Cognitive Behavioral Therapy and Aerobic Exercise for Gulf War Veterans' Illnesses

A Randomized Controlled Trial

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Context Gulf War veterans' illnesses (GWVI), multisymptom illnesses characterized by persistent pain, fatigue, and cognitive symptoms, have been reported by many Gulf War veterans. There are currently no effective therapies available to treat GWVI.

Objective To compare the effectiveness of cognitive behavioral therapy (CBT), exercise, and the combination of both for improving physical functioning and reducing the symptoms of GWVI.

Design, Setting, and Patients Randomized controlled 2×2 factorial trial conducted from April 1999 to September 2001 among 1092 Gulf War veterans who reported at least 2 of 3 symptom types (fatigue, pain, and cognitive) for more than 6 months and at the time of screening. Treatment assignment was unmasked except for a masked assessor of study outcomes at each clinical site (18 Department of Veterans Affairs [VA] and 2 Department of Defense [DOD] medical centers).

Interventions Veterans were randomly assigned to receive usual care (n=271), consisting of any and all care received from inside or outside the VA or DOD health care systems; CBT plus usual care (n=286); exercise plus usual care (n=269); or CBT plus exercise plus usual care (n=266). Exercise sessions were 60 minutes and CBT sessions were 60 to 90 minutes; both met weekly for 12 weeks.

Main Outcome Measures The primary end point was a 7-point or greater increase (improvement) on the Physical Component Summary scale of the Veterans Short Form 36-Item Health Survey at 12 months. Secondary outcomes were standardized measures of pain, fatigue, cognitive symptoms, distress, and mental health functioning. Participants were evaluated at baseline and at 3, 6, and 12 months.

Results The percentage of veterans with improvement in physical function at 1 year was 11.5% for usual care, 11.7% for exercise alone, 18.4% for CBT plus exercise, and 18.5% for CBT alone. The adjusted odds ratios (OR) for improvement in exercise, CBT, and exercise plus CBT vs usual care were 1.07 (95% confidence interval [CI], 0.63-1.82), 1.72 (95% CI, 0.91-3.23), and 1.84 (95% CI, 0.95-3.55), respectively. The OR for the overall (marginal) effect of receiving CBT (n=552) vs no CBT (n=535) was 1.71 (95% CI, 1.15-2.53) and for exercise (n=531) vs no exercise (n=556) was 1.07 (95% CI, 0.76-1.50). For secondary outcomes, exercise alone or in combination with CBT significantly improved fatigue, distress, cognitive symptoms, and mental health functioning, while CBT alone significantly improved cognitive symptoms and mental health functioning. Neither treatment had a significant impact on pain.

Conclusion Our results suggest that CBT and/or exercise can provide modest relief for some of the symptoms of chronic multisymptom illnesses such as GWVI.

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In 1990 and 1991, 700 000 US troops were deployed to the Persian Gulf in what became known as the Gulf War. Upon their return, many Gulf War veterans from both the US and other allied forces began to report chronic, unexplained fatigue, pain,

For editorial comment see p 1436.

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cognitive, and other symptoms.[1-3] The Department of Veterans Affairs (VA) and Department of Defense (DOD) collectively refer to these symptoms as *Gulf War veterans' illnesses* (GWVI) because they do not represent a unique illness as implied by the commonly used term *Gulf War syndrome*. Many studies have sought to determine the etiology of these symptoms, but no single cause or pathogenic mechanism has been identified.[4-7]

The symptoms of GWVI cannot be distinguished from other chronic multisymptom illnesses, such as fibromyalgia and chronic fatigue syndrome.[1,8,9] Since 2 treatments, cognitive behavioral therapy (CBT) and aerobic exercise, have been effective in improving the symptoms and functional status of individuals with other multisymptom illnesses, we hypothesized that these therapies would also improve the functional status and reduce the symptoms of veterans with GWVI.[10-13]

METHODS

Study Design

The VA Cooperative Study #470 was a randomized, multicenter, controlled trial of CBT and/or aerobic exercise in veterans with GWVI.[14] The study was initiated in April 1999 at 18 VA and 2 DOD medical centers and ended in September 2001. The trial was monitored by the human rights committee at the coordinating center, the institutional review boards at each participating site, and an independent data and safety monitoring board (DSMB).

Study Participants

Veterans were eligible for the study if they were deployed to the Gulf War theater of operations between August 1990 and August 1991 and reported at least 2 of the following 3 symptoms that began after August 1990, lasted for more than 6 months, and were present at the time of screening: fatigue that limited usual activity; musculoskeletal pain involving 2 or more regions of the body; and cognitive symptoms (memory, concentration, or attention difficulties). Veterans were excluded from the study for any of the following: a health condition precluding exercise or CBT; past CBT for treatment of GWVI; concurrent enrollment in another clinical trial; pregnancy; a clearly defined disease that accounted for the veteran's symptoms; severe psychiatric illness (any history of psychiatric hospitalization in the past 2 years, any history of psychoses or use of antipsychotic medication, alcohol or substance abuse within the past 2 years, or current suicidal thoughts or a suicide attempt within the past 2 years) as measured by the Primary Care Evaluation of Mental Disorders (Prime MD)[15]; self-reported regular (weekly) activity level raising the metabolic rate to 7 times the resting rate (7 metabolic equivalents [METs]), as determined by study personnel based on information provided in the study protocol and giving the energy requirements (in METs) for a wide variety of occupational and recreational activities; or a score of at least 40 on the Physical Component Summary (PCS) scale of the Veterans Short Form 36-Item Health Survey (V/SF-36). A score of 40 is approximately equal to 1 SD below the general US population and 0.5 SD above the population of veterans who use the VA health care system.[16] Low PCS scores are indicative of poor physical functioning.

