Original Article

Gulf War Illness: A Randomized Controlled Trial Combining Mindfulness Meditation and Auricular Acupuncture

Global Advances in Integrative Medicine and Health
Volume 12: 1–15

DOI: 10.1177/27536130231171854
journals.sagepub.com/home/gam
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Abstract

Background: Many Gulf War (GW) Veterans report chronic symptoms including pain, fatigue, and cognitive impairment, commonly defined as Gulf War Illness (GWI). Complementary and integrative health (CIH) therapies may potentially improve multiple symptoms of GWI.
Objective: To examine the effectiveness of combining 2 commonly available CIH therapies, mindfulness meditation and auricular acupuncture, in improving health-related functioning and multiple symptom domains of GWI (e.g., pain, fatigue).
Methods: This study was a randomized controlled trial in which Veterans with GWI were randomly assigned to either the intervention group (n = 75), wherein they received 2 distinct CIH therapies – mindfulness meditation and auricular acupuncture, or the active control group, wherein they received a GW Health Education (GWHE) program (n = 74), each lasting 8 weeks. Self-report health measures were assessed at baseline, endpoint, and 3 month follow-up.
Results: In the intention-to-treat analyses, there were significant between-group differences for mental-health related functioning, fatigue, depression symptoms, and Kansas total severity scores for symptoms in which the CIH group had improved scores for these outcomes at endpoint compared to the GWHE group (all $P \leq .05$). The CIH group also had significant reductions in pain interference at endpoint and follow-up compared to baseline (estimated marginal mean difference: −2.52 and −2.22, respectively; all $P = .01$), whereas no significant changes were observed in the GWHE group. For pain characteristics, the GWHE group had a worsening of pain at endpoint compared to baseline (estimated marginal mean difference: +2.83; $P = .01$), while no change was observed in the CIH group.
Conclusion: Findings suggest a possible beneficial effect of combining 2 CIH therapies, mindfulness meditation and auricular acupuncture, in reducing overall symptom severity and individual symptom domains of fatigue, musculoskeletal, and mood/cognition in Veterans with GWI.
Trial Registration: Clinical Trials identifier NCT02180243

Keywords

gulf war illness, veterans, complementary and integrative health, acupuncture, mindfulness meditation, randomized controlled trial

Received October 7, 2022; Revised March 3, 2023. Accepted for publication April 9, 2023

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Introduction

Veterans deployed during Operations Desert Shield/Desert Storm (ODSS) or the Gulf War (GW) between 1990 to 1991 have a history of seeking treatment for a myriad of chronic symptoms and health problems that were medically unexplainable following return from deployment.[1] More than 30 years after ODSS, these chronic unexplained symptoms continue to persist among many Veterans, and include, but are not limited to fatigue, gastrointestinal difficulties, sleep disturbance, widespread pain, and cognitive dysfunction. The clustering of these chronic symptoms is often referred to as GW Illness (GWI) and, depending on the research case definition, the prevalence of GWI can range from 4% to 65%, with higher rates observable among deployed GW Veterans compared to non-deployed Veterans of the same era.[2] Clinical case definitions do not exist for GWI and whether there is an unexplainable syndrome versus a collection of multiple discrete disorders remains an area of some debate. Nevertheless, what we refer to as GWI represents a broad-spectrum illness in which multiple biological systems can be affected within 1 individual.

Although many pharmacological and psychological interventions for GWI have been attempted, few effective or specific treatments have been strongly supported with evidence, potentially due to many treatments having been designed for single, discrete disorders. Reports summarizing treatments over the past few decades have indicated that there remains no comprehensive or transdiagnostic treatments that satisfactorily address the multiple symptoms associated with GWI.[3,4] One recent qualitative study noted that there is a tendency for health care providers to take an atomized approach to GWI, in which symptoms are treated separately.[5]

In an attempt to alleviate their varied symptoms, Veterans with GWI often seek alternative approaches to supplement usual care, including complementary and integrative health (CIH) therapies.[6] The Veterans Affairs (VA) health care system offers CIH therapies as a treatment option, with availability becoming more widespread throughout the U.S. In 2014, the VA established the Integrative Health Coordinating Center (IHCC) within the Office of Patient Centered Care and Cultural Transformation to increase the accessibility of CIH across the Veteran Health Administration (VHA) system.[7] There are presently 8 CIH therapies approved for inclusion in VA medical benefits package and are made accessible to Veterans across the VHA system, including acupuncture, biofeedback, clinical hypnosis, guided imagery, massage therapy, meditation, Tai Chi/Qi Gong, and yoga.[7]

