persistent viral infection, autoimmune reaction, or abnormal immune activation. This report did find an association of anxiety with the development of PASC, a relationship also reported by Wang et al.[15] However, the concept that psychological factors may drive PASC may not seem to explain reported idiopathic physiologic changes such as inappropriate tachycardia or postural orthostatic hypotension.[16]

One conceptual model that explains both physical and psychological PASC symptomology is that such symptoms are psychophysiologic in nature. Psychophysiologic responses or syndromes are those that have physical/physiological outputs centrally mediated in the brain. To date, psychophysiologic processes have been commonly described in the context of acute responses, with the physiologic outputs ranging from benign (eg, blushing response) to mildly pathologic (eg, vasovagal syncope) to potentially life threatening (eg, Takotsubo's cardiomyopathy). Long-term psychophysiologic processes tend to be less recognized but have been recently described in some chronic pain syndromes[17,18] and have been reported in entities such as post-traumatic stress disorder.[19-21]

Our scientific premise, on the basis of initial encounters with patients with PASC without organ injury and an assessment of the literature, is that patients with PASC with mild/moderate initial COVID-19 infections and no identifiable organ injury could be suffering from a psychophysiologic process developed during or shortly after acute infection. On the basis of a similar premise of psychophysiologic origins for many forms of idiopathic pain,[17,18] we developed an intervention to treat such conditions [psychophysiologic symptom relief therapy (PSRT)] and successfully tested this approach in a cohort of patients with nonspecific back pain.[17] We hypothesized that a modified version of PSRT would attenuate a variety of symptoms in patients with PASC. To test this hypothesis, we evaluated the impact of PSRT in reducing somatic symptom burden as measured by Somatic Symptom Scale-8 (SSS-8). We secondarily examined the impact of PSRT on chronic fatigue, functional activity, dyspnea, pain intensity, anxiety from pain, pain interference with life activities, gastrointestinal (GI) symptoms, and "brain fog."

METHODS

Study Design and Setting

This was an interventional cohort study in which all participants received PSRT and served as their own control. The study team did not prescribe any medications for pain and/or other symptoms and did not interfere with treatment decisions made by participants and their clinical care teams.

The study was conducted between May 2021 and August 2022 using a virtual/video platform and approved by the Institutional Review Board of Beth Israel Deaconess Medical Center in Boston, MA. Participants were recruited through physician referrals, flyers, and social media, and provided written informed consent. The study was registered on clinicaltrials.gov (NCT 04854772). We recruited participants primarily through 3 sources: flyers, Facebook ads, and an institution-specific research recruitment website. We described our study as "evaluating a mind-body approach to reducing COVID Long Haul Syndrome Symptoms." Participants were screened for their willingness to consider a mind-body approach for treating long COVID and were not considered eligible if they were not open to this type of approach.

Inclusion Criteria

Adults aged 18-60 years old with new symptoms attributed to PASC, such as extremity pain, dyspnea, headaches, chest pain, and fatigue occurring after an acute phase of COVID-19 disease, confirmed by a positive SARS-CoV-2 antigen or polymerase chain reactiontest (or confirmed SARS-CoV-2 antibodies before vaccination), were included. PASC symptoms must have persisted $\geq$12 weeks after the end of the acute COVID-19 infection and $\geq$1 month without identified organ damage or an identified organic disease

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unrelated to COVID-19. Eligible symptomatology was defined as scoring ≥3 on the SSS-8 survey at a frequency of ≥4 days/week. Eligible participants were also required consent to a mind-body intervention during the screening interview to participate.

Exclusion Criteria

Potential participants were excluded if they were >60 years of age (because of increased risk of organic symptom etiology) or had diagnosed non-COVID-19 organic disease as a cause of PASC symptoms, such as (but not limited to) malignancy, neurologic disorders (eg, amyotrophic lateral sclerosis), or autoimmune disease. Patients with previous severe COVID-19 disease, defined as having been admitted to the intensive care unitor by objective evidence of ongoing organ injury (eg, persistent chest radiographic abnormalities, myocarditis), were excluded. Participants suffering from chest pain or dyspnea with identified lung or cardiac injury (eg, chest radiograph abnormalities, cardiac ultrasound showing myocarditis, depressed ejection fraction) were excluded. Patients diagnosed with significant psychiatric comorbidities (eg, schizophrenia, dementia) were also excluded.