Randomization

Veterans who satisfied eligibility criteria and gave written informed consent were randomized to 1 of 4 treatment arms: usual care; CBT alone plus usual care; exercise alone plus usual care; or CBT plus exercise plus usual care. Randomization was stratified by medical center using a permuted block scheme with equal allocation among treatment arms. Because CBT was given in a group format, eligible participants were randomized in groups of 4 participants, whenever possible, to 1 of the 4 treatment arms using a permuted block design with a block size of 8. Randomization was centrally performed by the coordinating center after verification of eligibility criteria.

Interventions

Cognitive Behavioral Therapy. Cognitive behavioral therapy was delivered in groups of 3 to 8 participants.[14] Treatment sessions were 60 to 90 minutes long and groups met weekly for 12 weeks; participants remained in the same group throughout the treatment period. The CBT protocol was designed specifically to target physical function, with the goals of (1) teaching behavioral skills to help participants experience a safe and gradual improvement in physical functioning without experiencing a disabling exacerbation of symptoms and (2) teaching cognitive strategies to help participants learn systematic ways of analyzing and producing solutions to problems that serve as barriers to functioning. Components of CBT intervention included time-contingent activity pacing, pleasant activity scheduling, mnemonic strategies, sleep hygiene, assertiveness skills, confrontation of negative thinking and affect, and structured problem-solving skills. Although all of the CBT components were used to increase physical functioning, CBT did not specifically encourage exercise or its compliance in this study. All study therapists were licensed doctoral-level psychologists with previous training in CBT modalities; at most clinical sites, only 1 CBT therapist conducted treatment sessions. Each therapist received protocol training before study initiation. Treatment manuals were provided to therapists and participating veterans to ensure uniformity of the intervention across sites and to facilitate monitoring of treatment fidelity. The participants' treatment manual was designed for use either in supervised therapy or as a self-help tool.

Aerobic Exercise. The exercise intervention was designed specifically to increase activity level by allowing flexibility in selecting the types of exercise and by giving participants the ability to set the intensity of exercise based on their symptoms. A submaximal cycle ergometer exercise test was used to determine physical fitness at baseline and to develop individualized prescriptions for a low-intensity aerobic exercise program to increase the activity level of veterans assigned to exercise.[14] Participating vet-

erans were asked to exercise once per week for 1 hour in the presence of the exercise therapist during the 12-week treatment phase. Exercise therapists were either certified physical therapists or masters-level exercise physiologists. Therapists instructed participants about exercise, stretching techniques, and activity selection using ratings of perceived exertion, target heart rate, and METs. Participants were also asked to exercise independently 2 to 3 times per week during the 12-week treatment phase and throughout the follow-up period. Intensity and duration of exercise were gradually increased as tolerated.

Cognitive Behavioral Therapy Plus Aerobic Exercise. Veterans randomized to combination therapy were assigned to concurrently receive 12 one-hour weekly sessions of CBT and 12 one-hour weekly sessions of exercise training.

Usual Care. All study participants received usual care consisting of any and all care received from inside or outside of the VA or DOD health care systems. This care included a variety of nonsystematic interventions aimed at symptom relief. The control group received only usual care.

Baseline and Follow-up

Participants were evaluated at baseline, 3 months, 6 months, and 12 months. Evaluations included completion of the primary and secondary outcome assessment forms, the Prime MD,[15] a physical examination, a dolorimeter/tenderpoint examination, and a submaximal exercise test.

Outcome Measures

The primary study outcome measure was binary and was defined as the presence or absence of more than a 7-point increase (improvement) at 12 months relative to baseline on the PCS scale of the V/SF-36. The V/SF-36, a brief self-administered patient questionnaire assessing health status and health-related quality of life, is a modification of the well-established Medical Outcomes Study SF-36, used in ambulatory care veterans standardized to a US population mean of 50 points with an SD of 10 points.[17,18] The PCS scale was selected because it integrates measures of functional status that span 8 domains of health that are relevant to GWVI and because there is no validated disease-specific measure for this illness. The first 5 domains of PCS are physical (physical functioning, role limitations due to physical problems, bodily pain, general health, and vitality) and are given greater weight; the last 3 domains are mental and given smaller weight (social functioning, role limitations due to emotional problems, and mental health). The common symptoms of GWVI (pain, fatigue, myalgia, rash, dyspnea, insomnia, various gastrointestinal symptoms, and sensitivity to odors) span a wide range of physical manifestations largely covered by the PCS concepts. The 7-point change was selected because a change greater than 7 points is outside the 95% confidence interval (CI) for an individual patient score, as estimated from the SD and score reliability.[19] Changes of this magnitude have also been shown to be clinically relevant in many studies of chronic illnesses.[19-24] A 12-month follow-up was selected because clinical trials using exercise and CBT have demonstrated benefits for this duration.[10,12,25,26]

Secondary outcome measures were assessments of pain,[27] fatigue,[28] cognitive symptoms,[29] distress, and mental health–related functioning, assessed by standardized instruments (TABLE 1).

