A Phase I Randomized Controlled Trial of a Positive Psychology Intervention for Patients With Multiple Sclerosis

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DETAILED PROTOCOL

I. BACKGROUND AND SIGNIFICANCE

Living with multiple sclerosis (MS), a chronic autoimmune disease characterized by an unpredictable and variable course, presents a significant challenge for many patients. Depression and anxiety are common, occurring in up to 50% [1]and 35% [2] of patients, respectively. Health-related quality of life (HRQOL) is often impaired and has been shown to deteriorate following a relapse [3]. Positive psychological constructs such as positive affect, optimism and subjective well-being may play an important role in adaptation to chronic disease [4]. In patients with MS, positive constructs have been shown to be negatively associated with depression and anxiety [5-7] and positively associated with physical, social and psychological adjustment [7, 8]. A psychosocial intervention aimed at increasing positive constructs may facilitate adjustment and improve HRQOL in patients with MS.

Positive psychology (PP) uses targeted activities to increase the frequency and intensity of positive emotional experiences [9]. Targeted activities span several domains, including gratitude (e.g., systematically recalling positive life events), using one's personal strengths in a deliberate manner and altruism (e.g., performing acts of kindness). Two meta-analyses of PP interventions (PPI) demonstrated that these interventions significantly enhanced subjective well-being and were effective in reducing depressive symptoms in both depressed and non-depressed individuals. Studies that included multiple PP exercises were more effective than approaches that used a single activity. The benefits of PPI were sustained for periods of up to 6 months [10, 11]

Although there are a few studies of PP for individuals with medical illnesses, no RCT of PP has been published in MS. Members of our team have experience adapting PP interventions for medically ill patients including patients with acute cardiovascular disease, type 2 diabetes and MS and delivering them in research interventions. PP interventions are broadly applicable, require little provider training and the exercises are well-accepted and easy to complete. The development of an at home, phone-based PP intervention could represent a low cost, innovative and effective tool to increase positive affect in patients with MS. This may lead to decreases in depression, anxiety and fatigue and improvements in HRQOL and self-reported functional activities such as work.

II. SPECIFIC AIMS

This phase I randomized controlled trial (RCT) will examine the efficacy of an at home positive psychology (PP) training intervention to increase positive affect in patients with multiple sclerosis (MS). The RCT will include a five-week intervention phase and a five-week extension phase.

Specific Aim 1: Evaluate the tolerability and acceptability of a five-week at home PP training intervention for MS patients. We will assess the tolerability of the intervention by calculating the proportion of subjects who complete four of the five weekly exercises. We will determine the acceptability of each exercise by having subjects rate the ease and utility of each exercise after it is completed.

Specific Aim 2: Examine the efficacy of PP training to improve positive affect, emotional function, health-related quality of life (HRQOL), and self-reported functional activities. We will compare positive affect in subjects in the intervention and control group at the completion of the intervention phase. We will also assess between-group differences in depression, anxiety, fatigue, HRQOL and work productivity following the intervention phase.

Specific Aim 3: Determine if improvements in positive affect, emotional function, HRQOL and self-reported functional activities following PPI training are maintained. For subjects in the intervention group who demonstrate a benefit from PPI, we will determine if that benefit is maintained by comparing positive affect, depression, anxiety, fatigue, HRQOL and work productivity at the completion of the intervention and extension phases.

III. SUBJECT SELECTION

Thirty subjects with MS will be enrolled at the Partners MS Center. Subjects will be recruited from the Comprehensive Longitudinal Investigation of Multiple Sclerosis at the Brigham and Women's Hospital Partners MS Center: The CLIMB Study (1999P010435).

Inclusion criteria:

1. Diagnosis of clinically isolated syndrome or MS
2. Age 18-65
3. Able to read and write in English
4. Enrollment in the CLIMB study

Exclusion criteria:

5. Moderate or marked cognitive abnormalities on brief mental status testing identified by the treating neurologist during routine visits to the Partners MS Center that would preclude meaningful participation in the PP exercises

IV. SUBJECT ENROLLMENT

All CLIMB subjects being seen at the Partners MS Center for a routine clinical visit will be identified. They will be approached by their physician about participation in a PP study and will be given a study flyer. Additional flyers may be posted at the Partners MS Center. Interested individuals will be brought by their physicians to meet with a member of the research staff to learn about the study in more detail. They will be given a copy of the consent form to review. They will have the opportunity to discuss the study with their physician as well as other members of the research study staff prior to giving consent. Individuals will have at least 12 hours to consider participation. Consent will be obtained by study co-investigators or by the research coordinators listed on the protocol during the enrollment visit at the Partners MS Center.