Intervention

The rationale for PSRT is that nonspecific pain and other symptoms can be somatic manifestations of psychophysiological processes caused and exacerbated by stress, repressed emotions, and other psychological processes.[22,23] These symptoms can then be perpetuated not only by ongoing stressors but by a classical conditioning-like model. We recently published a randomized controlled study assessing the efficacy of PSRT in people suffering from nonspecific chronic back pain.[17] The PSRT treatment paradigm used for that study was adapted to address the broader symptom profile in PASC for this trial. The PSRT course was led by a physician (author M.D.) and a mind-body expert (author P.H.), with one session taught by a collaborator (R.T. in the Acknowledgments) who had found symptom relief from the same approach.

The goal of PSRT is to address underlying stressors and psychological contributors (such as underlying conflicts and aversive affective states) to mitigate conditioned symptom responses and fear-avoidant behaviors that are triggered by these factors. The first 4 weeks of PSRT comprised group classes twice per week (90-120 minutes per class) covering psychophysiologic education, desensitization (including visualization techniques), and emotional awareness exercises such as expressive writing (see Supplemental Materials for more detailed description, available online at http://www.mcpiqojournal.org). The final 9 weeks of PSRT is the mindfulness-based stress reduction course as outlined by the Center for Mindfulness at the University of Massachusetts.[24] This portion consisted of classes once per week for 90-120 minutes per class and focused on providing participants with mindfulness skills such as practicing awareness of breath, body scan, and sitting meditation. No new elements of PSRT were introduced but reminders about elements of the work were provided during the mindfulness-based stress reduction course. The detailed protocol of PSRT is described in the Supplemental Materials.

SAMPLE SIZE JUSTIFICATION

Because of the novelty of PASC, data on our primary outcome, the SSS-8 somatic symptoms score, were not available in this population. We, therefore, used the overall population mean SSS-8 score (3.2±4.0),[25] as the value that we hypothesized would be meaningful for participants to return to and estimated that score would represent a 45% reduction from baseline, on the basis of the effect size in a prior study in back pain.[17] Assuming a baseline SSS-8 of 5.8±4.0 and a 13-week SSS-8 of 3.2±4.0, 22 participants provided 83% power with α=.05 to detect this difference.

STATISTICAL ANALYSES

Descriptive statistics used frequencies and percentages for categorical variables and either means with standard deviations or medians with interquartile ranges (IQR) for continuous data, on the basis of distribution. A paired Student's t-test or Wilcoxon signed-rank test was performed for continuous data, as appropriate, to compare differences within participants over time. No adjustment was made for multiple comparisons. As a post hoc analysis, a

linear mixed model was run on the primary outcome of SSS-8, using scores at each time point calculated by subtracting that time's values from the baseline. Statistical analyses were performed using R Statistical Software (v4.1.1; R Core Team 2021), Stata 17.0 (College Station, TX), and a two-sided P value $<.05$ was considered significant.

MEASURES

Electronic surveys delivered through REDCap[26] were administered at baseline (0 weeks) and subsequently at 4, 8, and 13 weeks after enrollment. All of the scales described below were administered at each time point.

Primary Outcome

Change in somatic symptoms was assessed by the SSS-8.[25] Because the SSS-8 was measured at baseline and 4, 8, and 13 weeks and assessed as a change between the time point and baseline, we a priori chose the change between baseline and 13 weeks to be the primary outcome. The changes in 4 and 8 weeks were considered secondary. The SSS-8 asks participants to rank how bothered they have been by 8 separate groups of symptoms over the past week. Each symptom group is ranked from 0 (not at all) to 4 (very much). Results from the SSS-8 are summed to an overall score that ranges from 0 to 32. Scoring of the SSS-8 somatic symptom burden is categorized as follows: none to minimal (0-3 points), low (4-7 points), medium (8-11 points), high (12-15 points), and very high (16-32 points).[25]

Secondary Outcomes

Secondary outcomes included changes in pain intensity, anxiety from pain, fatigue, dyspnea, GI distress (as measured in the SSS-8), "brain fog," and physical functioning. These changes were measured by the Brief Pain Inventory Questionnaire,[27-29] Pain Anxiety Symptom Scale,[30] Fatigue Severity Scale (FSS-9),[31] Multidimensional Dyspnea Profile,[32] the GI component of the SSS-8, and Patient-reported Outcomes Measurement Information System (PROMIS-29).[33]

"Brain fog" was measured by an additional question in the traditional SSS-8 format: "During the past 7 days, how much have you been bothered by brain fog (difficulty thinking or concentrating)?" Response options were "not at all (0), a little bit (1), somewhat (2), quite a bit (3), and very much (4)." Because this additional question is not formally part of the SSS-8 and has not been validated, we reported it separately from the summed SSS-8 score.