Table 1. Description of Primary and Secondary Outcome Measures*

Outcome Measures	Description	Range of Scale	Pathologic Finding Indicated by
Primary outcome measure			
V/SF-36 Physical Component Summary	Physical health functioning	0-100	Low scores
Secondary outcome measures			
V/SF-36 Mental Component Summary	Mental health functioning	0-100	Low scores
McGill Short Form			
Sensory pain	Qualitative physical features of the pain experience	0-33	High scores
Affective pain	Qualitative affective features of the pain experience	0-12	High scores
Pain right now	Quantitative rating of current pain intensity	0-10	High scores
Typical level of pain	Average level of pain intensity	0-10	High scores
Multidimensional Fatigue Inventory			
General fatigue	Overall fatigue	4-20	High scores
Physical fatigue	Fatigue related to physical functioning	4-20	High scores
Reduced activity	Fatigue that affects activity level	4-20	High scores
Reduced motivation	Fatigue as measured by decreased incentive to be active	4-20	High scores
Mental fatigue	Fatigue that affects cognitive abilities such as concentration	4-20	High scores
Cognitive difficulties			
Cognitive Failures Questionnaire	Self-report of cognitive symptoms, such as concentration, attention, and memory	25-125	Low scores
V/SF-36 Mental Health Inventory	Emotional distress	0-100	Low scores

Abbreviation: V/SF-36, Veterans Short Form 36-Item Health Survey.
*Changes of more than 7 units in the Physical Component Summary and more than 8.5 units in the Mental Component Summary of the V/SF-36 have been shown to be clinically meaningful.[19] There has been no consensus in the literature to determine clinically relevant changes for any of the other outcome measures.

Research assistants who were masked to treatment assignment administered all primary and secondary outcome assessments.

Adverse Events

Site investigators were instructed to report all adverse events and to evaluate each event for its date of onset, relatedness to treatment (based on the investigator's clinical judgment), and resolution. Adverse events were defined as serious if they were fatal or life threatening or resulted in inpatient hospitalization or permanent disability. The DSMB and study chairs independently reviewed each serious adverse event to determine if further action was necessary.

Sample Size

Sample size was calculated to detect all 6 pairwise differences between treatment arms for the primary end point, assuming a 15% improvement with usual care, 30% with CBT or exercise alone, and 45% with CBT plus exercise. The target sample size was 1064 veterans for 80% power and a type I error of .0083 (2-sided and corrected for the 6 comparisons).

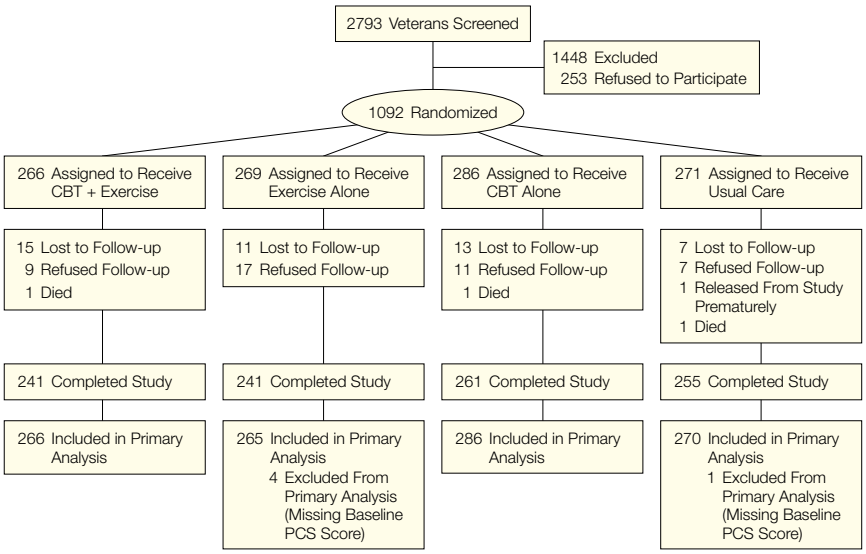
Statistical Analysis

A modified intent-to-treat analysis was used for the primary outcome measure; 5 participants without a calculable PCS score at baseline were excluded from the analysis per recommendation of the DSMB. Participants who withdrew from the study or missed the 12-month visit were classified as not improved[30] per protocol. A generalized linear mixed model[31-33] was used to analyze treatment efficacy, adjusted for the study design (randomization by site and by groups of veterans within site), baseline PCS score, and whether veterans reported a pending disability claim (unbalanced at baseline; $P=.009$). Statistical significance for the pairwise treatment comparisons was determined by the Hochberg procedure using an overall type I error of .05.[34] Treatment effects were summarized by adjusted odds ratios (ORs) and 95% familywise CIs (ie, CIs corrected for the multiple pairwise comparisons that preserve the overall type I error of .05). Since there was no interaction between treatment and the primary outcome measure, a secondary analysis evaluated the marginal effects of exercise and CBT using the methods described herein.