V. STUDY PROCEDURES

This RCT will include an intervention phase (Phase I) and an extension phase (Phase II).

Enrollment Visit (60 minutes)
Subjects will be enrolled at the Partners MS Center at the Brigham and Women's Hospital. At enrollment, all subjects will be consented and assigned a study subject ID. Subjects will complete a battery of patient reported outcome (PRO) measures in REDCap, a secure web application for building and managing online surveys. The PRO measures include:

1. Positive and Negative Affect Scale (PANAS) [12] is comprised of two 10-item mood scales, one measuring positive affect and the other negative affect.

2. Life Orientation Test-Revised (LOT-R) [13] is a 6-item measure of optimism and pessimism and the most widely used measure of optimism.

3. Center for Epidemiologic Studies Depression Scale (CES-D) [14] is a 20-item self-report measure of depression that focuses on the cognitive and affective rather than the somatic components of depression.

4. State Trait Anxiety Inventory (STAI) [15] includes two 20-item questionnaires designed to measure the current temporary condition of "state" anxiety and the more general and long-standing quality of "trait" anxiety.

5. Modified Fatigue Impact Scale (MFIS) [16] is a 21-item questionnaire used to assess the impact of fatigue on physical, cognitive and psychosocial functioning.

6. Health Status Questionnaire (SF-36) [17] is a widely-used generic measure of HRQOL. It yields an 8-scale profile of functional health as well as physical and mental health summary scores.

7. Work Productivity and Activity Impairment Questionnaire (WPAI) [18] is a 6-item measure of health-related work productivity (absenteeism and presenteeism) as well as the effect of health problems on the ability to perform regular daily activities.

8. Perceived Stress Scale (PSS) is a 10-item measure of the degree to which situations are perceived as stressful [19].

9. Brief Resilience Scale (BRS) is a 6-item scale that measures the ability to bounce back or recover from stress [20].

10. State Optimism Measure (SOM) is a 7-item measure of "state" optimism or optimism at the present moment.

Using a computerized random number generator, subjects will be randomized to the intervention or control group.

Intervention Phase (5 weeks)
In the intervention phase (Phase I: Weeks 1-5), subjects randomized to the intervention group will be given a study participant manual and asked to set up a time for weekly phone calls with the study trainer. They will complete five weeks of PP exercises, one exercise per week. They will be asked to rate their mood prior to and after completing each exercise. They will also be asked to rate the ease and utility of each exercise. The weekly calls with the study trainer will be used to review the completed exercise and introduce the next exercise. These calls will be recorded so that a percentage (10%) of these recordings can be reviewed to ensure that the PP and goal-setting portions of the intervention are being delivered as described in the protocol and study trainer manual. The control group will have no study activities during intervention phase and will be considered a wait-list control. At the completion of the intervention phase, all subjects will be emailed a link to complete PRO measures in REDCap.

Extension Phase (5 weeks)
In the extension phase (Phase II: Weeks 6-10), subjects in the control group will receive their study participant manual in the mail. They will be contacted by the study trainer to set up weekly phone calls. They will complete the PPI as described above. The intervention group will complete no study activities in the extension phase. At the completion of the extension phase, all subjects will be emailed a link to complete PRO measures.
Intervention: The PP intervention consists of five weeks of PP training using the following exercises:

1. Gratitude for positive events: Recall three positive events that occurred in the past week and write about the events and how the events made you feel.

2. Personal strengths: Complete a brief survey of personal strengths and select a strength such as perseverance or humility and use it deliberately in the next 24 hours. Write about how you used the strength and how you felt while using it.

3. Gratitude letter: Recall another individual's kind act that resulted in joy, relief, serenity or other positive feelings. Write a letter to the person describing feelings of gratitude associated with this event.