The Brief Pain Inventory Questionnaire (Short Form) is a 9-item instrument that measures pain intensity and interference in daily life.[27-29] Participants were asked to highlight areas where they experience pain on a full body diagram and respond to 9 questions regarding pain intensity in which participants ranked their pain from 0 ("no pain") to 10 ("pain as bad as you can imagine"). This was followed by a 7-item assessment of pain interference in which participants ranked how their pain has interfered with facets of daily life (eg, General Activity, Mood, etc.) on a scale of 0 ("Does not Interfere") to 10 ("Completely Interferes"). Pain intensity was calculated by averaging the scores from the first 4 elements (average pain, worst pain, least pain, and current pain). Pain interference was calculated by summing the 7 rated components.

The 20-item Pain Anxiety Symptom Scale measures a participant's anxiety and fear relating to their pain.[30] Participants were asked how often they engage in thoughts or activities (eg, "I think that if my pain gets too severe, it will never decrease"). Each item was ranked on a 6-point frequency scale from 0 ("Never") to 5 ("Always"). The scores from each question were summed to create an overall score and range from 0 to 100.

In the FSS-9,[31] participants ranked how 9 statements regarding fatigue (eg, "Fatigue interferes with my physical functioning") relate to their life in the past week on a scale of 1 (Strong Disagree) to 7 (Strongly Agree). The FSS-9 score was the sum of all of the statement scores except the response to the first question. Scoring ranges from 0 to 63. The FSS-9 also includes a question asking participants to rank their "global fatigue" on a sliding visual analog scale from worst (0) to normal (100).

The Multidimensional Dyspnea Profile is a 4-item scale that assesses multiple qualities surrounding breathing including general discomfort and emotional response.[32] Participants were asked to answer each question on the basis of their experience over the previous 7 days. Participants were first asked to rank the general discomfort of breathing on a scale

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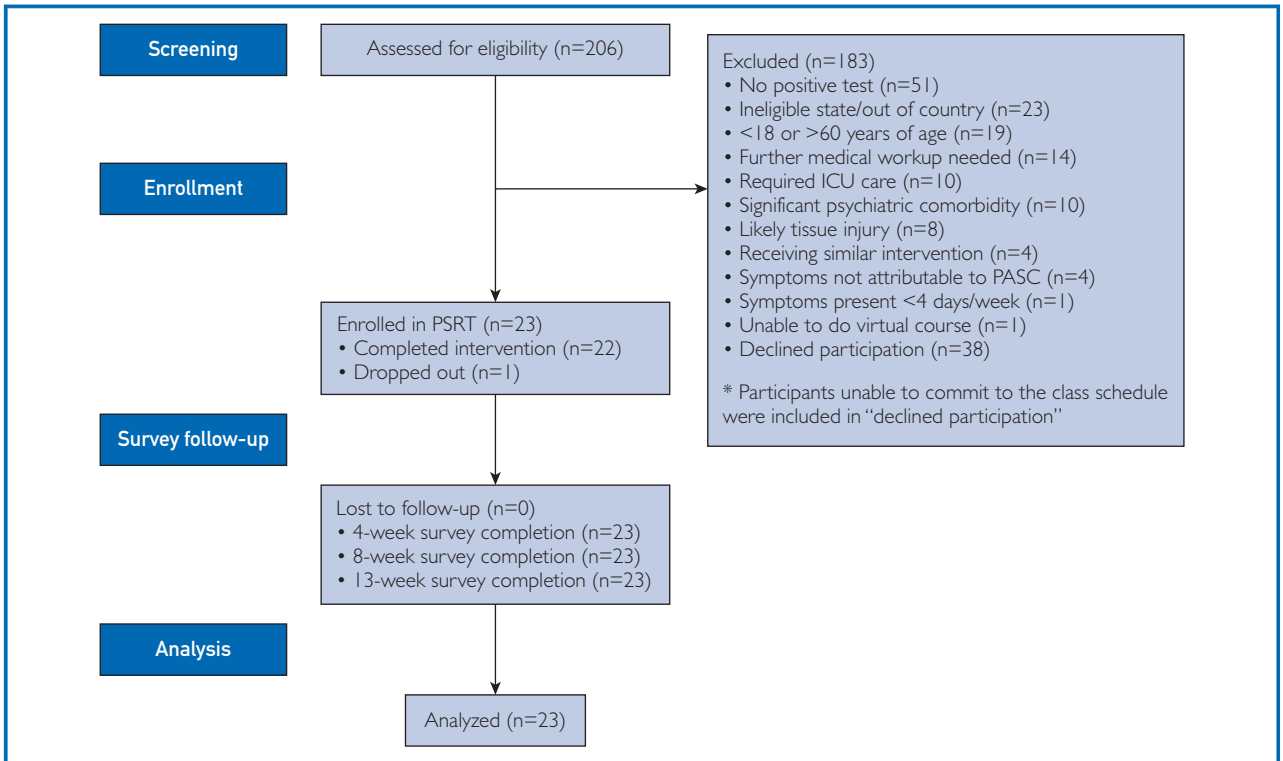

FIGURE 1. Participant flow through the study.

of 0 ("neutral") to 10 ("unbearable"). They then ranked the intensity of their breathing sensations and their emotional experience during dyspneic episodes on a scale of 0 ("None") to 10 ("As Intense as I can imagine"/"The most I can imagine"). The overall score was summed and ranges from 0 to 110.