A modified intent-to-treat analysis also was used for the secondary outcome measures, including actual PCS scores. Participants without a baseline value or without any follow-up measurements were excluded from the analysis. Treatment efficacy was analyzed by mixed models, adjusted for study design and pending disability claims.[35] The outcome variable in each mixed model was the change at 3, 6, and 12 months relative to baseline, with the baseline value as a covariate in the model. Mixed models were fitted by maximum likelihood methods using all available data. A type I error rate of .025 was used for all tests of significance for secondary end points, and P values for pairwise treatment comparisons were determined by the Hochberg procedure.[34] Since there were no significant treatment × time interactions (ie, the treatment effect was the same for all time points), the marginal effects of each treatment are presented as least-squares mean differences from baseline (ie, the average treatment effect over the follow-up period). Sensitivity analyses were conducted with imputed missing values by multiple imputation using the stated baseline covariates,[36-38] and the results were similar.

We also conducted analyses based on adherence, defined as attending at least two thirds of the treatment sessions (8 sessions for CBT alone, 8 sessions for exercise alone, and 16 sessions for CBT plus exercise). SAS Version 8.2 (SAS Institute Inc, Cary, NC) was used for all analyses.

Figure 1. Participant Flow Through the Trial



CBT indicates cognitive behavioral therapy; PCS, Physical Component Summary of the Veterans Short Form 36-Item Health Survey.

RESULTS

Enrollment and Entry Characteristics

Between April 1999 and September 2000, 1092 veterans were enrolled of 2793 screened (FIGURE 1). The most frequent reason for exclusion was a PCS score of at least 40. Eight randomized veterans were later determined to be ineligible but were included in analyses per DSMB recommendation.

Baseline characteristics were generally comparable among the 4 treat-

ment arms (TABLE 2). Overall mean (SD) V/SF-36 PCS and Mental Component Summary (MCS) scores were 33.7 (7.5) and 37.5 (12.1), respectively. The overall mean PCS score was approximately 1.6 SDs below the US population mean and 0.2 SD below that of veterans who use the VA health care system, while the overall mean MCS score was about 1.3 SD below the US population and 0.6 SD below that of veterans who use the VA health care system.[16] The mean (SD) age was 40.7 (8.7) years, 15% were female, and 81% presented with all 3 cardinal symptoms of GWVI at the time of screening; the mean duration of symptoms was 6.7 years. Based on the Prime MD,[15] 45% of veterans had either a major depressive disorder or dysthymia, 35% had an anxiety disorder, and 43% had posttraumatic stress disorder; 23% were receiving medication for a psychiatric disorder. Twenty-four percent had a pending disability claim (significantly different among treatment arms; $P = .009$) and 42% were receiving disability payments.

Follow-up and Adherence

Between July 1999 and September 2001, a total of 913 participants (84%) completed the 3-month follow-up visit, 939 (86%) completed the 6-month follow-up visit, and 998 (91%) completed the 12-month follow-up visit. Of the 94