Current evidence supporting the clinical effectiveness of CIH therapies for GWI is limited. One systematic review, based on literature available before September 2019, identified 12 published, randomized controlled trials (RCT) targeting multiple symptom domains of GWI, each with widely different treatment modalities.[8] Out of the 12 identified RCTs, only 6 investigated a CIH therapy including mindfulness-based mediation and mind-body bridging, acupuncture, detoxes, or nutritional supplements. The mindfulness-based approaches appeared to provide the most therapeutic benefit among Veterans with GWI compared to the other CIH therapies, showing improvements in pain, cognitive function, depression, fatigue, sleep, and posttraumatic stress disorder (PTSD) symptoms.[9,10] Acupuncture also demonstrated a beneficial effect; however, improvements were only observed in overall physical health and pain, and the strength of evidence was ranked as insufficient due to small sample size.[8,11] In a more recent review, the Department of VA and the Department of Defense (VA/DoD) rated the strength of their recommendation for mindfulness-based approaches and acupuncture as weak for military populations with chronic multisymptom illness (CMI; which includes GWI),[12] mainly due to paucity of research, variability in methods, and limited generalizability. A weak recommendation was viewed as "clinically important and evidence-based" despite the low quality of evidence which is why the VA/DoD suggested offering mindfulness-based approaches and acupuncture to patients with CMI.[12] Thus, additional research is warranted in order to determine definitive recommendations for CIH approaches in GWI.

We conducted a RCT of Veterans with GWI to examine the effectiveness of a combined program of 2 CIH therapies, mindfulness meditation (iRest® Yoga Nidra) and auricular acupuncture, compared to an active control group receiving a course of GW Health Education (GWHE). We hypothesized that the combination of these 2 CIH therapies may prove to be more effective in improving health-related functioning and multiple symptom domains of GWI (e.g., pain, fatigue) as compared to an active control group. As individuals often engage in multiple wholistic methods to affect chronic conditions,[13] the purpose of the current study was not to compare these 2 therapies (meditation vs acupuncture), but to assess whether an intervention combining 2 commonly available CIH therapies would result in multiple symptom improvement in Veterans with GWI.

Materials and Methods

Study Overview

A two-arm, single-masked RCT was used to evaluate the effectiveness of a CIH intervention combining 2 therapies, iRest® Yoga Nidra (hereafter referred to as iRest®) and auricular acupuncture, for improving health-related functioning and multiple symptom domains of GWI. The study was conducted at the War Related Illness and Injury Study Center (WRIISC-DC) located at the Washington, DC VA Medical Center (VAMC) which has been offering CIH therapies, including iRest® and acupuncture,

as a complement to standard care for Veterans since 2007. An evaluation of patient experiences revealed that both iRest® and acupuncture were beneficial in improving multiple symptoms among Veterans.[14] The early adoption of CIH therapies by WRIISC-DC initiated the development of the Integrative Health and Wellness (IHW) Program in 2012 which expanded the number of CIH services offered to Veterans within the Washington, DC VAMC. Our colleagues within the IHW Program observed that patients were participating in both iRest® and acupuncture concurrently. An exploratory study was conducted examining clinical data to determine if this approach was more effective than acupuncture alone (n = 63).[15] The results demonstrated that the combined approach resulted in significant reductions in psychological symptom severity, depression, and perceived stress, while only 1 significant reduction was observed in perceived stress within the acupuncture-only group. Comparison of the 2 groups did not reveal any significant differences, likely due to the small sample size. Given the clinical expertise of WRIISC-DC and these preliminary findings, iRest® and group auricular acupuncture were selected and combined for the CIH intervention.

All participants were pre-screened to determine eligibility prior to being randomized to either the CIH group receiving iRest® and auricular acupuncture or the GWHE group. Participants provided written consent after reviewing the demands of the study. Masking the participants to treatment conditions was not possible; however, each treatment was presented as a plausible therapeutic therapy, and participants were not aware of which 1 was intended as the control condition. The study protocol was approved by the institutional review board at the Washington, DC VAMC and registered with ClinicalTrials.gov (NCT02180243).

Participants

Participants were recruited via flyers, internet postings, referrals from primary care providers at the Washington, DC VAMC, and targeted outreach mailings to GW Veterans. Telephone or in-person interviews were conducted to determine eligibility. Veterans were enrolled based on the following criteria: (a) U.S. Veteran who was deployed to the 1990-1991 Gulf War; and (b) met the CDC case definition for CMI defined as self-reporting 1 or more symptoms lasting 6 months from at least 2 of 3 symptom domains (fatigue, musculoskeletal, and/or mood/cognition).[16] The CDC case definition was used for screening purposes only because it is considered a less stringent criteria compared to the alternative Kansas case definition.[17] Exclusion criteria included: (a) current substance dependence (Structured Clinical Interview for DSM Disorders, or SCID); (b) current psychotic symptoms or bipolar disorder (SCID); (c) current suicide ideation or recent suicidal attempt ("recent" defined as an attempt made within the calendar year); (d) hearing loss that would prevent participation in a group intervention; and (e) current involvement in meditation or acupuncture (defined as within the last 6 months of interview).