We used the physical subsection of the PROMIS-29 (v2.1),[33,34] a four-item questionnaire in which participants are asked about their physical functionality. Participants ranked their physical function ability (eg, "Are you able to do chores such as vacuuming or yard work") on a 4-point scale ranging from "without any difficulty" (1) to "with much difficulty" (5). These scores were summed to represent an overall score, ranging from 0 to 16.

Percent attendance was calculated for each participant using the number of classes attended divided by the number of classes offered. A participant was marked as having attended the class if they were present for at least half of the class.

Symptom Visualization Test: one of the techniques used during PSRT includes visualization of activities that typically trigger symptoms (visual motor imagery). Participants were asked to remain stationary and imagine an activity or movement that tends to result in symptoms. We evaluated the percentage of participants who were able to reproduce their symptoms in this way. This process and technique is supported by the theory of predictive coding, which suggests that perception is an inferential process in which prior information is used to generate expectations about future perception.[35] Predictive coding proposes that perception is a process that favors expected outcomes and weighs down information that is incongruent with prior expectation, and this process has been suggested to contribute to pain conditions.[36,37] Therefore, by visualizing an activity that is believed to trigger symptoms, some individuals are able to reproduce symptoms or pain sensations.

TABLE 1. Demographic and Clinical Characteristics of Participants[a]

Characteristics	Full cohort (n=23)
Female, n (%)	14 (60.9)
Age (y), mean ± SD	42.6±9.6
BMI (kg/m^2), mean ± SD[b]	26.7±5.8
Number of specialists seen, median (IQR)[c]	3 (2, 3)
Tried previous mind-body interventions, n (%)	12 (52.2)
Race, n (%)	
White	19 (82.6)
African American	2 (8.7)
Other	1 (4.3)
Unknown	1 (4.3)
Ethnicity—Hispanic, n (%)[d]	1 (6.6)
Past medical history, n (%)	
None	10 (43.5)
Heart disease	0 (0.0)
Cancer	0 (0.0)
COPD	0 (0.0)
Diabetes	1 (4.3)
Hypertension	3 (13.0)
Liver disease	0 (0.0)
Kidney disease	0 (0.0)
Anxiety	10 (43.5)
Depression	7 (30.4)
Other	3 (13.0)
Education, n (%)[e]	
High school	1 (4.5)
Some college	2 (9.1)
College degree	13 (59.1)
Graduate degree	6 (27.3)
Marital status, n (%)[f]	
Divorced	3 (13.6)
Married	15 (68.2)
Single	4 (18.2)

[a]COPD, chronic obstructive pulmonary disease; IQR, interquartile range.
[b]1/23 (4%) missing BMI data.
[c]1/23 (4%) missing number of specialists seen data.
[d]8/23 (35%) missing ethnicity data.
[e]1/23 (4%) missing education data.
[f]1/23 (4%) missing marital status data.

The final 10 participants were asked a series of open-ended, free-text questions on their experience with PSRT. A summary of the responses to these questions can be found in the Supplemental Materials. This survey elicited experiences and feedback from these 10 participants, was introduced partway through the study, and is considered only exploratory.

RESULTS

Participant Flow Through the Study and Demographic Characteristics

Two hundred six participants were screened for enrollment. Of these, 183 did not meet inclusion criteria or met exclusion criteria and 23 were enrolled (Figure 1). All participants completed the protocol except for one who discontinued attending classes yet completed surveys through 13 weeks between May 18, 2021, and August 7, 2022. The mean participant age was 42.6±9.6 years, 14 (61%) were female, and the median duration of PASC symptoms was 267 (IQR: 144, 460) days. Baseline characteristics are displayed in Table 1. All participants completed surveys at all timepoints and had complete capture of the outcomes unless noted below. The median percent attendance of classes was 100% (IQR: 90%, 100%), with 16 (70%) of participants attending all classes; the range for those who did not attend all classes was 50%-95% attendance (mean of 78%±17% in those without perfect attendance). Seven groups of classes were held, ranging in size from 1 patient to 7 patients, with a median group size of 3 (IQR: 2, 5). Before entering the study, participants had tried a large variety of different therapies (Supplemental Table 1, available online at http://www.mcpiqojournal.org).

