A combined analysis of two randomized controlled trials evaluating the effect of Mindfulness-Based Stress Reduction on self-reported emotional experience and physiological symptoms among veterans with Posttraumatic Stress Disorder

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A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Public Health

University of Washington

2016

Committee:

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Program Authorized to Offer Degree:

Public Health

University of Washington

Abstract

A combined analysis of two randomized controlled trials evaluating the effect of Mindfulness-Based Stress Reduction on self-reported emotional experience and physiological symptoms among veterans with Posttraumatic Stress Disorder

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Background: Approximately 13% of military veterans meet diagnostic criteria for Posttraumatic Stress Disorder (PTSD), indicated by the presence of emotional numbing and behavioral avoidance, re-experiencing the traumatic event (e.g. through flashbacks or nightmares), hyper-vigilance, and cognition and mood disturbances. Since individuals with PTSD often experience additional problems that affect their quality of life, such as anger, fatigue, and depression, worsened physical and social functioning, and compromised sleep quality, new treatments are needed for PTSD that improve multiple domains of health in addition to PTSD symptoms.

Methods & Analysis: Data from two randomized control trials comparing Mindfulness-Based Stress Reduction (MBSR) to a treatment-as-usual (TAU) control group among a sample of veterans with PTSD were analyzed in a combined analysis. Data measuring PTSD severity, mindfulness, and eleven different health domains were collected at baseline, post-MBSR, and 4 to 6-month follow-up. PTSD was measured with the PTSD Checklist civilian version (PCL-C) in one study and with the PSS-I in the other; mindfulness was measured with the Five Facet Mindfulness Questionnaire; and the eleven health domains were measured with the National Institutes for Health Patient-Reported Outcome Measurement Information System (PROMIS). An intent-to-treat analysis compared post-intervention and follow up outcomes for all subjects

randomized to MBSR to all subjects randomized to TAU, and a completer analysis compared outcomes between MBSR completers (those who completed at least 4 sessions of MBSR) to the TAU group.

Results: A significantly greater proportion of those randomized to MBSR reported a clinically significant decline in PTSD symptoms compared to those randomized to TAU at post-intervention (52.8% compared to 20.5%, $p<.005$), but this difference was not maintained at follow-up. In the intent-to-treat analysis, there were no statistically significant differences in all eleven PROMIS health domain outcomes at post-intervention or follow-up between those randomized to MBSR plus TAU and those randomized to TAU only. In the completer analysis, the MBSR group reported significantly better outcomes than TAU for pain interference (mean difference between groups, -5.20; 95% CI, -10.17 to -0.24, $p<.05$), and significantly worse outcomes than TAU for physical function at the 4 to 6-month follow-up (mean difference, -7.12; 95% CI, -14.2 to -0.01, $p=.05$). The completer analysis found significantly greater improvements for overall mindfulness at post-intervention (mean difference, 11.41; 95% CI, 1.35 to 21.46; $p<.05$) and follow-up (mean difference, 13.11; 95% CI, 3.06 to 23.15; $p<.05$) among those in MBSR than those in TAU.

Conclusions: Although our findings indicate that participation in MBSR resulted in increased overall mindfulness and a few specific mindfulness skills, it is unclear whether these skills are directly related to the decline in PTSD symptoms or the trends toward improvement in the PROMIS health domains in the MBSR groups compared to TAU. Additional research is warranted to further explore the impact of mindfulness-based interventions on PTSD symptoms and the potential role of mediating factors.

Keywords: mindfulness, posttraumatic stress disorder, patient-reported outcomes, veterans, quality of life

BACKGROUND

After a traumatic or potentially life-threatening experience such as rape, torture, assault, witnessing a murder, or surviving a devastating natural disaster, it is common to develop certain cognitive-emotional and behavioral patterns as a response known as Post-traumatic Stress. Symptoms of Post-traumatic Stress include avoidance of people, places or situations that trigger memories of the traumatic event, difficulty falling or staying asleep due to hypervigilance and/or anticipation of nightmares, and heightened arousal. For most people, these symptoms subside within approximately one month of the traumatic event. If symptoms persist longer than this, Posttraumatic Stress Disorder (PTSD) can develop and may last decades, especially if no treatment is received.

Although nearly 88% of adults in the United States (U.S.) have been exposed to at least one traumatic event (1), only a minority develop PTSD. Estimates for the overall prevalence of PTSD in the U.S. are much higher among military veterans than in civilians. A study of 2,695 civilian community members and 323 trauma-exposed military veterans (2) reported a PTSD prevalence of 13% among military veterans, compared to 0.6% among the civilians. Within another sample of 2,953 U.S. adults, inclusive of both veterans and non-veterans, lifetime PTSD prevalence was 8.3% using criteria from the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The highest rates of PTSD were among individuals with trauma from interpersonal violence or military combat (1).

The fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) categorized clinically diagnostic PTSD symptoms into three clusters: emotional and behavioral avoidance, re-experiencing (e.g. flashbacks and nightmares), and hyper-vigilance. Although the DSM-5 has added cognition- and mood-related symptoms to the diagnostic criteria,

the impact of PTSD on an individual's mental and physical health is not fully captured by these symptoms. Individuals with PTSD or a history of childhood trauma have a greater risk of increased anger (3-5), depression (6-9), fatigue (10-13), worsened physical health and functioning (14-21), pain (19, 20), and problems with social role functioning (19, 20) related to self-isolation, distrust toward self or others, or perceived lack of social support. Sleep disturbances, such as difficulty falling or staying asleep (22, 23) and recurring nightmares (24, 25), are also common features of PTSD. Some researchers consider diminished sleep quality to be the hallmark feature of PTSD (26). Therefore, patients with PTSD are in need of interventions that can improve multiple domains of physical and emotional health in addition to reducing the severity and frequency of characteristic symptoms of PTSD (i.e. avoidance, re-experiencing, and hyper-vigilance). As noted in a recent editorial by Kearney and Simpson (27), PTSD research trials tend to focus on treating the diagnostically relevant symptoms of PTSD rather than assessing additional domains of health and wellness that have been negatively affected by PTSD.

Considering the impact of PTSD on an individual's emotional and physical health beyond the prevalence of PTSD-specific symptoms (28), the potential of mindfulness-based interventions (MBIs) as an option for improving holistic health and wellness among those with PTSD merits closer examination. A widely used definition of mindfulness is "the awareness that emerges by way of paying attention on purpose, in the present moment, and nonjudgmentally to the unfolding of experience moment by moment" (29). MBIs provide guidance through practices designed to cultivate the skill of noticing thoughts, emotions, and sensory experiences with an attitude of openness, curiosity, acceptance, and love (30). These mindfulness skills are theorized to lead to cognitive and behavioral changes that impact – directly or indirectly – patients' symptoms and quality of life (31-33).

Several studies have demonstrated the clinical efficacy of mindfulness-based interventions as a treatment option for PTSD (34-37), and that mindfulness skills are directly associated with positive outcomes (35, 38-40). Additionally, studies have found that mindfulness interventions are often effective for addressing a range of emotional and physical problems in populations with or without PTSD, such as anger (41, 42), anxiety (43, 44), depression (43-45), fatigue (43, 46, 47), and pain (48-51).

There are many studies that examine the impact of MBIs on quality of life (QOL) in addition to changes in PTSD symptoms, and these QOL measures often include items for a range of physical and mental health symptoms. A 2013 pilot study of veterans with PTSD measured mental health-related quality of life (HRQOL) among patients before and after participation in a mindfulness intervention, and found that those participating in the intervention experienced clinically meaningful improvements in both mental HRQOL and PTSD symptoms at 4-month follow-up compared to the patients randomized to treatment-as-usual (52). A 2015 randomized controlled trial (RCT) of Mindfulness-Based Stress Reduction (MBSR) compared to present-centered group therapy among veterans with PTSD also reported greater improvements in a quality of life for those who participated in the mindfulness group at 2-month follow-up (34). However, since the quality-of-life measures vary between studies and the specific physical and mental symptoms included in these measures are not reported as distinct items, there is a need for patient-reported outcomes measures that can be used commonly and consistently across studies to allow for more direct comparisons. The National Institutes of Health have developed measures for this precise purpose, called the Patient-Reported Outcome Measurement Information System (PROMIS), which are used in the present study.

The present study aims to determine whether participation in Mindfulness-Based Stress Reduction (MBSR) plus treatment-as-usual (TAU) results in significantly greater changes in each of eleven PROMIS health domains from baseline to post-MBSR, and from baseline to follow-up (4 to 6 months following the end of MBSR), compared to treatment as usual only. To achieve these aims, data from subjects with PTSD from two RCTs were explored in a combined analysis. We hypothesized that veterans who received MBSR in addition to treatment as usual would report greater improvements at both post-intervention and 4-6 month follow-up for each health domain compared to those receiving only treatment as usual. In addition, we sought to compare the proportion of veterans who reported clinically significant improvement in PTSD symptoms after MBSR in addition to treatment as usual vs. treatment as usual only. We also analyzed differences between the MBSR and TAU groups

METHODS & ANALYSIS

Data Sources

Data from this study were derived from two previous RCTs that collected data to evaluate the impact of MBSR compared to treatment-as-usual (TAU) on eleven domains of health: anger, anxiety, depression, fatigue, physical function, pain-related behavior, pain interference, sleep disturbance, sleep-related impairment, satisfaction with social roles, and satisfaction with discretionary social activities.

MBSR is a widely available, 8-week clinical method for teaching mindfulness taught in a group format. The goals of the MBSR intervention were to teach participants to pay attention to the present moment in a nonjudgmental and accepting manner, and encourages openness to and acceptance of thoughts, feelings, and experiences without avoidance (53). The group meets once

a week for sessions lasting 2.5 hours each, and for seven hours on one Saturday between the sixth and seventh weeks, for a total of 9 sessions (27 hours) over an 8-week period.

Data for this study included no patient identifiers and was determined to be exempt from Institutional Review Board (IRB) review by the University of Washington Human Subjects Division. VA IRB approval was obtained for the data repository that provided the data from the RCTs used in this analysis, as well as for each of the original RCT studies.

Inclusion & Exclusion Criteria

Study 1 (54) included veterans who met criteria for Gulf War Illness, also referred to as Chronic Multi-Symptom Illness. Subjects in Study 1 had to meet the following inclusion criteria: 1) deployed to the Gulf War theater of operations between August 1990 and August 1991; 2) reported at least 2 of the following symptoms, lasting 6 months or longer to the present: a) fatigue that limits usual activity; b) musculoskeletal pain involving two or more regions of the body; c) neurocognitive dysfunction (difficulty with memory, concentration, and/or attention).

