CLINICAL RESEARCH STUDY

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Mindfulness-based Stress Reduction in Addition to Usual Care Is Associated with Improvements in Pain, Fatigue, and Cognitive Failures Among Veterans with Gulf War Illness

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ABSTRACT

BACKGROUND: Many Gulf War I veterans report ongoing negative health consequences. The constellation of pain, fatigue, and concentration/memory disturbances is referred to as "Gulf War illness." Prior research suggests that mindfulness-based stress reduction may be beneficial for these symptoms, but mindfulness-based stress reduction has not been studied for veterans with Gulf War illness. The objective of this trial was to conduct a pilot study of mindfulness-based stress reduction for veterans with Gulf War illness.

METHODS: Veterans (N = 55) with Gulf War illness were randomly assigned to treatment as usual plus mindfulness-based stress reduction or treatment as usual only. Mindfulness-based stress reduction was delivered in 8 weekly 2.5-hour sessions plus a single 7-hour weekend session. Pain, fatigue, and cognitive failures were the primary outcomes, assessed at baseline, after mindfulness-based stress reduction, and 6 months follow-up. Secondary outcomes included symptoms of posttraumatic stress disorder and depression.

RESULTS: In intention-to-treat analyses, at 6-month follow-up, veterans randomized to mindfulness-based stress reduction plus treatment as usual reported greater reductions in pain ($f = 0.33$; $P = .049$), fatigue ($f = 0.32$; $P = .027$), and cognitive failures ($f = 0.40$; $P < .001$). Depressive symptoms showed a greater decline after mindfulness-based stress reduction ($f = 0.22$; $P = .050$) and at 6 months ($f = 0.27$; $P = .031$) relative to treatment as usual only. Veterans with posttraumatic stress disorder at baseline randomized to mindfulness-based stress reduction plus treatment as usual experienced significantly greater reductions in symptoms of posttraumatic stress disorder after mindfulness-based stress reduction ($f = 0.44$; $P = .005$) but not at 6 months follow-up ($f = 0.31$; $P = .082$).

CONCLUSIONS: Mindfulness-based stress reduction in addition to treatment as usual is associated with significant improvements in self-reported symptoms of Gulf War illness, including pain, fatigue, cognitive failures, and depression.

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Approximately 700,000 US military personnel were deployed to the Persian Gulf in 1990 and 1991. At least one fourth have reported negative health consequences,[1] including musculoskeletal pain, fatigue, and concentration/memory disturbances, the constellation of which is referred to as "Gulf War syndrome," "Gulf War illness," or "chronic multisymptom illness."[2-4] For chronic multisymptom illness subsequent to Gulf War deployment, the term "Gulf War illness" is preferred.[4] Chronic multisymptom illness is common among patients in primary care[5] and in military combat veterans,[2,6] but Gulf War I veterans experience higher rates of chronic multisymptom illness than veterans from previous conflicts.[2,7,8] Much of the debate related to the nature of Gulf War illness has centered on the etiologic roles of psychologic stressors and environmental exposures.[1,9-11] Although Gulf War illness is often comorbid with posttraumatic stress disorder and depression,[8,12] many veterans with Gulf War illness do not have mental health conditions.[13] Some researchers have noted a link between exposure to neurotoxins encountered during deployment,[1] whereas others have not found evidence of an exposure-related cause.[3,11,14-17] It has been suggested that Gulf War illness emerged as a consequence of multiple insufficiently established causes.[11,15,18]

Although there have been numerous attempts to determine the cause of Gulf War illness,[16,17] studies of treatment approaches to Gulf War illness remain limited, and thousands of veterans continue to suffer.[19-21] Treatment models developed for Gulf War illness recommend interventions that are integrative.[22,23] To date, one clinical trial for Gulf War illness has evaluated an integrative approach, which showed a modest benefit of cognitive behavioral therapy or exercise on symptoms of Gulf War illness, which declined over time.[24] Also, there was no significant effect of cognitive behavioral therapy on fatigue relative to usual care and limited effects on pain.[24] Additional studies of integrative approaches are needed.

Mindfulness-based interventions have been applied to symptom-based syndromes.[25-27] Mindfulness has been defined as "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."[28] Mindfulness-based interventions are intended to foster the ability to attend to thoughts, emotions, and bodily sensations with an attitude of curiosity, openness, acceptance, and love,[29] which is theorized to promote cognitive and behavioral changes.[30] In mindfulness-based interventions, mindfulness skills are usually developed through a daily discipline of meditation and informal mindfulness practices. Evidence indicates that mindfulness-based interventions are associated with small to modest improvements in general symptom severity, pain, depression, and anxiety,[26,31,32] as well as reduced fatigue among individuals with chronic fatigue syndrome.[33] Although some studies indicate that mindfulness training influences attentional[34] and memory[35] abilities, extant research on these types of interventions has not specifically assessed their effect on the memory and cognitive deficits commonly found among veterans with Gulf War illness.[36-38] This evidence raises the possibility that mindfulness-based interventions might be particularly well suited for symptom management of Gulf War illness. A widely available clinical method of teaching mindfulness is an 8-week class series called "mindfulness-based stress reduction."[30]

We conducted a pilot study to assess the impact of participation in mindfulness-based stress reduction as an adjunct to treatment as usual for veterans with Gulf War illness presenting as chronic multisymptom illness.[2] It was hypothesized that participation in mindfulness-based stress reduction would be associated with improvement in pain, fatigue, and cognitive impairments for veterans with Gulf War illness, relative to treatment as usual only. As a secondary aim, we sought to assess the influence of mindfulness-based stress reduction on symptoms of depression and posttraumatic stress disorder, which are common among previously deployed veterans.