Table 2. Baseline Characteristics of Study Participants by Treatment Group*

Characteristics	Total No.†	CBT + Exercise	Exercise	CBT	Usual Care	*P* Value
Age, y	1092	39.9 (8.4)	40.9 (8.9)	40.6 (8.5)	41.3 (8.9)	.34
Female, No. (%)	1092	51 (19.2)	33 (12.3)	42 (14.7)	36 (13.3)	.12
Race/ethnicity, No. (%)	1090					
White, non-Hispanic		132 (49.6)	152 (56.5)	146 (51.0)	143 (52.8)	.42
Black, non-Hispanic		69 (25.9)	55 (20.4)	69 (24.1)	73 (26.9)	
Hispanic		55 (20.7)	56 (20.8)	59 (20.6)	44 (16.2)	
Other		10 (3.8)	5 (1.9)	12 (4.1)	10 (3.7)	
Education, y	1091	13.9 (1.8)	14.1 (1.9)	14.1 (2.0)	14.1 (1.9)	.79
GWVI symptoms, No. (%)	1092					
Fatigue		255 (95.9)	254 (94.4)	271 (94.8)	257 (94.8)	.89
Pain		251 (94.4)	253 (94.1)	271 (94.8)	257 (94.8)	.98
Cognitive		243 (91.4)	248 (92.2)	255 (89.2)	250 (92.3)	.55
Fatigue, pain, and cognitive		217 (81.6)	220 (81.8)	225 (78.7)	222 (81.9)	.69
V/SF-36 PCS	1087	33.9 (7.4)	34.0 (7.5)	33.4 (7.5)	33.6 (7.6)	.71
V/SF-36 MCS	1087	37.1 (12.4)	35.8 (11.3)	38.9 (12.6)	38.0 (12.1)	.05
McGill Short Form (pain)						
Sensory pain	1020	13.3 (7.2)	13.6 (6.8)	13.2 (6.9)	13.2 (6.6)	.90
Affective pain	1051	4.5 (3.2)	4.3 (3.0)	4.2 (2.8)	4.3 (3.0)	.96
Pain right now	1079	4.9 (2.3)	5.1 (2.3)	5.1 (2.3)	5.0 (2.3)	.51
Typical level of pain	1075	5.6 (2.1)	5.8 (2.0)	5.7 (2.2)	5.9 (2.0)	.32
Multidimensional Fatigue Inventory						
General fatigue	1090	16.4 (3.2)	16.7 (2.9)	16.3 (3.0)	16.3 (3.1)	.35
Physical fatigue	1088	14.8 (3.3)	15.1 (3.3)	14.8 (3.3)	15.0 (3.5)	.54
Reduced activity	1078	13.4 (4.0)	13.5 (3.7)	13.4 (3.9)	13.4 (4.2)	.98
Reduced motivation	1080	11.8 (3.8)	12.0 (3.3)	11.6 (3.6)	11.6 (3.7)	.44
Mental fatigue	1082	14.9 (3.8)	14.9 (3.9)	14.8 (3.9)	14.7 (4.1)	.97
Cognitive difficulties						
Cognitive Failures Questionnaire	1056	66.8 (16.7)	66.6 (18.2)	65.9 (17.2)	67.6 (18.1)	.63
V/SF-36 Mental Health Index	1087	53.9 (22.0)	52.4 (20.5)	57.3 (21.1)	54.7 (21.3)	.05
Major depression or dysthymia, No. (%)	1091	110 (41.4)	124 (46.1)	127 (44.4)	130 (48.1)	.44
Anxiety disorder, No. (%)	1091	105 (39.5)	100 (37.2)	95 (33.2)	80 (29.6)	.08
Posttraumatic stress disorder, No. (%)	1091	118 (44.4)	119 (44.2)	109 (38.1)	124 (45.9)	.25
Psychiatric medication, No. (%)	1086	56 (21.1)	69 (26.0)	59 (20.6)	64 (23.7)	.40
Receiving disability payments, No. (%)	1061	102 (38.3)	120 (44.6)	128 (44.8)	115 (42.4)	.43
Disability claims pending, No. (%)	1059	62 (23.3)	75 (27.9)	47 (16.4)	66 (24.4)	.009
Physical fitness						
Watts per kilogram	1031	1.4 (0.4)	1.3 (0.4)	1.4 (0.4)	1.4 (0.4)	.30
Peak heart rate attained, beats/min	1087	139.9 (19.3)	142.0 (17.1)	139.9 (20.5)	138.1 (18.5)	.16

Abbreviations: CBT, cognitive behavioral therapy; GWVI, Gulf War veterans' illnesses; MCS, Mental Component Summary; PCS, Physical Component Summary; V/SF-36, Veterans Short Form 36-Item Health Survey.
*Data are expressed as mean (SD) unless otherwise noted.
†Total No. is the number with data for each characteristic.

participants (8.6%) who did not complete the study, 46 were lost to follow-up, 44 refused further follow-up, 3 died, and 1 was released from the study prematurely for safety reasons (Figure 1).

The median number of exercise treatment sessions attended was 6; 68 participants (13%) did not attend any session and 87 (16%) attended all 12 sessions. The median number of CBT treatment sessions attended was 5; 83 participants (15%) did not attend any CBT session and 39 (7%) attended all 12 sessions. The number of veterans classified as adherent to treatment (attending at least two thirds of the treatment sessions) was 102 (38%) for CBT plus exercise, 103 (36%) for CBT alone, and 124 (47%) for exercise alone.

Receipt of nonprotocol treatment was tracked during the 3-month treatment phase. During this period, 27% of participants assigned to usual care exercised regularly and approximately 5% received some form of CBT outside of the study. Among those assigned to CBT alone, 23% exercised regularly; among those assigned to exercise alone, less than 1% received some form of CBT outside of the study.

Adverse Events

A total of 112 serious adverse events were reported: 23 with CBT plus exercise, 27 with exercise alone, 30 with CBT alone, and 32 with usual care. Most adverse events were hospitalizations for events unrelated to the study; however, 3 events were possibly related to the study, 2 with usual care (psychosis and angina) and 1 with exercise alone (back surgery).

Primary Outcome Measure

The percentage of veterans who improved more than 7 points on the PCS at 12 months relative to baseline was 11.5% (31/270) with usual care, 11.7% (31/265) with exercise alone, 18.4% (49/266) with CBT plus exercise, and 18.5% (53/286) with CBT alone. Corresponding percentages at 3 months were 9.3%, 12.8%, 16.5%, and 15.0% and at 6 months were 12.2%, 13.6%, 16.2%, and 12.9%, respectively. Several lower cut points for PCS improvement (4, 5, and 6 points) were also examined and the findings were similar (data not shown).