SSS-8 Outcome

For the primary outcome of SSS-8, we found a statistically significant reduction in somatic symptoms from baseline across all 3 timepoints with a mean decrease of −8.5 (95% CI: −11.4, −5.7) at 4 weeks, −9.4 (95% CI: −11.9, −6.9) at 8 weeks, and −10.9 (95% CI: −13.5, −8.3; primary outcome) at 13 weeks (all $P<.001$; see Tables 2 and 3; Figure 2; and Supplemental Figure 1, available online at http://www.mcpiqojournal.org). The largest percent change from baseline was seen at 13 weeks, with a median percent decrease of 55% (IQR: 29%, 76%); the median percent decrease from baseline at 4 and 8 weeks was 46% for both (IQR for 4 weeks: 16%, 63%; for 8 weeks: 21%, 65%). All participants had some numeric improvement from baseline to

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TABLE 2. Mean and Median Differences in Outcomes[a,b]

Variable	0-4 wk	0-8 wk	0-13 wk
SSS-8 (mean difference compared with baseline)	−8.5 (95% CI: −11.4, −5.7), *P*<.001	−9.4 (95% CI: −11.9, −6.9), *P*<.001	−10.9 (95% CI: −13.5, −8.3), *P*<.001
FSS-9 (median difference compared with baseline)	−21 (95% CI: −26, −12), *P*<.001	−18 (95% CI: −24, −11), *P*<.001	−20 (95% CI: −28, −12), *P*<.001
Dyspnea (median difference compared with baseline)	−17 (95% CI: −35, −6), *P*<.001	−21 (95% CI: −33, −16), *P*<.001	−27 (95% CI: −38, −17), *P*<.001
Average pain (mean difference compared with baseline)	−1.7 (95% CI: −2.6, −0.7), *P*=.002	−1.6, (95% CI: −2.8, −0.4), *P*=.01	−2.2 (95% CI: −3.3, −1.0), *P*<.001
Pain intensity (mean difference compared with baseline)	−1.8 (95% CI: −2.7, −0.9), *P*<.001	−2 (95% CI: −3.1, −0.9), *P*=.001	−2.4 (95% CI: −3.4, −1.3), *P*<.001
Pain interference (median difference compared with baseline)[c]	−20.5 (95% CI: −31, −7), *P*<.001	−21.5 (95% CI: −37, −6), *P*<.001	−23 (95% CI: −35, −16), *P*<.001
PASS-20 (mean difference compared with baseline)	−16.4 (95% CI: −25.2, −7.6), *P*<.001	−21.1 (95% CI: −31.4, −10.9), *P*<.001	−28.6 (95% CI: −37.7, −19.5), *P*<.001
PROMIS-29 (median difference compared with baseline)	−4 (95% CI: −6, −3), *P*<.001	−5 (95% CI: −7, −3), *P*<.001	−4 (95% CI: −7, −3), *P*<.001
Brain fog (median difference compared with baseline)	−1 (95% CI: −2, 0), *P*<.001	−1 (95% CI: −2, 0), *P*=.002	−1 (95% CI: −2, −1), *P*=<.001
SSS-8 GI (mean difference compared with baseline)	−0.6 (95% CI: −1.1, −0.1), *P*=.01	−1.0 (95% CI: −1.5, −0.4), *P*=.001	−0.9 (95% CI: −1.6, −0.2), *P*=.01
FSS-9 visual analog scale (VAS; mean difference compared with baseline)	32.5 (95% CI: 21.1, 43.9), *P*<.001	26.8 (95% CI: 14.8, 38.9), *P*<.001	33.5 (95% CI: 23.0, 44.1), *P*<.001

[a]FSS-9, Fatigue Severity Scale-9; GI, gastrointestinal; PASS-20, Pain Anxiety Symptom Scale-20; PROMIS-29, Patient-reported Outcomes Measurement Information System-29; SSS-8, Somatic Symptom Scale-8.
[b]Increase represents better health.
[c]1/23 (4%) missing values at 4 and 8 wk.

week 13. When performing the longitudinal analysis analyzing change from baseline, there was a significant overall difference from baseline (*P*<.001; overall mean difference: −9.6 (95% CI: −11.9, −7.3). The individual components of the SSS-8 from baseline to week 13 are displayed in Supplemental Table 2 (available online at http://www.mcpiqojournal.org). We also found similar improvements when looking only at the GI component of the SSS-8 with a mean decrease of −0.6 (95% CI: −1.1, −0.1), at 4 weeks, −1.0 (95% CI: −1.5, −0.4) at 8 weeks, and −0.9 (95% CI: −1.6, −0.2) at 13 weeks, all *P*<.02.