CLINICAL SIGNIFICANCE

- Attendance rates for Gulf War I veterans randomized to a mindfulness intervention (mindfulness-based stress reduction) were high.
- The addition of mindfulness-based stress reduction to usual care was associated with reductions in pain, fatigue, and cognitive failures compared with usual care alone at 6-month follow-up.
- Veterans with posttraumatic stress disorder at baseline randomized to mindfulness-based stress reduction in addition to usual care reported significant reductions in posttraumatic stress disorder symptoms immediately after mindfulness-based stress reduction and reductions at the level of a trend at 6-month follow-up.

MATERIALS AND METHODS

The study was approved by the institutional review board at VA Puget Sound Health Care System and registered with clinicaltrials.gov NCT01267045.

Participants

Fifty-five participants were randomized to treatment as usual plus mindfulness-based stress reduction or treatment as usual only (**Figure 1**). Participants met criteria for Gulf War illness, defined as deployment to the Gulf War theater of operations between August 1990 and August 1991 and self-report of at least 2 of the following symptoms that began after August 1990, lasted at least 6 months, and were present at the time of the interview: (1) fatigue that limits

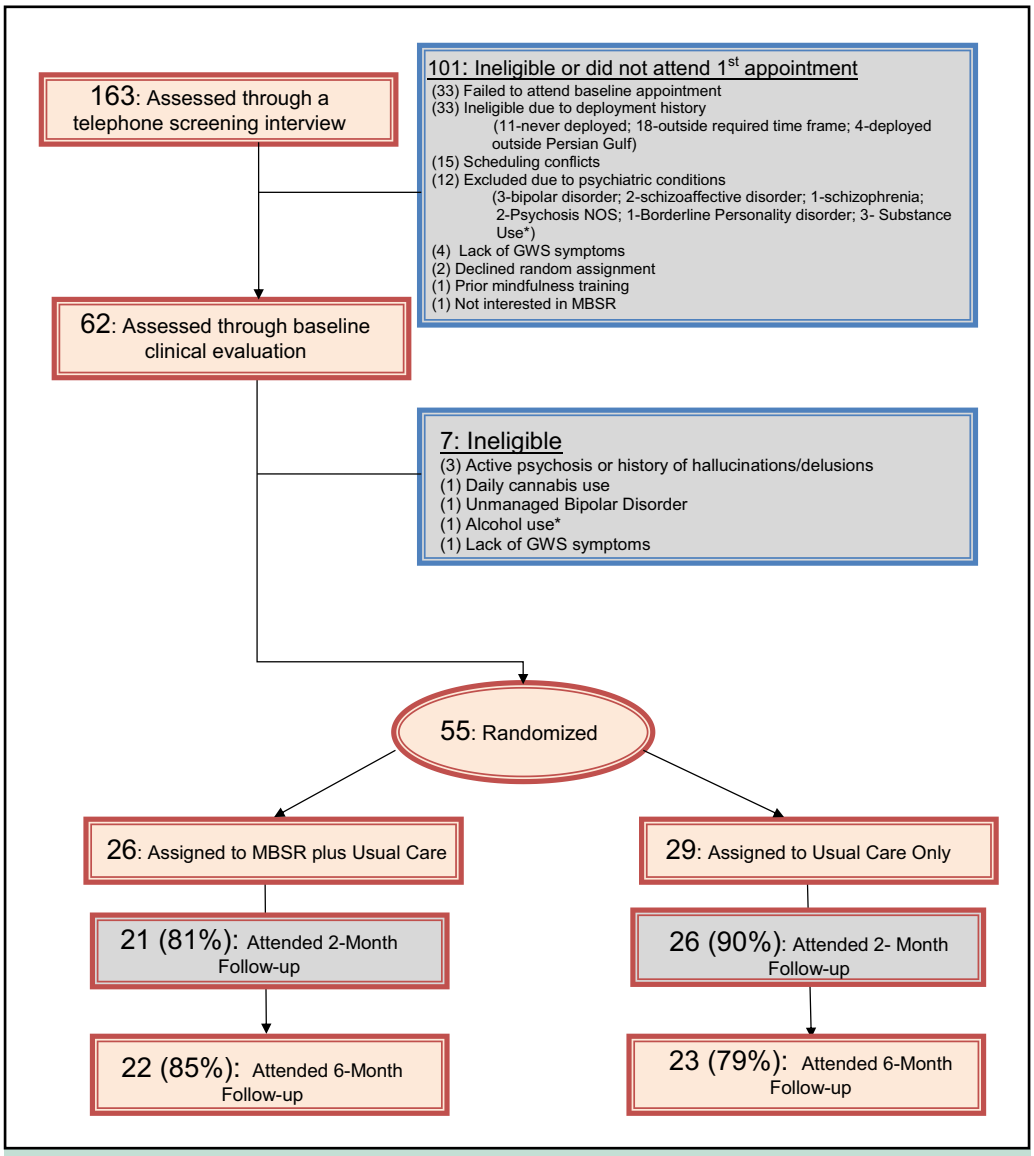

Figure 1 Participant flow through the trial. GWS = Gulf War Syndrome; MBSR = mindfulness-based stress reduction; NOS = not otherwise specified.

usual activity; (2) musculoskeletal pain involving 2 or more regions of the body; and (3) cognitive symptoms (memory, concentration, or attention difficulties).[2] The flow of subjects is shown in Figure 1.

Exclusion Criteria

At baseline, the Structured Clinical Interview for DSM-IV Axis I Disorders psychiatric interview[39] determined psychiatric exclusion criteria: (1) history of psychosis, (2) current mania, and (3) current suicidal or homicidal ideation. Additional exclusion criteria were prior participation in mindfulness-based stress reduction, active substance/alcohol abuse that posed a safety threat (current drinking and a past-year history of alcohol-related seizures or delirium tremens), or inpatient psychiatric admission within the past month.

Procedures

Recruitment sources included flyers in clinics and letters sent to Gulf War I veterans. Informed consent was obtained. After the baseline assessment, participants were stratified by baseline Patient Health Questionnaire-9 depression score $\geq$10 and randomly assigned (using concealed allocation) to treatment as usual plus mindfulness-based stress reduction or treatment as usual only. Measures were completed at baseline, 8 weeks later (the post−mindfulness-based stress reduction time point), and 6 months after the post−mindfulness-based stress reduction time point. The research assessor was blinded to the randomization arm. Participants continued to receive treatment as usual without intervention from the study team and received a small amount of monetary compensation for the research assessments. No compensation was provided to attend mindfulness-based stress reduction classes.

Clinical Assessment