Participants in Study 2 (unpublished data) included veterans if they had a current diagnosis of PTSD in their electronic health record. Patients meeting any of the following three criteria were excluded: 1) use of antibiotics in the prior 3 months; 2) medical record diagnosis of Irritable Bowel Syndrome, gastrointestinal cancer, or celiac sprue or 3) diagnosis of borderline personality disorder, schizoaffective disorder, obsessive compulsive disorder, or antisocial personality disorder. (Exclusion criteria 1 and 2 were part of the protocol because the project included procedures to study the intestinal microbiome.)

In addition to exclusion criteria described above, both studies further excluded patients with a history of psychosis, mania, or poorly controlled bipolar disorder; current suicidal and/or homicidal ideation; prior formal training in mindfulness meditation; active substance abuse or

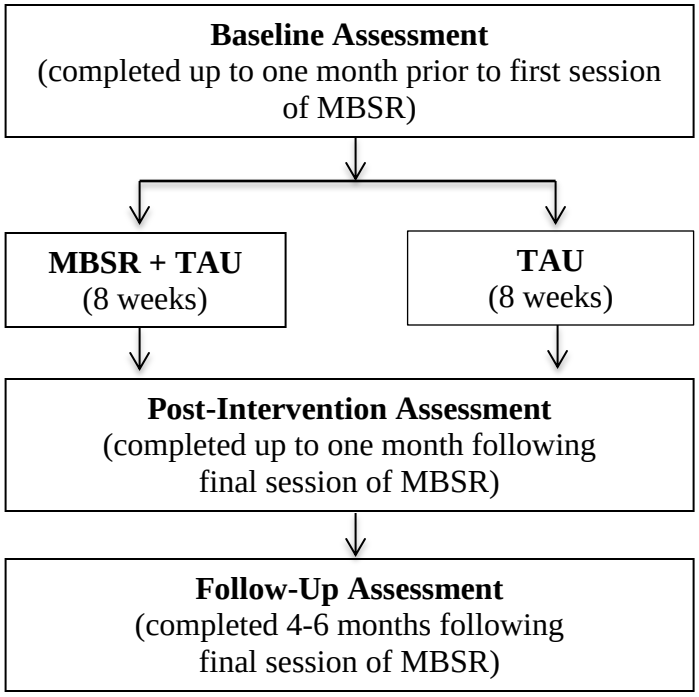
dependence; illicit drug use in the past 3 months; and current alcohol use in conjunction with an alcohol-related hospitalization, blackout, or seizure in the past year.

The present study narrowed the study sample to include only participants from the RCTs who met a minimum threshold for PTSD symptom severity (defined below), which resulted in a dataset with 75 subjects (38 from Study 1, 37 from Study 2; 36 randomized to MBSR, 39 randomized to TAU). Comparisons of the demographic characteristics of the study subjects, and number of weeks from baseline to post-assessment and from baseline to the follow-up assessment, between the MBSR-plus-treatment as usual group and the TAU group are outlined in Table 1.

Assessment Time Points

In both studies, participants completed a baseline assessment within one month prior to the start of the MBSR series. In both studies, post-intervention assessments were completed within one month following the last date (Week 8) of the MBSR series. In Study 1, the follow-up assessments were obtained 6-months following the last day of the MBSR series, and in Study 2, the follow-up assessments were obtained 4 months following the last day of the MBSR series. The timeline for each of the three assessments and the intervention is outlined in Figure 1.

Figure 1. Assessment Flow Chart



PTSD Symptom Severity & Sample Inclusion

PTSD symptom severity at baseline was measured using validated measures in both studies. Study 1 used the PTSD Symptom Scale Interview (PSS-I), a clinician-administered interview involving 17 questions that assess PTSD symptoms according to DSM-IV criteria. Frequency of symptoms experienced in the past month are recorded on a scale of 0 ("not at all") to 3 ("5 or more times per week/very much"). Subjects from this sample who met PSS-I criteria for a current PTSD diagnosis at baseline were included in the current analysis. To meet criteria, patients needed to report the presence of at least one Re-Experiencing symptom, at least three Avoidance symptoms, and at least two Increased Arousal symptoms in the past month (55).

Study 2 used the 17-item PTSD Checklist for Civilians (PCL-C), a self-report measure of PTSD symptom severity over the past month(56). Responses are provided on a scale of 1 ("not at all") to 5 ("extremely"). According to the VA-suggested PCL-C cut-point scores for patients

evaluated within VA primary care (the category which best fits the subject population), patients with a PCL-C score of 36 or above at baseline were included in the current analysis (56).

Patient-Reported Primary Outcomes

To measure patient-reported outcomes for multiple domains of health, we used measures from PROMIS, developed by the NIH. These tools have greater quality and precision than other self-reported outcome measures by adapting questions based on participants' previous responses using a statistical model called item response theory. The software that uses these statistical models is referred to as Computerized Adaptive Testing (CAT), and it generates relevant and maximally informative follow-up questions to an initial question, depending on the subject's response to prior questions.

PROMIS measures are administered through a public website (www.assessmentcenter.net), from which the raw scores and t-score results can be downloaded. All PROMIS measures use a mean of 50 for the t-scores (representing the average for the US General Population), and a standard deviation of 10. A high score means *more* of the domain being measured, whether the domain represents a desired or undesired outcome. For example, higher fatigue scores indicate more fatigue and higher physical functioning scores indicate more (healthier) physical functioning (57).