4. Enjoyable and meaningful activities: Intentionally complete three acts in a single day – a pleasurable act done alone, a pleasurable act done with others and a meaningful or important act.

5. Remembering past successes: Focus on a time when you experienced success and write about the event and the positive feelings and thoughts you had during the event

These exercises have all been described by Huffman et al. [21]. Exercises may require anywhere from 15 minutes to several hours to complete.

The study trainer, Melanie Freedman, serves as the supervising research coordinator for two PP intervention trials in medically-ill populations. She has experience completing phone and in-person study assessments with patients who have medical illnesses for numerous studies. She works under the supervision of Jeff Huffman, MD. She will receive training utilizing our standard protocol (via review of didactic materials, role play, and director work with supervisors) and ongoing supervision from our director of behavioral interventions. She will also receive didactic teaching from MS experts on the basics of MS care and will have shadowed in the MS clinic to better understand MS patients' experiences. During the study, Dr. Huffman or another physician study staff member will be available by phone or pager to intervene, if needed, due to subject discomfort or to answer specific questions about the study.

Two study manuals tailored to individuals with MS will be prepared: a study trainer manual and a study participant manual. At enrollment, subjects in the intervention group will be given the study participant manual and asked to schedule their first weekly phone call with the study trainer. The calls will last 45-60 minutes, and will be used by the study trainer to (a) review the weekly exercise and discuss the ease and utility ratings recorded by subjects after the exercise was completed; (b) discuss the rationale for the next exercise using a guided review of the study participant manual; and (c) describe the following week's exercise and brainstorm ways to complete it. Subjects in the control group will be mailed a copy of the study participant manual at the beginning of the extension phase of the study. This is to prevent subjects in the control group from completing the exercises during the intervention phase. They will be contacted by the study trainer to schedule their weekly phone calls. All subjects will complete PRO measures at enrollment, completion of the intervention phase and completion of the extension phase.

VI. BIOSTATISTICAL ANALYSIS

To assess the tolerability of the intervention (Specific Aim 1), our goal is to demonstrate that the proportion who will complete four out of five exercises is greater than 0.5. Given our sample size of 30 subjects, we will have 80% power to detect a difference if the true proportion of subjects who will complete four out of five exercises is 0.75 using a one sample binomial test of proportions (Stata routine: *power oneproportion*). For the comparison of the treatment groups in terms of PRO measures (Specific Aim 2), the intervention effect will be estimated using analysis of covariance (ANCOVA) model. In the ANCOVA model, the post-intervention scores will be compared between the groups controlling for baseline scores. All outcome measures (PANAS, LOT-R, CES-D, STAI, MFIS, SF-36**,** WPAI, PSS, BRS, and SOM) will be compared using the same model. To assess whether PPI benefits are maintained at 10 weeks (Specific Aim 3), we will first calculate the change from baseline to week 5 for each of the outcome measures. For the subjects who experience a benefit of the intervention, we will then assess if at least 50% of the benefit was maintained at the 10-week time point. The proportion of subjects who maintained the benefit will be reported.

VII. RISKS AND DISCOMFORTS

There are no major risks associated with participating in the study. Subjects may experience discomfort writing down and sharing emotional aspects of their lives. If they do experience discomfort, they may choose not to complete the weekly PP assignments. If they feel their participation is becoming too burdensome or is exacerbating ongoing symptoms, they have the option to decline further participation and withdraw from the study.

There is some potential for breach of confidentiality. No information will be shared with treatment providers unless a participant requires immediate assistance. In such cases, treatment providers will be informed and subjects will be referred to a mental health provider at the Partners MS Center**.**

VIII. POTENTIAL BENEFITS

This is a pilot study designed to determine the tolerability and efficacy of an at home PP training intervention for individuals with MS. If the results suggest that home PP training is tolerable and effective, it may advance the use of PP as a low cost, innovative and effective tool for increasing positive affect, decreasing depression and anxiety and improving HRQOL in patients with MS.

IX. MONITORING AND QUALITY ASSURANCE

Bonnie Glanz, the PI, will be responsible for assuring the validity and integrity of the data collected, and adherence to the IRB-approved protocol. The study team will meet weekly to review subject recruitment, subject satisfaction and study progress.