Secondary Outcomes

For the other key secondary end points, we found a statistically significant reduction in symptoms from baseline in terms of fatigue, dyspnea, pain, pain anxiety, physical functioning, and brain fog across all 3 timepoints (Tables 2 and 3).

With respect to the question of whether exercise-induced fatigue (as asked by the FSS-9), participants had a decrease in this belief at all 3 timepoints; this reduction was statistically significant at weeks 4 and 13 (median difference from baseline at 4 weeks: −2 (95% CI: −3, −1), *P*<.001; at 8 weeks: −2 (95% CI: −3, −1), *P*=.085; at 13 weeks: −2 (95% CI: −3, −1), *P*=.01).

At baseline, 13 (57%) participants indicated that they strongly agreed with the FSS-9 statement that exercise made their symptoms worse. By 4 weeks, only 2 (9%) participants strongly agreed. This number

TABLE 3. Outcome Scores over Time[a]

Variable	Week 0	Week 4	Week 8	Week 13
SSS-8, median (IQR)	20 (16, 24)	12 (7, 16)	10 (6, 14)	8 (5, 13)
FSS-9, median (IQR)	52 (44, 55.5)	28 (20, 37)	32 (26.5, 36.5)	29 (12.5, 37.5)
Dyspnea, median (IQR)	54 (26.5, 60.5)	19 (6.5, 26)	15 (4, 36)	11 (1, 30.5)
Average pain, median (IQR)	6 (4, 6)	4 (3, 5)	4 (2, 5)	3 (2, 5)
Pain intensity, median (IQR)	5.25 (4.25, 6)	3.25 (1.75, 5)	2.75 (2, 4.75)	2.5 (1.25, 4)
Pain interference, median (IQR)	43 (33, 52)	20.5 (6, 31)	14.5 (2, 34)	10 (0, 28)
PASS-20, median (IQR)	43 (31, 62)	29 (13, 40)	18 (14, 34)	11 (5, 22)
PROMIS, median (IQR)	13 (8, 15)	8 (5, 9)	6 (5, 9)	6 (4, 9)
Brain fog, median (IQR)	3 "quite a bit" (3, 4)	2 "somewhat" (1, 3)	2 "somewhat" (0.5, 3)	1 "a little bit" (1, 2)
SSS-8 GI, median (IQR)	2 (1, 3)	1 (0, 2)	1 (0, 2)	1 (0, 2)
FSS-9 VAS, median (IQR)	25 (21, 35)	62 (37, 81)	52 (30, 69)	63 (46, 79)

[a]FSS-9, Fatigue Severity Scale-9; GI, gastrointestinal; IQR, interquartile range; PASS-20, Pain Anxiety Symptom Scale-20; PROMIS-29, Patient-reported Outcomes Measurement Information System-29; SSS-8, Somatic Symptom Scale-8; VAS, visual analog scale.

continued to drop with only 1 (4%) participant strongly agreeing with the statement at 8 and 13 weeks.

When asked to visualize scenarios in which they often felt symptoms, most participants had symptoms occur from imagining the activity (Supplemental Table 3, available online at http://www.mcpiqojournal.org).

Two participants suffered substantial weight loss (about 20-30 pounds) before entry into the study secondary to food intolerances with one requiring a nasogastric feeding tube for approximately 3 months. Both had an extensive medical evaluation, which did not reveal an organic cause of weight loss. By the end of the intervention period, the food intolerances for both participants resolved, the feeding tube was not needed for the one participant, and weight was regained.

Two participants developed acute COVID-19 while participating in the program. Despite this, both found numerical improvement in symptoms by week 13.

DISCUSSION

The purpose of this study was to examine the efficacy of PSRT in reducing overall somatic symptom burden and an array of individual symptoms in patients diagnosed with PASC. We found that PSRT provided a statistically significant and clinically meaningful reduction[38] in somatic symptoms within 4 weeks and that this effect persisted through the 8- and 13-week measurements, with the change at 13 weeks representing the primary outcome. All participants experienced at least some reduction in SSS-8 score over the duration of the study. In addition, PSRT statistically significantly reduced fatigue, dyspnea, intensity of pain, pain anxiety, pain interference with activities, and improved activity levels.

In our study, each participant served as their own control; thus, there was no direct comparison group. However, the median duration of symptoms before entering the study was 267 (IQR: 144, 460) days, and participants had seen a median of 3 (IQR: 2, 3) physicians before entry into the study, indicating that their symptoms had been persistent. Moreover, participants had tried a large variety of different therapies without relief (Supplemental Table 3), including 52% having tried some form of mind-body therapy. These data suggest that this study cohort had refractory PASC and would be unlikely to experience a marked reduction in symptoms in a short period of time without intervention.