Measuring Clinically Significant Changes in PTSD Symptoms

Clinically significant changes in PTSD symptoms between time points were assessed by calculating the proportion of subjects in each study who reported a clinically meaningful decrease in PTSD symptoms. For the PCL-C, the Reliable Change Index (RCI) has been used to define a 10-point decrease in overall PCL-C score as an indicator of clinically significant change

(58). Because no prior studies have measured *clinically* significant change when using the PSS-I, the Reliable Change Index (RCI) was used to calculate clinically significant change (59, 60).

The RCI is calculated for each patient by dividing the difference between the pretreatment and posttreatment scores by the standard error of the difference (SE_{diff}) for the measure. SE_{diff} is calculated by multiplying the standard deviation of the measure (PSS-I) by the square root of 2, multiplied again by the square root of 1 minus the scale reliability (e.g. the Cronbach's Alpha). In our sample, the standard deviation and Cronbach's alpha for the PSS-I at baseline were 7.694 and 0.865, respectively. Therefore, the RCI was calculated as follows:

$$SE_{diff} = 7.694 * \sqrt{2} * \sqrt{(1 - 0.865)} = 4.00$$

$$RCI = (\text{Posttreatment score} - \text{pretreatment score}) / 4.00$$

An RCI greater than 1.96 (or in this case, less than -1.96 to indicate decrease in symptoms) indicates that the difference is reliable. In other words, the magnitude of change is great enough that it would not be expected due to the unreliability of the measure. For this study, we considered an RCI of -1.96 or lower to indicate a significant reduction in PTSD symptoms (see Table 2). An RCI of -1.96 is equivalent to a PSS-I score reduction of 8 points.

Measuring Mindfulness

Mindfulness was measured using the 39-item Five Facet Mindfulness Questionnaire (FFMQ) (61). Subjects respond to each item by indicating how often the statement is true on a scale from 1 ("Never or very rarely true") to 5 ("very often or always true"). Total FFMQ scores were included as well as the five separate facets of mindfulness: non-reacting, observing, describing, acting with awareness, and non-judging.

Statistical Models

To analyze changes in PROMIS health domains and mindfulness domains from baseline to post and from baseline to follow-up between the MBSR and TAU groups, we used mixed-effects linear models (62). An advantage of the mixed-effects model is that it accounts for within-subject correlation of responses over time and does not drop subjects with missing data, which improves statistical efficiency. In each of these analyses, we adjusted for the effects of age, gender, and ethnicity. The models for the PROMIS outcomes also adjusted for baseline values. Randomization arm (MBSR v. TAU) and assessment (baseline, post, and 4-6 month follow-up) were treated as fixed effects. The interaction between randomization arm and assessment was used to indicate whether subjects randomized to MBSR differed from those randomized to TAU-only with respect to changes in PROMIS outcomes and mindfulness skills from baseline to post-intervention, and from baseline to follow-up. We performed two separate analyses. The first was an intent-to-treat analysis, which includes all subjects randomized to MBSR and TAU, regardless of the degree to which those randomized to MBSR participated in the MBSR program (Table 3). The second was a completer analysis, which limited the subjects in the MBSR group to those who participated in at least 4 of the sessions in the 8-week MBSR series (Table 4). All statistical analyses were performed using SPSS 19 (IBM Corporation, Armonk, NY).

RESULTS

PTSD symptoms

In the intent-to-treat analysis, the MBSR group had a statistically significant greater proportion of subjects with clinically significant reductions in PTSD symptoms compared to the TAU group at post (52.8% compared to 20.5%, p=.004, Table 2). However, at the 4 to 6-month

follow-up, the difference between the groups was not maintained: 37.5% and 33.3% of those in MBSR and in TAU, respectively, had clinically significant reductions in PTSD symptoms since baseline.

The completer analysis shows a similar pattern, with significantly more MBSR-randomized participants indicating clinically significant reductions in PTSD symptoms than those randomized to TAU (50% in MBSR compared to 20.5% in TAU, p=0.012, Table 3), followed by statistically non-different rates of PTSD symptom decline at follow-up (30.8% in MBSR, 33.3% in TAU, p=.238).

Table 2. *Comparison of % of subjects with clinically significant reductions in PTSD symptoms* between MBSR and TAU groups*

	Intent-to-Treat			Completer Analysis		
	MBSR (n= 36)	TAU (n=39)	p-value	MBSR (n=28)	TAU (n=39)	p-value
Baseline to Post, n (%)	19 (52.8%)	8 (20.5%)	**.004**	14 (50%)	8 (20.5%)	**.012**
Baseline to Follow-Up, n (%)	12 (37.5%)	11 (33.3%)	.798	8 (30.8%)	11 (33.3%)	.238

Intent-to-Treat MBSR=Randomized to Mindfulness-Based Stress Reduction plus treatment as usual

Completer MBSR=Randomized to Mindfulness-Based Stress Reduction plus treatment as usual and attended 4 or more MBSR sessions

TAU=Randomized to treatment as usual only

PROMIS Outcomes.