Randomization

Participants were randomly assigned to either the CIH or the GWHE group in a 1:1 allocation using block randomization. Random allocation sequence was generated in fixed blocks of 20 using a computer random number generator. An independent biostatistician conducted the randomization. Treatment allocation was concealed until after a screened participant was determined to be eligible and provided informed consent. Participants discovered what group they were randomized to after they completed their baseline assessment.

Interventions

Participants were enrolled in predefined blocks of 20 to allow for equal treatment allocation and reasonable group attendance. In total, there were 7 blocks, and each intervention arm was administered to groups of 5 to ten individuals for a total of 8 weeks.

GWHE. Participants randomized to the GWHE group served as an active control group and received one-hour education sessions administered in a group setting by clinical staff with content expertise for 8 consecutive weeks. The GWHE program was modeled after commonly offered educational courses provided at VAMCs in which materials from those existing courses were adapted to provide health education to GW Era Veterans. The health topics were selected based on a decade of clinical and research experience of WRIISC-DC staff which gave them a particular sensitivity to issues faced by persons with GWI. The GWHE was intentionally devoid of acupuncture or meditation content and instead included specific sessions on fatigue management, insomnia/sleep hygiene, nutritional psychology, behavioral pain management, coping with chronic illness, environmental exposures, and cognitive health.

CIH. The CIH group received 2 distinct CIH therapies, mindfulness meditation (iRest®) and auricular acupuncture, administered 1 after another to participants, while maintaining the clinical integrity of each. In total, there were 8 sessions (each approximately 80 to 90 minutes long) over the course of the 8-week intervention. Both therapies were administered in a group setting and took place in the same room to maintain environmental conditions and reduce disruption. Due primarily to provider availability, 1 of the 7 blocks received iRest® first directly followed by auricular acupuncture while the remaining 6 blocks received the auricular acupuncture before iRest®.

iRest® meditation. The iRest®[18] component consisted of guided mindfulness meditation sessions conducted by 2 experienced iRest® instructors. A 10-stage iRest® protocol developed for clinical research was delivered across 8 weeks. Each group meditation began with an introduction to 1 or more of the 10 stages of the iRest® protocol followed by a guided meditation practice. For the guided meditation practice, standardized iRest® scripts written by Richard Miller, creator of iRest®, were read to the participants. The iRest® meditation component lasted approximately 20-30 minutes.

Auricular acupuncture. The auricular acupuncture component of the CIH intervention was administered by a licensed acupuncturist and lasted approximately 1 hour. During the first clinical encounter, 12 pre-determined, anatomically distinct auricular acupoints were tested for electrical reactivity using a Pointer Excel II Acupuncture Point Locator. The 12 acupoints selected were based on their capacity to restore underlying balance and regulation in the constellation of symptoms most commonly experienced by GW Veterans and included Shen Men, Point Zero, Sympathetic, Thalamus, Master Cerebral, San Jiao, Brain C, Adrenal C, Kidney C, Cingulate gyrus, Vitality Point, and Liver.[19,20] Each point's unique electrical reactivity was compared to the reactivity of the acupoint Shen Men and the 6 most highly reactive points were selected for treatment. The process for testing electrical reactivity was repeated halfway through the intervention and implemented in week 5. By selecting a custom subset of these points, each participant received a semi-standardized acupuncture treatment tailored to how their physiology was expressing its unique and highly variable experience of GWI. Each acupuncture component occurred with participants in a seated position in a quiet room with the lights dimmed. Participants cleaned the auricular region of their ears using isopropyl alcohol wipes. Sterile stainless-steel needles were inserted by an acupuncturist into both ears at the 6 points revealed during testing.

Measures

An Android tablet (Samsung Galaxy) was given to each participant for their use during the study, preloaded with a mobile "study app" developed to support data collection. Participants completed several questionnaires via the study app at baseline, endpoint (1 to 2 weeks following the intervention), and 3 months after the 8-week intervention. These questionnaires are widely used clinically and in research with Veteran populations.

Primary Outcomes. Given that GWI is defined by multiple symptom domains, the following measures of health-related functioning, pain, and fatigue served as the primary outcomes of this study.