Primary Outcomes. The following measures of pain, fatigue, and cognitive dysfunction were the primary outcomes: Pain was assessed by the Short-form McGill Pain Questionnaire,[40,41] a 22-item measure of pain (Cronbach's $\alpha = 0.93$). The total score, which has been shown to be responsive to patients' global impressions of change,[37] was used. Fatigue was assessed using the General Fatigue subscale of the Multidimensional Fatigue Inventory,[42] which been shown to be a valid measure of overall fatigue in multiple prior studies,[43] but had a Cronbach's $\alpha = 0.60$ in our study. Cognitive failures were assessed using the Cognitive Failures Questionnaire,[44] a 25-item questionnaire that assesses proneness to commit cognitive errors in everyday tasks (Cronbach's $\alpha = 0.95$).

Secondary Outcomes. Posttraumatic stress disorder symptoms were assessed using the Posttraumatic Stress Disorder Symptom Scale-Interview, a 17-item semistructured interview that assesses current posttraumatic stress disorder diagnostic status (Cronbach's $\alpha = 0.87$).[45] Depression was assessed using the Patient Health Questionnaire-9[46] (Cronbach's $\alpha = 0.86$). In addition, the extensively validated National Institutes of Health Patient Reported Outcomes Measurement Information System measure for fatigue[47,48] was administered as an ancillary measure and is included here because of the suboptimal psychometric properties of the Multidimensional Fatigue Inventory general fatigue subscale found in our data. Mindfulness Skills were assessed using the Five Facet Mindfulness Questionnaire[49] (Cronbach's $\alpha = 0.87$). The total Five Facet Mindfulness Questionnaire score was used.

At baseline, exposure to traumatic events was assessed by the Life Events Checklist.[50] Wartime exposures were assessed using the biological, chemical, and nuclear agents subscale from the Deployment Risk and Resilience Inventory.[51]

Intervention: Mindfulness-Based Stress Reduction. The mindfulness-based stress reduction courses closely followed the curriculum developed by the University of Massachusetts.[52,53] A single experienced instructor led each mindfulness-based stress reduction group of 20 to 25 veterans; the courses were offered for clinical purposes. Within each mindfulness-based stress reduction group, 2 to 6 veterans were participants in the current study. Each mindfulness-based stress reduction class series met once per week (2.5 hours per session) for 8 weeks, plus a 7-hour session on a Saturday between weeks 6 and 7. Participants received instruction on mindfulness meditation practices, including body scan meditation, breathing meditation, gentle yoga, walking meditation, and loving-kindness meditation. The instructions for these practices were intended to foster increased awareness of thoughts, bodily sensations, and emotions, with an attitude of curiosity, openness, and acceptance. Throughout mindfulness-based stress reduction, participants were assigned to practice meditation led by audio CD for 30 to 45 minutes per day, 6 days per week. Homework also included informal mindfulness practices, such as bringing mindful attention to everyday activities such as walking or eating. Each participant was given a workbook and the book *Full Catastrophe Living*,[54] which outlined learning goals and homework assignments, and provided supplemental reading material.