In the intent-to-treat analysis, there were no statistically significant differences in the PROMIS health domain outcomes at post-intervention or follow-up between those randomized to MBSR plus treatment and usual and those randomized to TAU (Table 3). However, the MBSR group consistently trended toward better outcomes than the TAU group for anxiety, depression, fatigue, pain interference, and sleep-related impairment at post and follow-up. The MBSR group reported greater decreases in pain behavior at follow-up but not at post-intervention. Both groups experienced overall increases in sleep disturbance from baseline to

follow-up, although not to a statistically significant degree. The domains of physical function, satisfaction with discretionary social activities, and satisfaction with social roles showed slightly better improvements in the MBSR group compared to TAU at post-intervention.

In the completer analysis, the MBSR group reported significantly better outcomes than TAU for Pain Interference (mean difference between groups, -5.20; 95% CI, -10.17 to -0.24, p=0.040), and better (but not statistically significant) outcomes for anxiety, depression, fatigue, and sleep-related impairment at post-intervention and 4 to 6-month follow-up (Table 4). However, the MBSR group reported significantly worse outcomes than TAU for physical function at the 4 to 6-month follow-up (mean difference, -7.12; 95% CI, -14.2 to -0.01, p=.05), despite a non-significant improvement at post-intervention. A pattern of the MBSR group reporting more favorable outcomes at post-intervention but faring less favorably at follow-up was also observed for the social satisfaction domains – satisfaction with discretionary social activities and satisfaction with social roles – although none of these differences were statistically significant.

Mindfulness Outcomes.

In the intent-to-treat analysis, the MBSR group experienced a greater increase in two facets of mindfulness – acting with awareness (mean difference, 5.27; 95% CI, 2.17 to 8.36; p=.001) and non-judging (mean difference, 3.77; 95% CI, 0.18 to 7.37; p=.040) – as well as overall mindfulness (mean difference, 11.40; 95% CI, 1.97 to 20.84; p=.018), compared to the TAU group, at 4 to 6-month follow up (Table 3). The completer analysis also found significant improvements in overall mindfulness (mean difference, 13.11; 95% CI, 3.06 to 23.15; p=.011) and acting with awareness at follow-up (mean difference, 6.09; 95% CI, 2.74 to 9.44; p<.001). Overall mindfulness was also significant in the MBSR group compared to TAU at post-

intervention in the completer analysis (mean difference, 11.41; 95% CI, 1.35 to 21.46; p=.011). The completer analysis indicated significant improvements for the "describing" facet of mindfulness at the 4 to 6-month follow up (mean difference, 2.80; 95% CI, 0.07 to 5.53; p=.045), but not for non-judging, which had been significant in the intent-to-treat analysis. Overall, the MBSR group trended toward higher levels of mindfulness skills compared to TAU group in all analyses of the FFMQ except for Observing (at 4-6 month follow-up).

Table 3: *PROMIS Outcomes from the Intent-to-Treat Analysis*

	MBSR (n=36) Mean (95% CI)	TAU (n=39) Mean (95% CI)	Between-Treatment Differences in Improvement from Baseline	P-value
Anger				
Baseline	59.0 (55.9, 62.1)	63.0 (60.0, 66.0)		.068
Post-Treatment	55.8 (52.5, 59.1)	59.7 (56.7, 62.8)	0.08 (-4.18, 4.35)	.969
4-6 Month Follow-Up	56.9 (53.5, 60.2)	60.4 (57.3, 63.5)	0.49 (-3.87, 4.85)	.824
Anxiety				
Baseline	61.3 (58.6, 64.0)	64.0 (61.5, 66.6)		.143
Post-Treatment	58.4 (55.5, 61.3)	62.4 (59.7, 65.0)	-1.22 (-5.39, 2.96)	.565
4-6 Month Follow-Up	57.9 (55.0, 60.9)	62.9 (60.1, 65.6)	-2.18 (-6.43, 2.08)	.313
Depression				
Baseline	58.7 (56.0, 61.5)	60.4 (57.7, 63.0)		.394
Post-Treatment	56.8 (53.8, 59.7)	60.1 (57.3, 62.8)	-1.65 (-5.92, 2.61)	.444
4-6 Month Follow-Up	55.9 (52.9, 58.8)	60.8 (57.9, 63.6)	-3.26 (-7.62, 1.09)	.140
Fatigue				
Baseline	61.1 (58.1, 64.1)	63.1 (60.2, 66.0)		.355
Post-Treatment	56.6 (53.3, 59.7)	61.7 (58.7, 64.7)	-3.23 (-7.17, 0.71)	.107
4-6 Month Follow-Up	57.8 (54.6, 61.0)	63.5 (60.6, 66.6)	-3.76 (-7.75, 0.24)	.065
Pain Behavior				
Baseline	58.6 (56.7, 61.2)	60.8 (58.7, 63.0)		.227
Post-Treatment	58.2 (55.8, 60.6)	58.6 (56.3, 60.8)	1.53 (-1.71, 4.77)	.352
4-6 Month Follow-Up	56.9 (54.5, 59.4)	60.7 (58.3, 63.0)	-1.80 (-5.12, 1.51)	.285
Pain Interference				
Baseline	62.0 (58.7, 65.2)	63.5 (60.4, 66.6)		.489
Post-Treatment	59.4 (55.9, 62.8)	62.5 (59.2, 65.7)	-1.53 (-6.76, 3.71)	.565