TABLE 3 displays the unadjusted and adjusted pairwise ORs and 95% familywise CIs for the proportion of participants who improved at 12 months for all treatment comparisons, along with the raw *P* values and *P* values corrected for multiple comparisons. Although none of the treatment comparisons was statistically significant after correcting for multiple comparisons, the adjusted ORs for CBT plus exercise (1.84) and CBT alone (1.72) relative to usual care were comparable, while the OR for exercise alone was 1.07, indicating that CBT accounts for most of the combined effect of treatment and that the treatments did not act synergistically.

TABLE 4 displays outcomes by treatment according to adherence. With exercise alone, the percentage of participants whose PCS score improved was significantly higher ($P = .02$) among adherent participants (16.9%) compared with nonadherent participants (7.1%). The associations were similar but not significant for CBT alone and CBT plus exercise. In contrast, the treatment effect was not significantly associated with the presence of disability (either receipt of disability claims or disability claims pending) or psychiatric disorders at baseline, use of psychiatric medications, or the receipt of nonprotocol exercise (data not shown).

Because there was little evidence of an interaction between treatment and the primary outcome measure ($P = .99$), the overall or marginal effects of exercise and

Table 3. Unadjusted and Adjusted Odds Ratios for Improvement in the V/SF-36 Physical Component Summary Score for Pairwise and Marginal Treatment Comparisons*

Comparisons	Unadjusted Odds Ratio	Adjusted Odds Ratio (95% Familywise Confidence Interval)	Raw *P* Value	Corrected *P* Value
Pairwise				
CBT + exercise vs usual care	1.74	1.84 (0.95-3.55)	.02	.09
CBT vs usual care	1.75	1.72 (0.91-3.23)	.03	.13
Exercise vs usual care	1.02	1.07 (0.63-1.82)	.79	.79
CBT + exercise vs CBT	0.99	1.07 (0.65-1.78)	.76	.79
CBT vs exercise	1.72	1.59 (0.88-2.88)	.06	.18
CBT + exercise vs exercise	1.70	1.71 (0.92-3.19)	.03	.13
Marginal†				
Exercise vs no exercise	1.00	1.07 (0.76-1.50)	.69	.69
CBT vs no CBT	1.73	1.71 (1.21-2.41)	.002	.005

Abbreviations: CBT, cognitive behavioral therapy; V/SF-36, Veterans Short Form 36-Item Health Survey.
*Adjusted odds ratios were determined from a generalized linear mixed model controlling for study design, pending disability claims, and baseline V/SF-36 Physical Component Summary scores. Corrected *P* values were adjusted for multiple treatment comparisons using the Hochberg procedure, and 95% familywise confidence intervals control for an overall type I error of 5%.
†For marginal comparisons, the exercise group includes exercise alone and exercise + CBT and the no-exercise group includes usual care and CBT alone. The CBT group includes CBT alone and CBT + exercise and the no-CBT group includes usual care and exercise alone.

Table 4. Improvement in V/SF-36 Physical Component Summary Scores by Treatment and Adherence*

Treatments	No./Total (%)†			Odds Ratio (95% Confidence Interval)‡	*P* Value
	All	Adherent	Nonadherent		
CBT + exercise	49/266 (18.4)	24/102 (23.5)	25/164 (15.2)	1.71 (0.92-3.20)	.10
CBT	53/286 (18.5)	23/103 (22.3)	30/183 (16.4)	1.47 (0.80-2.69)	.27
Exercise	31/265 (11.7)	21/124 (16.9)	10/141 (7.1)	2.67 (1.20-5.92)	.02

Abbreviations: CBT, cognitive behavioral therapy; V/SF-36, Veterans Short Form 36-Item Health Survey.
*Adherence is defined as attending at least 8 treatment sessions for CBT alone and exercise alone and 16 sessions for CBT + exercise.
†No./total is the number of participants whose V/SF-36 Physical Component Summary score improved relative to the number of participants who were nonadherent and/or adherent to treatment.
‡Odds ratio for improvement on the V/SF-36 Physical Component Summary score among adherent relative to nonadherent participants within each treatment group.

Table 5. Adjusted Mean Changes in Secondary Outcomes From Baseline by Treatment Group*

Outcomes	No.	CBT + Exercise	Exercise	CBT	Usual Care
V/SF-36 Physical Component Summary	1040	1.03	0.97	0.59	−0.04
V/SF-36 Mental Component Summary	1040	2.30‡	2.33‡	0.97†	−1.03
McGill Short Form (pain)					
Sensory pain	943	−0.38	−0.16	−0.26	0.61
Affective pain	978	−0.50‡	−0.24	−0.43‡	0.22
Pain right now	1008	0.10	−0.04	0.21	0.31
Typical level of pain	1002	−0.38	−0.48	−0.29	−0.11
Multidimensional Fatigue Inventory					
General fatigue	1016	−0.97‡	−0.87‡	−0.48	0.01
Physical fatigue	1014	−0.70†	−0.73†	−0.34	−0.01
Reduced activity	1005	−0.68‡	−0.69‡	−0.46	0.24
Reduced motivation	1006	−0.35†	−0.38‡	−0.12	0.36
Mental fatigue	1008	−1.08‡	−0.84†	−0.72	−0.07
Cognitive difficulties					
Cognition Failures Questionnaire	985	3.38‡	2.98‡	2.66‡	−0.67
V/SF-36 Mental Health Index	1040	2.95‡	3.27‡	1.37	−1.60