Health-related functioning was assessed using the Veterans RAND 36-Item Health Survey (VR-36), a self-report questionnaire that measures health-related functioning across mental and physical domains, with higher scores indicative of better functioning.[21]

Pain was assessed via the Patient-Reported Outcomes Measurement Information System® (PROMIS®) Adult Short Form v1.0 – Pain Interference 8a (PROMIS-PI), an eight-item self-reported pain instrument designed to measure the extent to which pain interferes with involvement in cognitive, emotional, physical, recreational, and social activities.[22]

Fatigue was assessed using the PROMIS® Adult Short Form v1.0 – Fatigue 8a (PROMIS-F), which consists of 8 items measuring the experience and impact of fatigue.[23]

Higher scores for the PROMIS-PI and PROMIS-F represented greater symptom severity. Total scores for the Mental and Physical Component Summary (MCS and PCS, respectively) scales of the VR-36, PROMIS-PI, and PROMIS-F were used in the analyses.

Secondary Outcomes. Pain was also assessed using a secondary measure called the Short-form McGill Pain Questionnaire (SF-MPQ-2), a 22-item scale with 4 subscales measuring continuous pain, intermittent pain, predominantly neuropathic pain, and affective descriptors.[24]

Fatigue was also quantified using a secondary measure called the Multidimensional Fatigue Symptom Inventory – Short Form (MFSI-SF), a 30-item measurement tool that assesses the multidimensional nature of fatigue across 5 domains: general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor. A total fatigue score was calculated by summing together the 4 fatigue subscales and subtracting the vigor subscale.[25]

Difficulties with cognitive abilities was assessed using the Neurology Quality-of-Life (Neuro-QOL) Applied Cognition – General Concerns (item bank v1.0), which is a health-related quality of life assessment tool that probes for difficulties with memory, attention, and decision-making,[26] where higher scores are indicative of better cognitive functioning.

Depression was measured using the Patient Health Questionnaire-Depression module (PHQ-9), a 9-item questionnaire that assesses symptoms and functional impairment of depression to derive an overall severity score.[27]

Posttraumatic stress disorder symptoms was assessed using the Posttraumatic Symptom Checklist – Civilian Version (PCL-C), a 17-item scale that measures the degree of distress a participant has experienced for a list posttraumatic symptoms.[28]

Subjective distress was measured using the Perceived Stress Scale (PSS), a 10-item scale that measures the degree to which situations in one's life are appraised as unpredictable, uncontrollable, and overwhelming over the past month.[29]

Psychological distress over the past 7 days was quantified using the Brief Symptom Inventory (BSI) across 9 symptom

domains: hostility, obsession-compulsion, phobic anxiety, interpersonal sensitivity, paranoid ideation, psychoticism, somatization, depression, and anxiety. The Global Severity Index was calculated as a weighted frequency score of the 9 symptom domains and served as an overall measure of psychological distress.[30]

Higher scores for the SF-MPQ-2, MFSI-SF, PHQ-9, PCL-C, PSS, and the BSI Global Severity Index are indicative of greater symptoms, stress, or psychological distress.

Severity of GWI symptoms was assessed with the Kansas Gulf War and Health Questionnaire[31] at baseline and endpoint, where higher scores are associated with greater symptom distress. Total severity scores were used in the statistical models. Participants who met the Kansas case definition for CMI, defined as self-reporting at least 1 moderately severe symptom or ≥ 2 symptoms lasting 6 months from at least 3 of the 6 symptom domains (fatigue/sleep problems, somatic pain, neurological/cognitive/mood, skin, gastrointestinal, and/or respiratory), were identified at baseline and endpoint.

Statistical Analyses

A power analysis was conducted using Power Analysis and Sample Size Software 2008 (NCSS, LLC, Kaysville, UT). Based on the results of previous studies, a minimal clinically important difference of 5 points with a standard deviation of ten on the PCS of the VR-36 was used in the power calculation.[32,33] A total sample size of 172 participants (86 per group) was estimated to provide 80% power to detect a mean difference of 5 (SD = 10) using a two-sample t-test with an alpha of .05, assuming a dropout rate of 25%.

All other analyses were performed using SPSS Statistics software – version 27 (IBM SPSS Statistics for Windows, IBM Corp, Armonk, N.Y, USA). Baseline demographics are reported as means and standard deviations or otherwise noted. Linear mixed effects models (MIXED procedure in SPSS) with random intercepts for individuals were used to assess whether there were differences in the change over time between participant groups for each of the primary and secondary outcomes separately. This modeling approach accounts for the correlation between repeated measures and allows for all observations across time points to be included in the model regardless of missing data. All models were adjusted for baseline age and gender, resulting in each model comprising of treatment group, time, treatment-by-time interaction, baseline age, and gender as fixed effects. Using information criterion-based model fit indices, the first-order autoregressive (AR1) covariance structure generated the best fit for the repeated measures of MCS, PCS, PROMIS-PI, Neuro-QOL, PSS, and BSI; a diagonal (DIAG) covariance structure for the repeated measures of PROMIS-fatigue, SF-MPQ-2, PHQ-9, PCL-C, and Kansas total severity scores; and a first-order factor analytic (FA1) covariance structure for MFSI-SF. For the random effects, the best fitting covariance structure for each primary and secondary outcome was the identity covariance structure.