4-6 Month Follow-Up	62.3 (58.9, 65.7)	67.0 (63.8, 70.2)	-3.13 (-8.33, 2.08)	.237
*Physical Function				
Baseline	41.5 (37.4, 45.7)	40.4 (36.5, 44.4)		.708
Post-Treatment	42.1 (37.6, 46.6)	40.0 (35.9, 44.2)	.94 (-6.54, 8.4)	.804
4-6 Month Follow-Up	45.4 (40.9, 49.8)	47.3 (43.2, 51.5)	-3.07 (-10.51, 4.38)	.417
Sleep Disturbance				
Baseline	59.9 (56.4, 63.4)	66.0 (62.6, 69.3)		**.016**
Post-Treatment	56.8 (53.0, 60.6)	61.2 (57.7, 64.8)	1.60 (-3.86, 7.05)	.563
4-6 Month Follow-Up	61.5 (57.7, 65.2)	66.1 (62.5, 69.6)	1.47 (-4.00, 6.89)	.593
Sleep-Related Impairment				
Baseline	62.0 (58.6, 65.5)	65.6 (62.3, 68.9)		.138
Post-Treatment	58.4 (54.7, 62.1)	63.2 (59.8, 66.7)	-1.22 (-6.62, 4.18)	.656
4-6 Month Follow-Up	61.8 (58.2, 65.5)	67.5 (64.1, 71.0)	-2.10 (-7.47, 3.27)	.440
*Satisfaction with Discretionary Social Activities				
Baseline	42.3 (38.5, 46.2)	41.2 (37.5, 44.9)		.667
Post-Treatment	44.6 (40.4, 48.8)	40.6 (36.7, 44.5)	2.90 (-4.55, 10.35)	.443
4-6 Month Follow-Up	47.0 (42.9, 51.2)	49.3 (45.4, 53.2)	-3.41 (-10.83, 4.00)	.364
*Satisfaction with Social Roles				
Baseline	39.8 (35.8, 43.8)	39.8 (36.0, 43.7)		.984
Post-Treatment	42.4 (38.0, 46.8)	40.0 (35.9, 44.1)	2.42 (-4.93, 9.77)	.516
4-6 Month Follow-Up	44.7 (40.3, 49.0)	44.9 (40.9, 49.0)	-0.22 (-7.53, 7.09)	.952
FFMQ Mindfulness Outcomes				
FFMQ Total				
Baseline	114.8 (107.8, 121.8)	114.7 (108.1, 121.3)		.983
Post-Treatment	125.3 (118.0, 132.6)	117.4 (110.7, 124.1)	7.76 (-1.56, 17.08)	.102
4-6 Month Follow-Up	128.5 (121.3, 135.7)	117.0 (110.0, 124.0)	11.40 (1.97, 20.84)	**.018**
Non-Reacting				
Baseline	18.9 (17.1, 20.6)	19.5 (17.9, 21.2)		.574
Post-Treatment	20.5 (18.7, 22.3)	19.9 (18.2, 21.6)	1.28 (-1.02, 3.59)	.274
4-6 Month Follow-Up	21.0 (19.2, 22.8)	21.0 (19.3, 22.8)	0.59 (-1.74, 2.93)	.615
Observing				
Baseline	27.1 (25.0, 29.1)	27.1 (25.1, 29.0)		.981
Post-Treatment	29.1 (27.0, 31.3)	27.4 (25.4, 29.3)	1.71 (-0.99, 4.41)	.212
4-6 Month Follow-Up	27.1 (24.9, 29.2)	27.5 (25.5, 29.6)	-0.51 (-3.25, 2.22)	.711
Describing				
Baseline	23.9 (21.5, 26.4)	24.3 (22.0, 26.5)		.852
Post-Treatment	26.0 (23.6, 28.5)	25.3 (23.0, 27.6)	1.06 (-1.52, 3.63)	.419

4-6 Month Follow-Up	26.5 (24.0, 29.0)	24.5 (22.1, 26.9)	2.33 (-0.28, 4.94)	.080
Acting with Awareness				
Baseline	22.1 (20.2, 24.1)	21.6 (19.8, 23.5)		.730
Post-Treatment	24.3 (22.2, 26.4)	22.0 (20.1, 23.9)	1.85 (-1.21, 4.91)	.234
4-6 Month Follow-Up	27.1 (5.0, 29.1)	21.3 (19.3, 23.3)	5.27 (2.17, 8.36)	**.001**
Non-Judging				
Baseline	22.8 (20.2, 25.4)	22.2 (19.7, 24.7)		.745
Post-Treatment	25.3 (22.5, 28.0)	22.8 (20.3, 25.3)	1.84 (-1.71, 5.39)	.306
4-6 Month Follow-Up	26.9 (24.2, 30.0)	22.5 (19.9, 25.1)	3.77 (0.18, 7.37)	**.040**

Model adjusted for age, gender, and ethnicity for all analyses; the model also adjusted for baseline values for each of the PROMIS outcome analyses

**Higher scores represent more desirable outcome (for other PROMIS domains, lower scores are desired)*

PROMIS= Patient-Reported Outcome Measurement Information System

MBSR=Randomized to receive Mindfulness-Based Stress Reduction plus treatment as usual