At least one previous study found that exercise may be helpful for PASC;[39] however, this finding conflicts with anecdotal reports from patients and a recent report suggesting that exercise can worsen symptoms.[39,40] In the current study, activity was encouraged beginning in the second week after the psychophysiologic education had been introduced. We hypothesized that the association of symptomatology with activity might have

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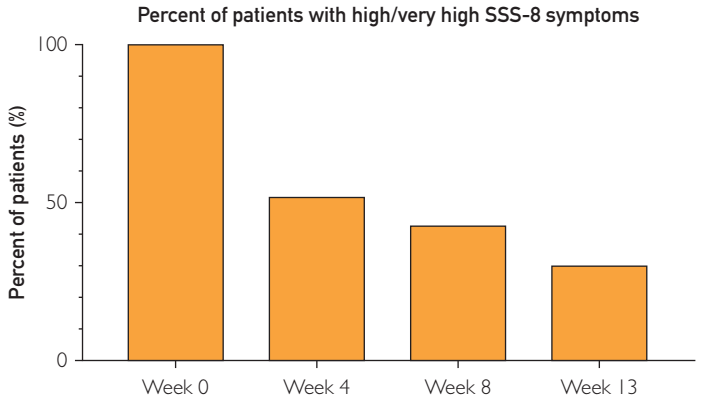

FIGURE 2. Percent of participants with high/very high SSS-8 symptoms. Scoring of the SSS-8 is categorized as follows: no to minimal (0-3 points), low (4-7 points), medium (8-11 points), high (12-15 points), and very high (16-32 points) somatic symptom burden. SSS-8, Somatic Symptom Scale-8.

developed, in part, through a classical conditioning-like model. As such, ongoing activity without knowledge of the underlying process strengthened the conditioning and worsened or did not allow for the improvement of symptoms. Our approach provided a method to break this cycle and desensitize participants from exercise-related conditioning (see desensitization portion of protocol in Supplemental Materials). This hypothesis was supported by results from survey responses to the question of whether exercise worsened their symptoms. At baseline, most participants (57%) strongly agreed that exercise would worsen symptoms; however, only 4% (1 patient) strongly endorsed this statement by the end of the study, which represented a statistically significant reduction in exercise-induced fatigue (this significant reduction was seen at 13 weeks as well as at every other time point). This change in the relationship with exercise was accompanied by an increase in activity levels (as measured by PROMIS-29). Taken together, these results may explain why exercise worsens symptoms in some patients (and in previous studies) but was helpful in the current study.

PSRT utilizes visualization techniques to help desensitize participants to symptomatology when encountering triggering stimuli. Specifically, participants are instructed to visualize a physical activity that would typically bring on symptoms such as walking across the room or up the staircase. This exercise brought on symptoms in most cases (Supplemental Table 2). Such visualization served 2 purposes. First, the visualization reinforced the psychophysiologic education by providing concrete evidence to participants that their symptoms could be generated by their mind. In addition, the visualization techniques also served as an exposure mechanism that further therapy could use to break the links between exertion and activity (see Supplemental Materials for details).

There have been a number of competing hypotheses about the underlying cause of PASC in patients without overt organ injury such as injury patterns not picked up through typical testing means (eg, chest radiographs, computed tomography, MRI, biopsy). The injury patterns proposed include the development of microclots,[8] mitochondrial dysfunction,[41] or differences in capillary blood flow.[42] In addition, a number of studies have reported immune system biomarker differences between PASC and controls. For example, one recent exploratory analysis reported differences in the immune phenotype in patients with PASC.[10] At present, these studies have yet to be confirmed; however, if a future study did validate one (or more) of

these findings, this does not necessarily negate our psychophysiological hypothesis. For example, the emotion of embarrassment results in changes in capillary blood flow (ie, microcirculation) and results in changes in the color of the skin (ie, flushing). This same pattern could hypothetically occur from chronic underlying emotions and in other tissue beds. Likewise, someone who is immobile for psychophysiologic reasons may be more likely to develop a microclot. Psychophysiologic syndromes also have been associated with changes to immune cells or predisposition to infection. One finding that would argue against our hypothesis would be the presence of chronically actively replicating virus with associated inflammatory changes. To date, that has not been identified, although some have reported the presence of a persistent spike protein. Of note, during the program, 2 participants developed acute COVID-19 but neither had worsening symptoms and both found numerical improvement by the end of the 13-week period.