Estimated marginal means and standard errors were obtained for each outcome at each time point (baseline, endpoint, and follow-up) using the linear mixed methods described above. Irrespective of the significance status of the treatment-by-time interaction, we examined pairwise comparisons of the estimated marginal means between and within the 2 treatment groups to determine if there were significant differences between groups at endpoint and follow-up, as well as between timepoints within each group.

All participants were included in the initial analyses regardless of their compliance to the treatment (intention-to-treat [ITT]). A sensitivity analysis was performed to examine the effect of missing data patterns on each outcome using pattern mixture models. A missing data pattern was found to be significantly related to only 2 of our outcomes: MCS (missing at endpoint and follow-up) and BSI (missing at endpoint). Therefore, the effects of these patterns of missingness were controlled for in the linear mixed effects models by including a dummy variable that identified participants with that specific pattern of missingness.

Based on previous work by Kearney et al, secondary analyses were conducted among those who attended at least 4 of the 8 sessions (50%) in each group ("completers").[9,34] Plots of the estimated marginal means for each primary outcome by time were created for the completer analysis to visualize differences between treatment conditions. Hedges' g was calculated as a measure of effect size for between-group differences at endpoint and follow-up for each primary and secondary outcome measure. Statistical significance was defined as $P \leq .05$ and adjustments were made to P-values for multiple comparisons using the Dunn-Šidák correction.

Results

Recruitment started in May 2016 and ended in September 2019 on a predetermined date based on the project's funding timeline. Data collection for the 3-month follow-up continued through August 2020. A total of 149 Veterans were randomized to either the CIH group (n = 75) or the GWHE group (n = 74; see Figure 1). Of the initial 149 participants, 125 received at least 1 session of their allocated intervention (CIH: 82.7%; GWHE: 85.1%), with the remaining 24 (16.1%) dropping out of the study directly after completing their baseline assessment. Of the 125 participants who received their assigned intervention, 111 completed the endpoint measurement (CIH: 82.3%; GWHE: 95.2%) and 98 completed the 3-month follow-up measurement (CIH: 74.2%; GWHE: 82.5%). The mean number of treatment sessions attended overall in the CIH group was 4.84 (SD = 2.99), with GWHE averaging 5.66 (SD = 2.82). There were 51 of 62 participants (82.3%) randomized to the CIH group and 59 of 63 participants (93.7%)

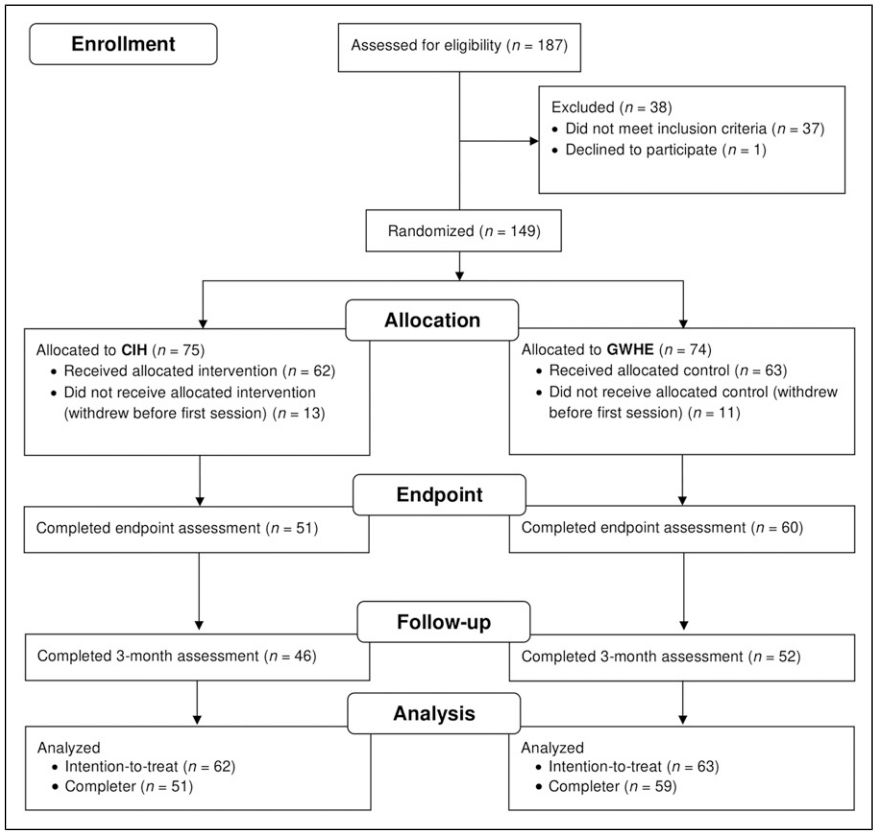

Figure 1. Flow diagram of study enrollment, allocation, and follow-up. CIH = complementary and integrative health; GWHE = Gulf War Health Education.