Statistical Analyses. Patient characteristics are presented using descriptive statistics. Independent sample *t* tests and chi-square tests were used to evaluate baseline differences between treatment arms. Mean scores at baseline, post−mindfulness-based stress reduction, and 6-month follow-up were derived from linear mixed-effects models. Mixed-effects models account for within-subject correlation of responses over time and allow use of all available data across all time points to increase statistical efficiency. Randomization arm and time point were treated as fixed effects. Time × treatment interaction was assessed to determine whether subjects randomized to mindfulness-based stress reduction differed from those randomized to usual care with respect to change from baseline to post−mindfulness-based stress reduction and 6-month time points on outcomes; the significance level is presented for the time × treatment interaction. Between-group effect sizes were calculated using linear mixed-effects models as Cohen's f (0.10 small; 0.25 medium; 0.40 large). The primary analysis was conducted on an intention-to-treat basis. For secondary analyses, identical comparisons were conducted limiting the intervention group to those randomized to mindfulness-based stress reduction who attended ≥4 classes ("completer" analyses).[55] Additional secondary analyses were performed limiting the patient population to those who met symptom criteria for posttraumatic stress disorder at baseline.[45] A 2-sided *P* value of less than .05 was considered statistically significant. No adjustments were made for multiple comparisons.[56] All statistical analyses were performed using Stata (Release 11; StataCorp LP, College Station, Tex).

RESULTS

The treatment groups did not differ significantly on demographic characteristics, trauma exposure, medication use, baseline prevalence of chronic conditions, disability status, scores on the primary or secondary outcome measures (**Table 1**), or deployment-related exposures (**Table 2**). Receipt of other treatments from baseline to 6-month follow-up also did not differ according to randomization arm (**Table 1**).

By using a definition of "completer" as participation in 4 or more mindfulness-based stress reduction classes,[55] 19 of 26 veterans (73%) randomized to mindfulness-based stress reduction were treatment completers. The mean number of mindfulness-based stress reduction class sessions attended

Table 1 Baseline Characteristics of Participants

Characteristic	MBSR (n = 26)	Treatment as Usual (n = 29)	*P* Value
Age (y, mean ± SD)	51.3 ± 6.8	48.6 ± 7.4	.16
Women, n (%)	3 (11.5)	5 (17.2)	.55
Ethnicity, n (%)			.24
White	17 (72)	17 (58.6)	
African American	2 (8.0)	8 (27.6)	
Asian	1 (4)	2 (6.9)	
Native American	0 (0.0)	1 (3.5)	
Other	3 (12)	1 (3.5)	
Married, n (%)	16 (61.5)	15 (51.7)	.52
McGill Pain Questionnaire scores	75.0 ± 32.5	81.2 ± 41.9	.55
Multidimensional Fatigue Inventory scores			
General fatigue	16.0 ± 2.8	15.5 ± 3.2	.53
Physical fatigue	14.4 ± 2.7	15.3 ± 2.9	.28
Reduced activity	14.9 ± 4.1	14.3 ± 3.8	.63
Reduced motivation	11.5 ± 2.4	11.6 ± 2.4	.92
Mental fatigue	15.5 ± 3.6	15.6 ± 3.2	.97
Cognitive Failures Questionnaire	59.6 ± 16.5	58.3 ± 18.7	.78
PTSD Symptom Scale Interview	29.0 ± 11.2	26.2 ± 10.6	.35
Total No. of traumas	4.23 ± 2.8	4.72 ± 3.7	.58
Direct experience	2.76 ± 2.8	2.65 ± 2.2	.79
Learned about traumatic event	0.52 ± 1.1	0.30 ± .7	.88
Witnessed traumatic event	1.72 ± 1.6	1.65 ± 1.6	.40
Conditions listed in medical record at baseline, n (%)			
Musculoskeletal pain	20 (76.9)	27 (93.1)	.48
1 diagnosis	7 (26.9)	3 (10.3)	
2-3 diagnoses	16 (61.5)	5 (17.2)	
≥4 diagnoses	8 (30.8)	8 (27.6)	
Neurologic Pain	14 (53.9)	15 (51.7)	.06
1 diagnosis	6 (23.1)	11 (37.9)	
≥2 diagnoses	8 (30.8)	4 (13.8)	
Any chronic pain condition	21 (80.8)	23 (79.3)	.89
Gastrointestinal	10 (38.5)	19 (65.5)	.50
Respiratory	10 (38.5)	12 (41.4)	.67
Depression	13 (50.0)	20 (69.0)	.15
Anxiety disorder other than PTSD	5 (19.2)	5 (17.2)	.85
Baseline medication use, n (%)			
Opiate	14 (53.8)	5 (17.2)	.43
Antidepressant	13 (50.0)	14 (48.3)	.68
Benzodiazepine	4 (15.4)	4 (13.8)	.58
Amphetamine	2 (7.7)	3 (10.3)	.55
Service-connectedness			
None (0%)	3 (11.5)	2 (6.9)	.55
<50%	2 (7.7)	5 (17.2)	.29
50%-100%	21 (80.8)	22 (75.9)	.66
Other treatments received during the study period			
Pain treatment	6 (23.1)	8 (27.6)	.70
Cognitive-behavioral therapy	0 (0.0)	1 (3.5)	.34
Acceptance and commitment therapy	0 (0.0)	2 (6.9)	.17
Prolonged exposure therapy	0 (0.0)	0 (0.0)	
Addiction treatment	1 (3.8)	0 (0.0)	.29
Psychiatric medication management	7 (26.9)	10 (34.5)	.55
Cognitive processing therapy	0 (0.0)	1 (3.4)	.34
Other/unspecified mental health treatment	7 (26.9)	11 (37.9)	.39