X. REFERENCES

1. Marrie, R.A., et al., *The burden of mental comorbidity in multiple sclerosis: frequent, underdiagnosed, and undertreated.* Mult Scler, 2009. **15**(3): p. 385-92.
2. Korostil, M. and A. Feinstein, *Anxiety disorders and their clinical correlates in multiple sclerosis patients.* Mult Scler, 2007. **13**(1): p. 67-72.
3. Healy, B.C., et al., *The impact of a recent relapse on patient-reported outcomes in subjects with multiple sclerosis.* Qual Life Res, 2012. **21**(10): p. 1677-84.
4. Huffman, J.C., et al., *A Positive Psychology Intervention for Patients with an Acute Coronary Syndrome: Treatment Development and Proof-of-Concept Trial.* J Happiness Stud, 2016. **17**(5): p. 1985-2006.
5. Fournier, M., D. De Ridder, and J. Bensing, *Optimism and adaptation to chronic disease: The role of optimism in relation to self-care options of type 1 diabetes mellitus, rheumatoid arthritis and multiple sclerosis.* Br J Health Psychol, 2002. **7**(Part 4): p. 409-432.
6. Fournier, M., D. de Ridder, and J. Bensing, *Optimism and adaptation to multiple sclerosis: what does optimism mean?* J Behav Med, 1999. **22**(4): p. 303-26.
7. Dennison, L., R. Moss-Morris, and T. Chalder, *A review of psychological correlates of adjustment in patients with multiple sclerosis.* Clin Psychol Rev, 2009. **29**(2): p. 141-53.

8. De Ridder, D., 7. de Ridder, D., Schreurs, K., Bensing J., *The relative benefits of being optimistic: optimism as a coping resource in multiple sclerosis and Parkinson's disease.* Br J Health Psychol, 2000. **5**(2): p. 141-55.
9. Seligman, M.E.P., *Learned Optimism: How to Change Your mind and Your Life*. 1991, New York: Alfred A. Knopf.
10. Sin, N.L. and S. Lyubomirsky, *Enhancing well-being and alleviating depressive symptoms with positive psychology interventions: a practice-friendly meta-analysis.* J Clin Psychol, 2009. **65**(5): p. 467-87.
11. Bolier, L., et al., *Positive psychology interventions: a meta-analysis of randomized controlled studies.* BMC Public Health, 2013. **13**: p. 119.
12. Watson, D., L.A. Clark, and A. Tellegen, *Development and validation of brief measures of positive and negative affect: the PANAS scales.* J Pers Soc Psychol, 1988. **54**(6): p. 1063-70.
13. Scheier, M.F., C.S. Carver, and M.W. Bridges, *Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test.* J Pers Soc Psychol, 1994. **67**(6): p. 1063-78.
14. Radloff, L.S., *The CES-D scale: a self-report depression scale for research in the general population.* Appl Psychol Meas, 1977. **1**: p. 1385-401.
15. Spielberger, C.D., Gorsuch, R.L., Lushene, R., Vagg, P.R., Jacobs, G.A. , *Manual for the state-trait anxiety inventory*. 1983, Menlo Pasrk, CA: Mind Garden.
16. Fisk, J.D., et al., *The impact of fatigue on patients with multiple sclerosis.* The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques, 1994. **21**(1): p. 9-14.
17. Ware, J.E., Jr. and C.D. Sherbourne, *The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection.* Med Care, 1992. **30**(6): p. 473-83.
18. Reilly, M.C., A.S. Zbrozek, and E.M. Dukes, *The validity and reproducibility of a work productivity and activity impairment instrument.* Pharmacoeconomics, 1993. **4**(5): p. 353-65.
19. Cohen, S., Williamson, G., *Perceived stress in a probability sample of the United States*, in *The Social Psychology of Health: Claremont Symposium on Applied Social Psychology*, S.S.S. Oskamp, Editor. 1988, Sage: Newbury Park, CA.
20. Smith, B.W., et al., *The brief resilience scale: assessing the ability to bounce back.* Int J Behav Med, 2008. 15(3): p. 194-200.
21. Huffman, J.C., et al., *Development of a positive psychology intervention for patients with acute cardiovascular disease.* Heart Int, 2011. **6**(2): p. e14.