TAU=Randomized to receive treatment as usual only

FFMQ= Five Facet Mindfulness Questionnaire

Table 4. *PROMIS & FFMQ Outcomes from the 4+ Completer Analysis*

	MBSR (n=36) Mean (95% CI)	TAU (n=39) Mean (95% CI)	Between-Treatment Differences in Improvement from Baseline	P-value
Anger				
Baseline	59.6 (56.0, 63.2)	63.0 (60.0, 66.0)		.155
Post-Treatment	55.6 (51.8, 59.4)	59.7 (56.6, 62.8)	-0.76 (-5.48, 3.96)	.750
4-6 Month Follow-Up	57.4 (53.6, 61.2)	60.4 (57.2, 63.6)	0.36 (-4.42, 5.14)	.882
Anxiety				
Baseline	60.9 (57.7, 64.1)	64.0 (61.4, 66.7)		.136
Post-Treatment	57.6 (54.2, 61.0)	62.4 (59.6, 65.1)	-1.65 (-6.31, 3.00)	.483
4-6 Month Follow-Up	57.9 (54.5, 61.3)	62.9 (60.0, 65.7)	-1.82 (-6.53, 2.89)	.446
Depression				
Baseline	59.2 (56.0, 62.5)	60.4 (57.7, 63.1)		.592
Post-Treatment	56.1 (52.7, 59.5)	60.1 (57.3, 62.9)	-2.86 (-7.51, 1.80)	.226
4-6 Month Follow-Up	56.0 (52.6, 59.4)	60.8 (57.8, 63.7)	-3.62 (-8.33, 1.10)	.132
Fatigue				
Baseline	62.1 (58.7, 65.6)	63.1 (60.2, 66.0)		.674
Post-Treatment	57.0 (53.4, 60.6)	61.7 (58.7, 64.7)	-3.73 (-8.00, 0.55)	.087
4-6 Month Follow-Up	59.2 (55.6, 62.8)	63.5 (60.5, 66.6)	-3.39 (-7.73, 0.94)	.124
Pain Behavior				

Baseline	59.2 (56.8, 61.6)	60.8 (58.8, 62.9)		.315
Post-Treatment	57.9 (55.3, 60.4)	58.6 (56.5, 60.7)	0.92 (-2.38, 4.22)	.582
4-6 Month Follow-Up	57.9 (55.4, 60.5)	60.6 (58.5, 62.8)	-1.12 (-4.47, 2.22)	.508
Pain Interference				
Baseline	63.0 (59.7, 66.3)	63.5 (60.7, 66.4)		.804
Post-Treatment	59.3 (55.7, 62.8)	62.5 (59.5, 65.4)	-2.66 (-7.63, 2.30)	.290
4-6 Month Follow-Up	61.3 (57.7, 64.8)	67.0 (64.1, 69.9)	-5.20 (-10.17, -0.24)	**.040**
*Physical Function				
Baseline	40.8 (36.4, 45.2)	40.4 (36.7, 44.2)		.901
Post-Treatment	41.9 (37.2, 46.6)	40.0 (36.1, 43.9)	1.60 (-5.51, 8.71)	.657
4-6 Month Follow-Up	40.6 (35.9, 45.3)	47.4 (43.5, 51.3)	-7.12 (-14.2, -0.01)	**.050**
Sleep Disturbance				
Baseline	59.7 (56.0, 63.4)	66.0 (62.8, 69.1)		**.012**
Post-Treatment	56.3 (52.3, 60.2)	61.2 (58.0, 64.5)	1.35 (-4.12, 6.81)	.625
4-6 Month Follow-Up	59.5 (55.6, 63.5)	66.1 (62.8, 69.3)	-0.26 (-5.72, 5.19)	.924
Sleep-Related Impairment				
Baseline	61.8 (58.1, 65.5)	65.6 (62.5, 68.8)		.123
Post-Treatment	58.6 (54.7, 62.5)	63.2 (60.0, 66.5)	-0.81 (-6.12, 4.50)	.763
4-6 Month Follow-Up	59.0 (55.1, 63.0)	67.5 (64.3, 70.8)	-4.67 (-9.99, 0.64)	.084
*Satisfaction with Discretionary Social Activities				
Baseline	41.7 (37.7, 45.7)	41.2 (37.7, 44.6)		.843
Post-Treatment	44.4 (40.0, 48.7)	40.5 (36.9, 44.2)	3.27 (-4.01, 10.55)	.375
4-6 Month Follow-Up	42.9 (38.6, 47.3)	49.3 (45.7, 52.9)	-6.85 (-14.13, 0.43)	.065
*Satisfaction with Social Roles				
Baseline	39.1 (34.8, 43.3)	39.8 (36.2, 43.4)		.784
Post-Treatment	42.0 (37.4, 46.5)	40.0 (36.2, 43.8)	2.75 (-4.42, 9.91)	.450
4-6 Month Follow-Up	40.1 (35.5, 44.6)	45.0 (41.2, 48.7)	-4.11 (-11.28, 3.05)	.258
FFMQ Mindfulness Outcomes				
Mindfulness Total Score				
Baseline	112.6 (104.7, 120.5)	114.7 (108.1, 121.2)		.695
Post-Treatment	126.8 (118.5, 135.1)	117.4 (110.8, 124.1)	11.41 (1.35, 21.46)	**.027**
4-6 Month Follow-Up	128.1 (120.0, 136.1)	117.0 (110.1, 123.9)	13.11 (3.06, 23.15)	**.011**
Non-Reacting				
Baseline	18.6 (16.7, 20.5)	19.5 (17.9, 21.1)		.454
Post-Treatment	20.4 (18.4, 22.5)	19.9 (18.3, 21.5)	1.49 (-0.98, 3.96)	.234
4-6 Month Follow-Up	20.4 (18.4, 22.3)	21.0 (19.4, 22.7)	0.26 (-2.20, 2.72)	.835
Observing				