The symptoms described in our participants and the PASC literature resembles previously reported reactions to traumatic experiences in patients without physical injury. For example, multiple reports dating back to the American Civil War era report physical symptoms from some soldiers returning from the battlefield with pain, dyspnea, fatigue, exertional fatigue, tachycardia, and sleep problems even when not wounded physically.[19-21,43] In addition, post-traumatic stress disorder has been associated with changes in cognition[44-46] and even changes in the brain as noted in MRIs.[44,45] The existence of such psychophysiologic syndromes with a constellation of symptoms similar to PASC provides a historical precedent for a relationship between psychological states and these physical manifestations.

Although the Centers for Disease Control and Prevention does not require proof of prior COVID-19 infection as part of their definition for PASC, having a population that definitively had COVID-19 was important to limit variability in our sample. With that context, the most common reason for exclusion from the study was the lack of a positive test for COVID-19 (see Figure 1). However, the presence of identifiable organ injury from acute COVID-19 was one of the least common reasons for exclusion. This pattern of exclusions is consistent with our overall scientific premise. Of note, the constellation of symptoms described in this report can also represent serious pathology; because of this, all participants were evaluated by a physician(s) before screening by the study team, which also included a physician.

Limitations and Future Directions

The limitations of the current study include the small sample size and the lack of a comparator group. The later concern is mitigated somewhat for the reasons noted above and particularly in that these participants seem to have been refractory in their symptoms. During participant recruitment, the study was advertised as a mind-body intervention resulting in people who are open to this type of intervention self-selecting to participate, which limits generalizability because of the selection bias. Other limitations include the subjective reporting of symptoms, which we attempted to mitigate by using validated tools measuring multiple domains. The optimal duration and content of the program remains unknown, including the possibility that there could be differential needs depending on individual participants. The course was taught by the same 2 instructors. Therefore, we cannot assess the effect the intervention may have had if administered by different instructors. Another limitation is the lack of long-term follow-up. Participants completed their final surveys at the end of the intervention, so we do not know whether the improvements seen during the intervention were maintained after the study ended. The measure of brain fog used has not been externally validated but we felt was important to capture because it was reported as a common symptom in the PASC literature. Future work may consider the incorporation of this parameter into the SSS-8 questionnaire and validating the overall tool with this parameter. Despite the efficacy of PSRT seen in this study, our results do not necessarily prove the scientific premise of the psychophysiologic model. Specifically, PSRT could theoretically be helpful even if there was an underlying primary organic source of symptoms. However, the techniques utilized and described rely heavily

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on this psychophysiologic premise. Lastly, the population studied focused on patients without identified organ injury and should not be generalized to other populations where organ injury is present (eg, lung fibrosis, myocarditis, cerebrovascular accident, demyelination disease, or any of a number of other processes).

CONCLUSION

PSRT reduced symptomatology across multiple domains within 4 weeks in a cohort of patients with PASC without identified organ injury and this benefit persisted over the 3-month study period.

POTENTIAL COMPETING INTERESTS

This work has been supported by Adam D'Angelo and Jim O'Shaughnessy. The authors report no competing interests.

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M.D.: conceptualization, methodology, investigation, resources, writing—original draft, writing—reviewing and editing, visualization, supervision, project administration, and funding acquisition. P.H.: methodology, investigation, and writing—reviewing and editing. S.M.: investigation, writing—original draft, and project administration. J.S.: investigation, writing—original draft, supervision, and project administration. M.J.C.: investigation, writing—original draft, visualization, and project administration. J.B.Y.: writing—original draft and writing—reviewing and editing. L.B.: formal analysis, data curation, and visualization. K.M.B.: writing—reviewing and editing. S.H.: writing—reviewing and editing, visualization, and conceptualization. R.E.: conceptualization and methodology. A.V.G.: methodology, software, formal analysis, and data curation.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **COVID-19**, Coronavirus disease 2019; **FSS-9**, Fatigue Severity Scale; **GI**, gastrointestinal; **IQR**, interquartile range; **MRI**, magnetic resonance imaging; **PASC**, post-acute sequelae of COVID-19; **PROMIS-29**, Patient-reported Outcomes Measurement Information System; **PSRT**, Psychophysiologic Symptom Relief Therapy; **SARS-CoV-2**, severe acute respiratory syndrome coronavirus 2; **SSS-8**, Somatic Symptom Scale-8

Correspondence: Address to Michael Donnino, MD, Beth Israel Deaconess Medical Center, 1 Deaconess Road, Boston, MA 02215 (mdonnino@bidmc.harvard.edu).

ORCID

Jolin B. Yamin: https://orcid.org/0000-0002-3845-6551; Lakshman Balaji: https://orcid.org/0000-0001-7189-4775; Katherine M. Berg: https://orcid.org/0000-0003-1897-1086; Anne V. Grossestreuer: https://orcid.org/0000-0001-7316-5576

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