Table 1. Baseline Demographics Overall and by Treatment Group.

		Treatment Group	
Characteristic	Overall (n = 149)	CIH (n = 75)	GWHE (n = 74)
Age (years) [*M* (*SD*)]	54.31 (7.36)	53.46 (7.15)	55.16 (7.52)
Male [n (%)]	120 (81)	58 (77)	62 (84)
Race [n (%)]			
African American	103 (69)	50 (66)	53 (72)
White	31 (21)	17 (23)	14 (19)
Other	15 (10)	8 (11)	7 (9)
Hispanic ethnicity [n (%)]	5 (3)	4 (5)	1 (1)
Education [n (%)]			
HS/GED	28 (19)	9 (12)	19 (26)
> HS/GED	121 (81)	66 (88)	55 (74)
Married [n (%)]	92 (62)	47 (64)	45 (61)
Employed [n (%)]	82 (55)	40 (53)	42 (57)
Disabled [n (%)]	46 (31)	23 (31)	23 (32)

Note. CIH = Complementary and integrative health; GED = General Education Development; GWHE = Gulf War Health Education; HS = high school.

randomized to the GWHE group who were classified as treatment "completers". Among the treatment "completers", the mean number of treatment sessions attended in the CIH and GWHE groups was 6.76 (*SD* = 1.12) and 7.02 (*SD* = 1.03), respectively.

Baseline demographics are shown by treatment group in Table 1. Similarities were observed between both groups for the baseline demographic characteristics, except for education level in which there were more participants in the CIH group who had greater than a high school diploma or

equivalent compared to the control group (88% vs 74%, respectively). Overall, participants were predominantly middle-aged (M_{age} = 54.31y, SD = 7.36), male (81%), African American (69%), married (62%), and employed (55%). Baseline demographic characteristics were also similar between "completers" and "non-completers", except for employment status where slightly more "non-completers" were employed full-time compared to "completers" (62% vs 53%, respectively). No adverse events were reported by either group during the intervention or follow-up.

Intention-to-Treat Analysis

Table 2 depicts the estimated marginal means and standard errors for each primary and secondary outcome by treatment group at baseline, endpoint, and follow-up, adjusted for age and gender.

Primary Outcomes. **Health-related functioning**. The treatment-by-time interaction term was not significant for the MCS score of VR-36 ($P > .05$), but the pairwise comparisons revealed a significant difference between groups at endpoint ($P = .05$, Hedges' $g = .33$), in which the CIH group had higher total scores, indicating greater mental health-related functioning compared to the GWHE group. The treatment-by-time interaction term was significant for the PCS score of VR-36 ($F_{2,148.24} = 4.14$, $P = .02$), suggesting that the rate of change over time differs between groups. Pairwise comparisons revealed no significant differences between or within the groups for PCS.

Pain interference. There was a significant treatment-by-time interaction for PROMIS-PI ($F_{2,\ 208.88} = 4.76$, $P = .01$), suggesting that the rate of change over time differs between groups. Pairwise comparisons revealed no significant differences between treatment groups at endpoint or follow-up for PROMIS-PI. There were, however, 2 significant within-group differences observed in the CIH group in which PROMIS-PI scores were significantly lower at endpoint and follow-up compared to baseline (mean difference between endpoint and baseline: −2.52, $P = .01$; mean difference between follow-up and baseline: −2.22, $P = .01$, respectively), indicating an improvement in pain interference. No significant changes were observed in the GWHE group (mean difference between endpoint and baseline: +.55, $P = .85$; mean difference between follow-up and baseline: −.09, $P = .99$).

Fatigue. For the PROMIS-F scale, the treatment-by-time interaction was not significant and the pairwise comparisons revealed no significant differences between or within the groups ($P > .05$).

Secondary Outcomes. **Secondary Pain Measure**. There was a significant treatment-by-time interaction for SF-MPQ-2 ($F_{2,\ 104.72} = 3.20$, $P = .05$), suggesting that the rate of change over time differs between groups. Pairwise comparisons revealed no significant differences between treatment groups at endpoint ($P = .06$) or follow-up ($P = .41$). However, there was a significant within-group difference in the GWHE group only, in which pain characteristics increased significantly at endpoint compared to baseline (mean difference: +2.83, $P = .01$). No significant changes were observed in the CIH group (mean difference: −.42, $P = .95$). In both groups, follow-up scores were not significantly different from the other time points (all $P > .05$).