Baseline	26.6 (24.2, 28.9)	27.1 (25.1, 29.0)		.766
Post-Treatment	29.3 (26.8, 31.7)	27.4 (25.4, 29.4)	2.36 (-0.47, 5.19)	.101
4-6 Month Follow-Up	27.6 (25.2, 30.0)	27.5 (25.5, 29.6)	0.51 (-2.31, 3.34)	.719
Describing				
Baseline	23.4 (20.6, 26.2)	24.3 (21.9, 26.6)		.645
Post-Treatment	26.6 (23.7, 29.5)	25.3 (22.9, 27.7)	2.11 (-0.63, 4.84)	.130
4-6 Month Follow-Up	26.4 (23.6, 29.3)	24.5 (22.1, 26.9)	2.80 (0.07, 5.53)	**.045**
Acting with Awareness				
Baseline	21.4 (19.1, 23.7)	21.6 (19.7, 23.5)		.877
Post-Treatment	24.2 (21.8, 26.6)	22.0 (20.0, 23.9)	2.44 (-0.91, 5.80)	.151
4-6 Month Follow-Up	27.2 (24.8, 29.5)	21.3 (19.3, 23.3)	6.09 (2.74, 9.44)	**<.001**
Non-Judging				
Baseline	22.6 (19.6, 25.6)	22.2 (19.7, 24.7)		.819
Post-Treatment	26.2 (23.1, 29.4)	22.8 (20.3, 25.4)	2.92 (-0.97, 6.82)	.139
4-6 Month Follow-Up	26.5 (23.4, 29.5)	22.5 (19.9, 25.1)	3.49 (-0.40, 7.37)	.078

Model adjusted for age, gender, and ethnicity for all analyses; the model also adjusted for baseline values for each of the PROMIS outcome analyses

**Higher scores represent more desirable outcome (for other PROMIS domains, lower scores are desired)*

PROMIS= Patient-Reported Outcome Measurement Information System

MBSR=Randomized to MBSR plus treatment as usual and attended 4 or more MBSR sessions out of 9

TAU=Randomized to treatment as usual only

FFMQ= Five Facet Mindfulness Questionnaire

DISCUSSION

The findings confirm the results of a prior pre-post MBSR study of veterans with PTSD showing an approximately 50% rate of clinically significant reduction in PTSD symptoms (36). This rate of clinically significant reduction is also similar to what was found among veterans with PTSD randomized to MBSR as part of a well-designed RCT (34). In this way, our findings at post-MBSR are consistent with prior research. However, we found that these improvements were not significantly different than treatment as usual only over a longer duration of follow-up.

In the intent-to-treat and completer analyses, the subjects in our study randomized to MBSR reported significant improvements in overall mindfulness and acting with awareness, which have been shown to be significantly associated with reduced PTSD symptoms (39),

especially reductions in hyperarousal and emotional numbing. This finding could contribute to the observed reductions in their PTSD symptoms among MBSR subjects compared to TAU subjects.

Although very few of the PROMIS health domain scores improved significantly among those randomized to MBSR compared to those randomized to TAU, more favorable outcomes were reported among the MBSR group for the majority of the domains at post-intervention, suggesting that the lack of statistically significant findings could be due to low power. Additionally, changes at post-intervention resulting from MBSR were also generally not statistically significant. Assessing the magnitude of MBSR attributable changes, one possible explanation for the PROMIS health domain improvements at post-intervention and decline at follow-up is that MBSR "refresher" courses or other continuing practice opportunities are needed to maintain and build clinical gains beyond the period of the 8-week MBSR course. Additional training may be necessary for MBSR participants to learn how to apply the mindfulness skills to different types of symptoms and experiences related to, or exacerbated by PTSD.

Additionally, it is possible that although about 50% of those in the MBSR group experienced clinically significant reductions in PTSD symptoms, even those with a clinically significant reduction may still meet the threshold for clinically diagnosed PTSD. Consequently, other domains of health may still be affected by ongoing PTSD symptoms. Therefore, despite a 10-point reduction on the PCL-C or an 8-point reduction on the PSS-I, those who reported a significant reduction in PTSD symptoms could still be experiencing difficulty with sleep, anger, anxiety, and the other domains of health affected by PTSD. It is also worth noting that since the study sample did not include a measure of current pain as an inclusion criterion and neither of the RCTs studies focused on pain populations specifically (pain can be a component of Gulf

War Illness, but was not specifically an inclusion criterion), the clinical relevance of the pain measures is unclear.

From a public health perspective, mindfulness-based treatment options have potential to lead to improvements in a range of health and wellness areas in an inexpensive way, thereby providing very high value for the public health dollar. Exposure to trauma is, unfortunately, very common, and can lead to a wide range of psychosomatic health problems and lowered quality of life. Although this study does not provide definitive evidence that MBSR could be used as an evidence-based method to address a range of physical and mental health problems among people with PTSD, the results suggest further research assessing MBSR is warranted. Future research investigating the impact of MBSR on multiple domains of health among individuals with PTSD could improve upon our methods by 1) utilizing larger sample sizes in order to increase statistical power, 2) including a form of additional mindfulness training or support to participants between post-intervention and follow-up, and 3) collect treatment-as-usual data for both groups, so that non-MBSR treatments that may contribute to improvements in PTSD symptoms and the other health domains can be accounted for in analyses.

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