Abbreviations: CBT, cognitive behavioral therapy; V/SF-36, Veterans Short Form 36-Item Health Survey.
*Data are expressed as least-squares mean changes from the linear mixed model adjusted for study design, pending disability claims, and baseline values. Positive changes for the V/SF-36 Physical Component Summary, V/SF-36 Mental Component Summary, V/SF-36 Mental Health Index, and Cognitive Failures Questionnaire indicate improvement while negative changes for the McGill Short Form and Multidimensional Fatigue Inventory indicate improvement.
†*P* value <.025 for comparisons with usual care (corrected for multiple treatment comparisons).
‡*P* value <.01 for comparisons with usual care (corrected for multiple treatment comparisons).

CBT were evaluated (Table 3). Of the 531 veterans who were assigned to exercise, 80 (15.1%) improved more than 7 points on the PCS compared with 83 (14.9%) of 556 veterans who were not assigned to exercise, with an adjusted OR of 1.07 (95% CI, 0.76-1.50). In contrast, 101 (18.3%) of the 552 veterans who received CBT improved compared with only 62 (11.6%) of 535 veterans who did not receive CBT, with an adjusted OR of 1.71 (95% CI, 1.21-2.41), corresponding to a number needed to treat of about 15.

Secondary Outcomes

The overall adjusted mean change in scores relative to baseline (ie, the average treatment effect over the entire follow-up period) for each secondary end point are displayed in TABLE 5. For the MCS, mean changes were −1.03 for usual care, 0.97 for CBT alone, 2.30 for CBT plus exercise, and 2.33 for exercise alone. All comparisons with usual care were statistically significant at the .025 level. Similar results were observed for cognitive symptoms. All 5 measures of fatigue and the measure of distress (V/SF-36 Mental Health Index) exhibited statistically significant and comparable effects for exercise alone and CBT plus exercise compared with usual care. In contrast, only 1 of the 4 measures of pain (affective) showed significant treatment differences for CBT alone and CBT plus exercise compared with usual care. None of the treatment comparisons was significant for changes in PCS score.

For all secondary outcome measures, significant treatment differences were seen at 3 months and remained constant over the follow-up period. There was, however, deterioration in each measure over the follow-up period across all treatment arms. This is demonstrated graphically in FIGURE 2, which displays the percentage change in the raw mean score for representative secondary outcome measures at 3, 6, and 12 months relative to baseline. Most measures improved with exercise and/or CBT, with maximum improvement at 3 months and deterioration thereafter. In contrast, there was little or no improvement in scores at 3 months for usual care, with subsequent worsening over time.