MBSR = mindfulness-based stress reduction; PTSD = posttraumatic stress disorder; SD = standard deviation.

Table 2 Participant Exposure to Biological, Chemical, and Nuclear Agents

Characteristic	MBSR (n = 26) No. (%)	Treatment as Usual (n = 29) No. (%)	*P* Value
Pyridostigmine pills and vaccines	20 (77)	26 (90)	.33
Chemical and biological weapons	7 (27)	9 (31)	.81
Pesticides and insect repellent	18 (69)	22 (76)	.75
Smoke and diesel fume	22 (85)	28 (97)	.24
Depleted uranium	10 (38)	6 (21)	.13
Nonmilitary food	19 (73)	23 (79)	.78
Exploding artillery or missiles	14 (54)	20 (69)	.33
Entering enemy tank, bunker, or facility	12 (46)	17 (59)	.45

Values present the number and percentage of participants responding in the affirmative to items from VA Deployment Risk and Resiliency Inventory 2 Section F.
MBSR = mindfulness-based stress reduction.

was 5.7 (median number of sessions attended = 7; range, 0-9 sessions). Research compliance was high; 85% completed the post-test assessment; 82% completed the 6-month assessment.

Intention-To-Treat Analyses

Primary Outcomes. Table 3 and Figure 2 show the mean scores for outcome measures over time. Veterans randomized to mindfulness-based stress reduction did not report greater reductions in pain at immediate post-test but reported greater reductions at 6 months, with a medium to large effect size (f = 0.33; P = .049). Reductions in cognitive failures were greater for veterans randomized to mindfulness-based stress reduction at both immediate post-test and at 6 months with large effect sizes: f = 0.44 (P = .002) and f = 0.40 (P < .001), respectively. Those randomized to mindfulness-based stress reduction did not report greater reduction in fatigue (Multidimensional Fatigue Inventory) at immediate post-test but reported greater reductions in fatigue at 6 months with a medium to large effect size (f = 0.32; P = .027).

Secondary Outcomes. Depressive symptoms showed a greater decline for those randomized to mindfulness-based stress reduction at immediate post-test and at 6 months with a medium effect size: f = 0.22 (P = .050) and f = 0.27 (P = .031), respectively. The National Institutes of Health Patient Reported Outcomes Measurement Information System fatigue measure showed greater reductions for veterans randomized to mindfulness-based stress reduction at both immediate post-test (f = 0.35; P = .015) and at 6 months (f = 0.26; P = .047) relative to treatment as usual only. Veterans randomized to mindfulness-based stress reduction demonstrated a greater increase in mindfulness skills, with a medium to large effect size at immediate post-test (f = 0.28; P = .046) and at 6 months (f = 0.38; P = .005) relative to treatment as usual only.

Because posttraumatic stress disorder is frequently comorbid with Gulf War illness,[8,12] analyses were conducted on the subset of veterans who met symptom criteria for posttraumatic stress disorder at baseline (n = 45).[45] For veterans with posttraumatic stress disorder at baseline who were randomized to mindfulness-based stress reduction plus treatment as usual, there were greater reductions in symptoms of posttraumatic stress disorder at the immediate post-test (with a large effect size, f = 0.44; P = .005), whereas at 6 months there was a trend toward greater reduction in posttraumatic stress disorder symptoms (f = 0.31; P = .082) compared with treatment as usual only.

Completer Analyses. Veterans randomized to mindfulness-based stress reduction who attended at least 4 classes (completers) were compared with veterans randomized to treatment as usual (Table 3). Analyses of primary outcome measures were similar to the intention-to-treat results. For secondary outcomes, mindfulness-based stress reduction completer results were similar to those of intention-to-treat analyses. For the National Institutes of Health Patient Reported Outcomes Measurement Information System fatigue measure, compared with usual care, mindfulness-based stress reduction completers reported greater reductions in fatigue at the post−mindfulness-based stress reduction time point (f = 0.43; P = .008), whereas at 6 months there was a trend toward significance (f = 0.23; P = .073).