Secondary Fatigue Measure. The treatment-by-time interaction term was not significant for MFSI-SF ($P > .05$). However, examination of the pairwise comparisons revealed a significant between-group difference at endpoint ($P = .04$, Hedges' $g = .40$), in which the CIH group reported less fatigue at endpoint compared to the GWHE group. The CIH group also had significant reductions in MFSI-SF scores at endpoint compared to baseline (mean difference: −8.10, $P = .05$), indicating a reduction in fatigue, whereas no significant changes were observed in the GWHE group (mean difference: +.54, $P = .99$). In both groups, follow-up scores were not significantly different from the other 2 time points (all $P > .05$).

Other Secondary Outcomes. There was a significant treatment-by-time interaction for Kansas total severity scores ($F_{1,\ 108.29} = 4.09$, $P = .05$). Pairwise comparisons revealed a significant between-group difference at endpoint in which the CIH group had lower total severity scores compared to the GWHE group ($P = .05$, Hedges' $g = .42$). No within-group differences were observed for the Kansas total severity scores. For the remaining secondary outcomes, the treatment-by-time interaction terms were not significant (all $P > .05$). Pairwise comparisons revealed a significant difference between groups at endpoint for depression symptoms (PHQ-9, $P = .05$, Hedges' $g = .34$), in which the GWHE group self-reported higher depression symptoms at endpoint compared to the CIH group. There were no significant differences observed between the groups at follow-up for depression symptoms ($P = .21$). Though no significant between-group differences were observed for psychological distress (BSI), the GWHE group self-reported significantly higher Global Severity Index scores at endpoint compared to baseline and follow-up (mean difference between endpoint and baseline: +.25, $P < .01$; mean difference between follow-up and endpoint: −.36, $P = .02$), indicating greater psychological distress at endpoint. No change was observed in the CIH group at endpoint compared to baseline (mean difference: −.04, $P = .94$), but there was a significant difference between endpoint and follow-up in which Global Severity Index scores were lower at follow-up compared to endpoint (mean difference: −.31, $P = .05$). For Neuro-QoL, PTSD, and perceived stress scales, the pairwise comparisons revealed no significant differences between or within groups (all P > .05).

Table 2. Estimated marginal means and standard errors for each primary and secondary outcome by treatment group at baseline, endpoint, and follow-up.

	Intention-To-Treat Analysis			Completer Analysis		
Outcomes	Baseline EMM *(SE)*	Endpoint EMM *(SE)*	Follow-up EMM *(SE)*	Baseline EMM *(SE)*	Endpoint EMM *(SE)*	Follow-up EMM *(SE)*
Primary						
Health-related functioning (VR-36)						
Mental component summary[a]						
CIH	40.98 (1.13)	43.25 (1.20)	43.28 (1.23)	42.83 (1.28)	43.42 (1.30)	43.36 (1.32)
GWHE	39.98 (1.25)	40.38 (1.18)	41.29 (1.22)	41.09 (1.26)	39.74 (1.27)	40.64 (1.29)
Effect size (between-group)	-	.33	.23	-	.42	.31
P-value (between-group)	.47	.05	.20	.28	.03	.10
Physical component summary						
CIH	36.97 (1.24)	38.62 (1.32)	37.34 (1.37)	37.20 (1.49)	38.76 (1.51)	37.67 (1.52)
GWHE	37.33 (1.30)	36.02 (1.34)	37.13 (1.38)	36.60 (1.48)	35.22 (1.48)	36.22 (1.50)
Effect size (between-group)	-	.26	.02	-	.36	.15
P-value (between-group)	.87	.14	.86	.75	.06	.45
Pain interference (PROMIS-PI)						
CIH	18.30 (1.15)	15.78 (1.23)[b]	16.08 (1.23)[b]	18.04 (1.40)	15.33 (1.42)[b]	15.74 (1.43)[b]
GWHE	17.76 (1.21)	18.31 (1.25)	17.67 (1.26)	18.43 (1.39)	19.28 (1.40)	18.39 (1.41)
Effect size (between-group)	-	.27	.17	-	.41	.28
P-value (between-group)	.72	.11	.31	.82	.03	.14
Fatigue (PROMIS-F)						
CIH	21.14 (1.05)	19.41 (1.14)	19.84 (1.05)	20.37 (1.27)	18.52 (1.31)	19.20 (1.22)
GWHE	21.38 (1.11)	21.30 (1.16)	21.47 (1.11)	22.03 (1.26)	22.08 (1.29)	22.18 (1.21)
Effect size (between-group)	-	.24	.21	-	.44	.36
P-value (between-group)	.86	.20	.22	.30	.03	.05
Secondary						
Pain (SF-MPQ-2)						
CIH	16.21 (1.23)	15.79 (1.36)	16.52 (1.54)	16.10 (1.46)	15.52 (1.52)	15.92 (1.68)
GWHE	16.22 (1.29)	19.05 (1.37)[b]	18.17 (1.52)	16.61 (1.45)	19.52 (1.49)[b]	18.72 (1.62)
Effect size (between-group)	-	.34	.17	-	.42	.30
P-value (between-group)	.99	.06	.41	.78	.04	.19
Fatigue (MFSI-SF)						
CIH	36.37 (2.97)	28.27 (3.53)[b]	33.01 (3.73)	35.88 (3.61)	27.58 (3.82)	32.62 (4.00)
GWHE	37.19 (3.11)	37.73 (3.42)	37.93 (3.60)	36.56 (3.56)	38.11 (3.69)	38.46 (3.83)
Effect size (between-group)	-	.40	.21	-	.44	.24
P-value (between-group)	.83	.04	.31	.88	.03	.25
Applied cognition – General concerns (Neuro-QOL)						
CIH	50.11 (2.29)	53.10 (2.41)	52.99 (2.53)	52.28 (2.63)	54.63 (2.67)	54.45 (2.73)
GWHE	49.93 (2.41)	49.61 (2.46)	51.62 (2.54)	49.17 (2.61)	48.97 (2.63)	50.98 (2.66)
Effect size (between-group)	-	.20	.08	-	.33	.21