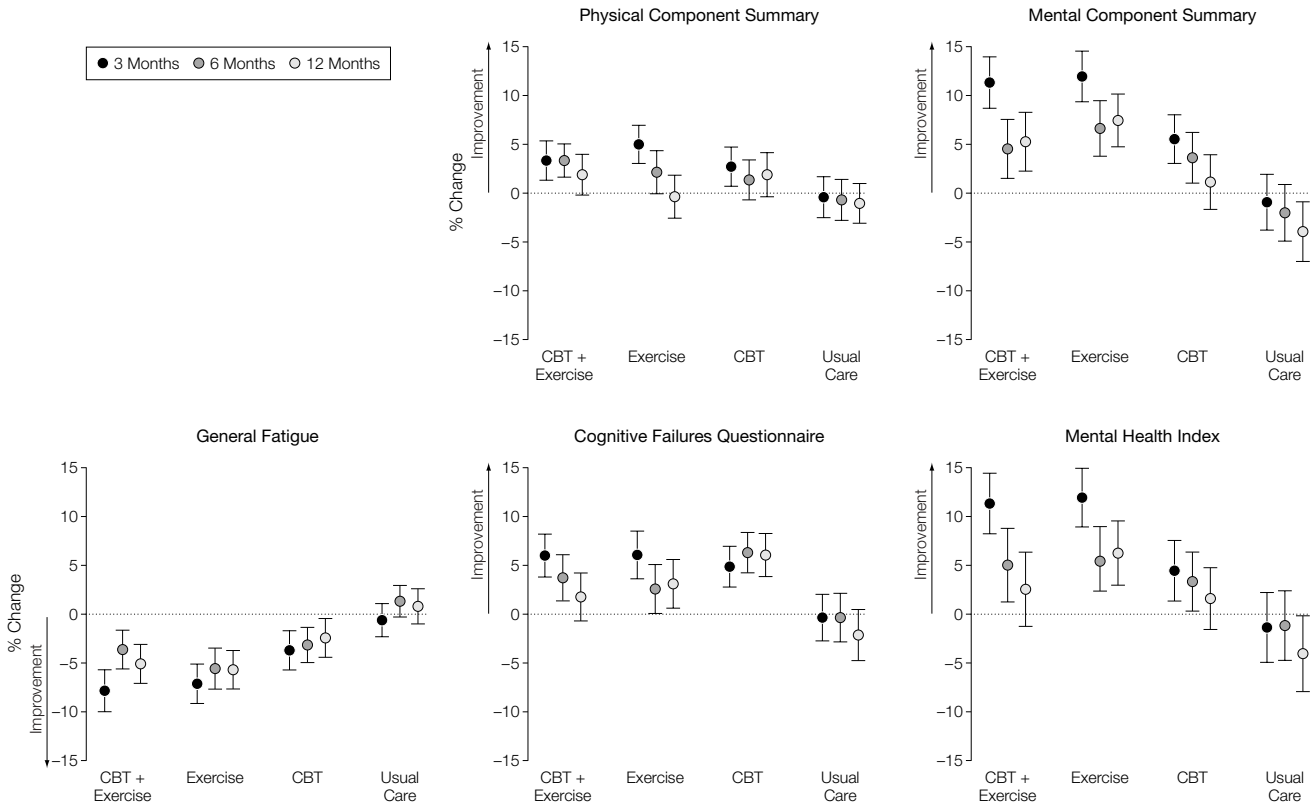
COMMENT

In this cohort of Gulf War veterans with chronic multisymptom illnesses, a 12-week program of CBT led to a modest improvement in the primary outcome measure of physical function at 1 year and accounted for nearly all of the combined effect of both treatments. In contrast, almost no improvement in physical function was observed with exercise. Those assigned to exercise, however, demonstrated modest improvements in fatigue, cognitive symptoms, distress, and mental health functioning compared with usual care, whereas CBT showed modest improvements only in cognitive symptoms and mental health functioning. Neither treatment had much of an impact on pain.

The overall findings of this study can be related to differences in the 2 interventions. Since evidence from prior studies suggests that the effects of CBT are maximized when it is tailored to address specific targeted outcomes, our CBT protocol was designed specifically to target physical function. Hence, many secondary outcome measures that were not specifically targeted by CBT did not improve.[39,40] In contrast, the exercise intervention was specifically designed to improve activity level by incorporating the patient's symptoms into the treatment regimen. This may explain why we observed symptom improvement that did not translate into functional improvement. Other studies of aerobic exercise in patients with fibromyalgia and chronic fatigue syndrome have also demonstrated improvements in symptoms but not physical function.[26,41,42]

The benefits observed in this study were modest and smaller than those observed in previous studies of this spectrum of illness.[10-13,43,44] There are several possible reasons for this finding. First, testing these interventions in a large-scale multicenter trial, rather than in the typical small-scale, single-site efficacy trial with a highly selected population, may have dampened the effectiveness of the treatment. For example, CBT was administered in a group format, rather than individual sessions, by therapists with a wide range of experience, resulting in

Figure 2. Percentage Change in Selected Unadjusted Mean Secondary Outcome Measures at 3, 6, and 12 Months Relative to Baseline by Treatment Assigned



CBT indicates cognitive behavioral therapy. Error bars indicate SEs.

highly variable treatment effects across study sites. Second, participants were relatively noncompliant with both therapies, attending on average only 50% of the sessions (13%-15% did not attend any sessions). However, the rate of adherence in this trial is typical of most studies using these forms of therapy.[45-50] Nevertheless, adherence was strongly predictive of outcome for participants assigned to exercise alone and marginally related to outcome for the other 2 treatment arms. Finally, in contrast with nearly all studies of this spectrum of illnesses, participating veterans were predominantly men who may have exhibited a different response than women.

This is the first large-scale, multicenter trial comparing the effectiveness of CBT and exercise in GWVI. Overall, we found that CBT improved physical function whereas exercise relieved many of the symptoms of GWVI; both therapies improved cognitive symptoms and mental health functioning but neither therapy improved pain. Our results are consistent with the reported modest beneficial effects of these therapies in similar multisymptom illnesses and demonstrate that such treatments are safe and could be implemented in a large health care system.

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Author Contributions: As director of the VA Cooperative Studies Program Coordinating Center, West Haven, Conn, and the lead biostatistician for the study, Dr Peduzzi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. Drs Donta, Clauw, and Engel were the study cochairmen and served on the planning and executive committees; Mr Guarino and Dr Peduzzi served on the planning and executive committees and conducted the statistical analyses; Dr Williams served on the planning and executive committees and wrote the CBT treatment manuals along with Dr Engel; Dr Skinner served on the planning and executive committees and wrote the exercise treatment manual; Dr Barkhuizen served on the planning

and executive committees and was a primary site investigator; Dr Taylor served on the executive committee and was a primary site investigator; Dr Kazis served on the planning and executive committees; Dr Sogg was the national study coordinator and served on the executive committee; and Dr Feussner initiated the planning effort and served on the planning committee. All other authors were primary site investigators.

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