DISCUSSION

In this small trial, we found that veterans with Gulf War illness randomized to mindfulness-based stress reduction plus treatment as usual had significantly greater improvements, compared with treatment as usual alone, on the primary outcome measures of pain, fatigue, and cognitive failures when assessed 6 months after the intervention. We also found improvement in key secondary outcomes for those randomized to mindfulness-based stress reduction, including symptoms of posttraumatic stress disorder (among veterans who met diagnostic criteria for posttraumatic stress disorder at baseline), which improved at immediate post-test in intention-to-treat analyses but diminished somewhat at 6-month follow-up. At both follow-up time points, we found

Table 3 Mean Summary Scores and Cohen's f Effect Sizes* for Mindfulness-Based Stress Reduction (n = 26) vs Treatment as Usual (n = 29) for Intention-To-Treat and Completer Analyses

	Intention-To-Treat Analysis			Completer Analysis		
Summary Scores	Baseline Mean ± SD	Post-treatment Mean ± SD	6 Months Mean ± SD	Baseline Mean ± SD	Post-treatment Mean ± SD	6 Months Mean ± SD
Primary Outcomes						
MPQ-2						
MBSR	75.0 ± 32.5	54.0 ± 44.2	57.1 ± 44.7	69.6 ± 26.4	40.9 ± 23.9	46.6 ± 24.2
TAU	81.2 ± 41.9	65.5 ± 43.4	76.6 ± 49.3	81.2 ± 41.9	65.5 ± 43.4	76.6 ± 49.3
Effect size*		0.13	0.33		0.28	0.40
P value		.45	**.05**		.12	**.01**
MFI General Fatigue						
MBSR	16.0 ± 2.8	14.9 ± 3.6	13.6 ± 3.4	16.3 ± 2.7	14.7 ± 3.2	13.6 ± 3.4
TAU	15.5 ± 3.2	15.5 ± 2.9	15.3 ± 3.6	15.5 ± 3.2	15.5 ± 2.9	15.3 ± 3.6
Effect size*		0.18	0.32		0.25	0.33
P value		.27	**.03**		.13	**.02**
CFQ						
MBSR	59.6 ± 16.5	46.9 ± 18.1	46.6 ± 15.4	59.3 ± 16.1	58.3 ± 17.7	44.1 ± 14.8
TAU	58.3 ± 18.7	58.6 ± 18.1	61.9 ± 18.6	58.3 ± 18.7	58.6 ± 18.1	61.9 ± 18.6
Effect size*		0.44	0.40		0.64	0.49
P value		**.002**	**<.001**		**<.001**	**<.001**
Secondary Outcomes						
PSS-I						
MBSR	29.0 ± 11.2	20.7 ± 9.1	21.7 ± 10.8	28.3 ± 12.1	19.1 ± 9.1	20.4 ± 11.5
TAU	26.2 ± 10.6	24.7 ± 10.2	23.6 ± 10.7	26.2 ± 10.6	24.7 ± 10.2	23.6 ± 10.7
Effect size*		0.40	0.27		0.55	0.37
P value		**.004**	.08		**.001**	**.02**
PHQ-9						
MBSR	14.4 ± 5.5	10.2 ± 6.2	9.5 ± 4.7	14.5 ± 5.4	9.2 ± 5.6	8.9 ± 4.8
TAU	12.8 ± 5.2	12.4 ± 6.7	12.3 ± 6.8	12.8 ± 5.2	12.4 ± 6.7	12.3 ± 6.8
Effect size*		0.22	0.27		0.31	0.38
P value		**.05**	**.03**		**.01**	**.01**
PROMIS fatigue						
MBSR	62.2 ± 5.4	56.0 ± 8.6	57.5 ± 9.6	62.4 ± 5.0	55.3 ± 9.0	58.0 ± 10.0
TAU	62.1 ± 8.8	61.5 ± 9.3	62.0 ± 10.0	62.1 ± 8.8	61.5 ± 9.3	62.0 ± 10.0
Effect size*		0.35	0.26		0.43	0.23
P value		**.02**	**.05**		**.008**	.07
FFMQ						
MBSR	115.8 ± 17.3	126.5 ± 22.7	129.4 ± 22.4	116.9 ± 18.0	129.7 ± 23.3	131.3 ± 20.9
TAU	115.1 ± 16.3	115.0 ± 15.1	114.6 ± 19.6	115.1 ± 16.3	115.0 ± 15.1	114.6 ± 19.6
Effect size*		0.28	0.38		0.30	0.48
P value		.046	**.005**		**.03**	**.003**

*Cohen's f 0 .10 small; 0.25 medium; 0.40 large.

Bolded values are statistically significant.

CFQ = Cognitive Failures Questionnaire; FFMQ = Five Facet Mindfulness Questionnaire; MBSR = mindfulness-based stress reduction; MFI = Multidimensional Fatigue Inventory; MPQ-2 = McGill Pain Questionnaire 2; PHQ-9 = Patient Health Questionnaire-9; PROMIS = Patient Reported Outcomes Measurement Information System; PSS-I = PTSD Symptom Score Interview; SD = standard deviation; TAU = treatment as usual.

that veterans with Gulf War illness randomized to mindfulness-based stress reduction demonstrated increased mindfulness skills, with large effect sizes, suggesting that they learned the skills intended by the intervention. Overall, this study provides initial evidence to support offering mindfulness-based stress reduction as an intervention for Gulf War illness presenting as chronic multisymptom illness.

Outcomes of a mindfulness-based intervention have not been previously reported for Gulf War illness. However, our findings are consistent with studies of mindfulness-based interventions on symptoms that occur as a component of Gulf War illness.[26] For fatigue, evidence suggests that mindfulness-based interventions are associated with improvement in chronic fatigue syndrome.[33,57] One mechanism by which mindfulness is theorized to influence fatigue is through reappraisal of thoughts and feelings that contribute to fatigue.[33,57] For chronic pain, a meta-analysis of mindfulness-based interventions for chronic pain reported significant effects for pain intensity,[27] and a review

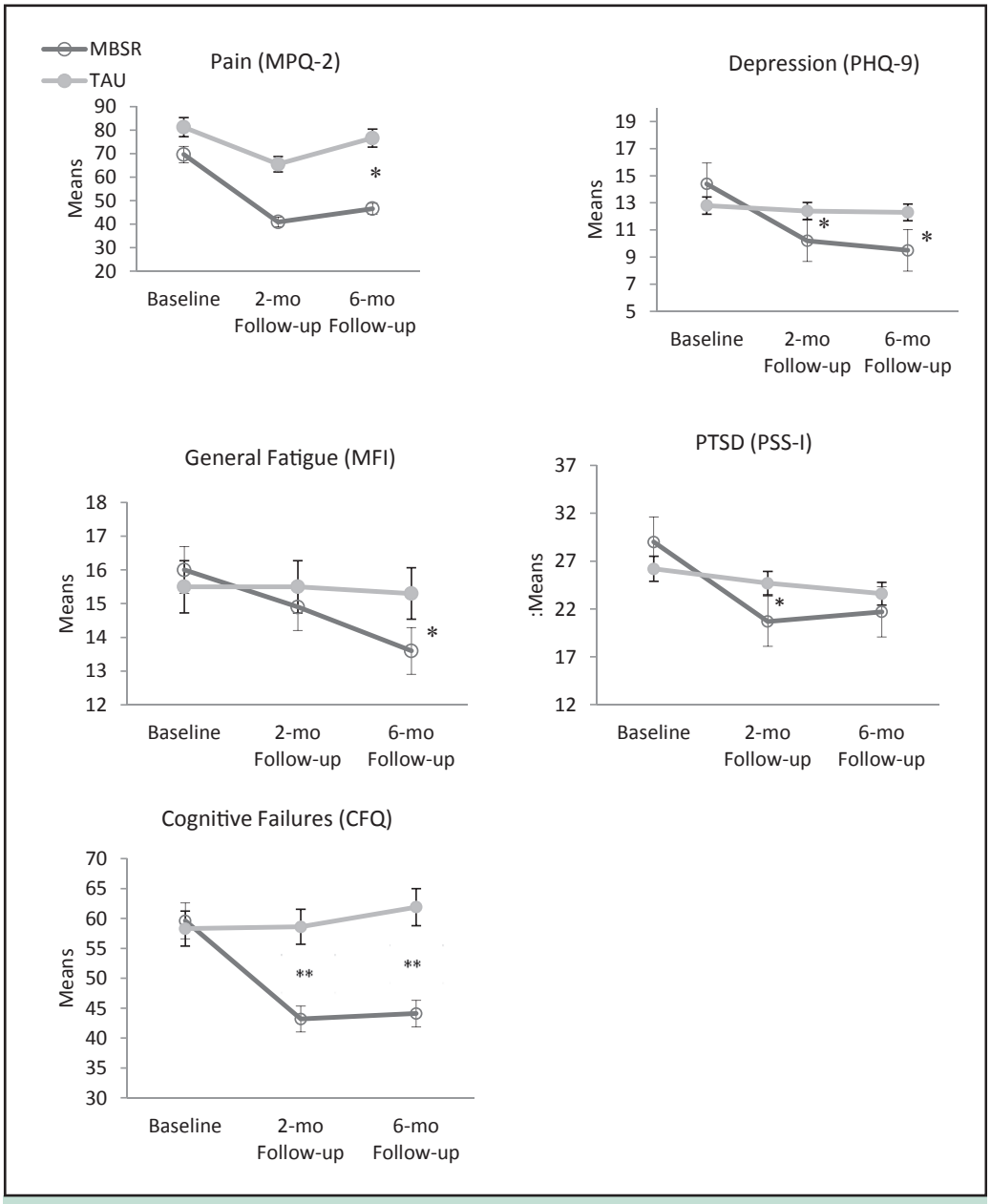

Figure 2 Outcomes over time for mindfulness-based stress reduction compared with treatment as usual for veterans with Gulf War illness (intention-to-treat analyses). CFQ = Cognitive Failures Questionnaire; MFI = Multidimensional Fatigue Inventory; MPQ-2 = McGill Pain Questionnaire 2; PHQ-9 = Patient Health Questionnaire; PSS-I = PTSD Symptom Scale Interview; PTSD = posttraumatic stress disorder. *$P \leq .05$, **$P \leq .01$ for significance of group × time interaction.

found reductions in pain intensity in 6 of 8 randomized controlled trials.[25] A meta-analysis of mindfulness-based interventions for symptom-based syndromes also found significant benefit when pain outcomes were assessed.[26] The pain measure used in our study (McGill Pain Questionnaire 2) can be considered a measure of the distress caused by pain.[58] It has been postulated that mindfulness allows uncoupling of the cognitive and emotional elements from the sensory experience of chronic pain, which could decrease distress or suffering.[59] Mindfulness practices also may constitute a form of exposure therapy for people with chronic pain.[30,60] In addition, anxiety decreases pain threshold and lowers pain tolerance,[61] and interventions that reduce anxiety and reactivity could be especially helpful. Gulf War illness also can include changes in concentration and memory, and our study findings are consistent with a small prior literature that shows a negative correlation between measures of mindfulness and cognitive failures.[62-64] Mood disturbances often occur in chronic multisymptom illness,[3] and as in multiple prior studies of mindfulness-based

interventions,[31,32] we found improvements in depressive symptoms. One possibility is that the observed changes in the self-reported primary outcomes could be mediated by the changes in depression or anxiety, but this initial study was not designed to test this hypothesis. Of note, our intention-to-treat analyses included 3 veterans randomized to mindfulness-based stress reduction who attended zero classes. Seventy-three percent of veterans randomized to mindfulness-based stress reduction attended at least 4 classes, which is similar to our prior experience with mindfulness-based stress reduction among veterans.[65,66] The apparent acceptability of mindfulness-based stress reduction is consistent with the larger body of literature that shows that veterans use complementary and alternative medicine at high rates.[67,68]

The reduction in symptoms of posttraumatic stress disorder found in our study is generally consistent with prior studies of mindfulness-based interventions for posttraumatic stress disorder. Uncontrolled studies have shown improvement in posttraumatic stress disorder symptoms over time after mindfulness-based stress reduction,[66,69] as did a small trial that compared mindfulness-based cognitive therapy with usual care.[70] A recent well-designed randomized controlled trial (N = 116) compared mindfulness-based stress reduction with an active control and found that those randomized to mindfulness-based stress reduction had greater improvement in posttraumatic stress disorder symptom severity, depression, and quality of life at 2-month follow-up.[71] However, a prior small randomized controlled trial (N = 47) compared mindfulness-based stress reduction with usual care for veterans with posttraumatic stress disorder and did not find a significant overall effect on symptoms of posttraumatic stress disorder, although a subset had clinically meaningful improvement in a post hoc analysis.[65] The findings of the current study provide additional evidence to indicate that participation in mindfulness-based stress reduction is associated with reductions in symptoms of posttraumatic stress disorder; this supports the need for additional, more definitive trials.

This study was not intended to address questions or propose theories regarding the cause or causes of Gulf War illness, but rather to focus on the suffering and health concerns currently experienced by this cohort of veterans. The perspective of the study was that serious health conditions such as Gulf War illness, regardless of original cause, involve symptoms and functional impairments that may be amenable to amelioration by learning and practicing mindfulness.

Study Limitations

This study has a number of limitations. This was designed as a pilot study; thus, we did not adjust for multiple comparisons, so that we would not miss potential associations that could lead to additional treatments for Gulf War illness.[56] Although the treatment as usual arm accounts for changes due to regression to the mean, it does not allow conclusions regarding whether changes occurred because of the mechanism conceptualized by the intervention vs nonspecific effects of group participation. An additional limitation is that we did not track change in medication use over the course of the study, such as opiates, which might influence study results. In addition, the reliability statistic for the Multidimensional Fatigue Inventory general fatigue subscale was suboptimal in our data, but we included a well-validated overlapping measure of fatigue (the National Institutes of Health Patient Reported Outcomes Measurement Information System fatigue measure), which showed improvement, supporting a significant effect of mindfulness-based stress reduction on fatigue.

CONCLUSIONS

The findings in this small trial provide initial support for offering mindfulness-based stress reduction to veterans with Gulf War illness and warrant larger randomized controlled trials of mindfulness-based stress reduction for Gulf War illness.

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