(continued)

Table 2. (continued)

Outcomes	Intention-To-Treat Analysis			Completer Analysis		
	Baseline EMM *(SE)*	Endpoint EMM *(SE)*	Follow-up EMM *(SE)*	Baseline EMM *(SE)*	Endpoint EMM *(SE)*	Follow-up EMM *(SE)*
P-value (between-group)	.95	.26	.67	.34	.09	.31
Depression (PHQ-9)						
CIH	11.48 (.98)	10.66 (1.03)	10.80 (1.00)	10.08 (1.17)	9.81 (1.16)	9.79 (1.13)
GWHE	12.31 (1.03)	13.22 (1.04)	12.40 (1.02)	12.51 (1.16)	13.29 (1.14)	12.62 (1.11)
Effect size (between-group)	-	.34	.22	-	.47	.39
P-value (between-group)	.51	.05	.21	.10	.02	.04
PTSD (PCL-C)						
CIH	31.01 (2.80)	27.96 (2.85)	28.15 (2.81)	26.32 (3.30)	24.61 (3.20)	24.71 (3.17)
GWHE	30.80 (2.94)	33.20 (2.89)	30.28 (2.86)	30.90 (3.27)	33.47 (3.15)	30.59 (3.12)
Effect size (between-group)	-	.24	.10	-	.43	.28
P-value (between-group)	.99	.40	.14	.27	.03	.13
Perceived stress (PSS)						
CIH	18.62 (1.00)	18.24 (1.08)	17.24 (1.11)	17.18 (1.17)	17.30 (1.20)	16.17 (1.22)
GWHE	18.59 (1.04)	19.41 (1.08)	19.34 (1.11)	18.19 (1.16)	19.07 (1.17)	19.23 (1.19)
Effect size (between-group)	-	.14	.25	-	.22	.37
P-value (between-group)	.98	.35	.14	.49	.24	.05
Psychological distress (BSI)[a]						
CIH	1.24 (.14)	1.28 (.15)	.97 (.12)[c]	.95 (.13)	.93 (.13)	.89 (.13)
GWHE	1.29 (.15)	1.54 (.15)[b]	1.18 (.12)[c]	1.14 (.13)	1.32 (.13)[b]	1.25 (.13)
Effect size (between-group)	-	.30	.24	-	.45	.41
P-value (between-group)	.73	.08	.16	.23	.02	.03
Kansas total severity score						
CIH	39.07 (2.25)	35.95 (2.84)	-	39.71 (2.58)	36.37 (3.15)	-
GWHE	41.27 (2.39)	43.37 (2.87)	-	43.30 (2.58)	45.59 (3.08)	-
Effect size (between-group)	-	.42	-	-	.55	-
P-value (between-group)	.45	.05	-	.26	.02	-

Note. BSI = Brief Symptom Inventory; CIH = Complementary and Integrative Health; EMM = Estimated Marginal Means; GWHE = Gulf War Health Education; MFSI-SF = Multidimensional Fatigue Symptom Inventory – Short Form; Neuro-QOL = Neurology Quality-of-Life; PCL-C = Posttraumatic Symptom Checklist – Civilian Version; PHQ-9 = Patient Health Questionnaire-Depression module; PROMIS-F = Patient-Reported Outcomes Measurement Information System® (PROMIS®) Adult Short Form v1.0 – Fatigue; PROMIS-PI = Patient-Reported Outcomes Measurement Information System® (PROMIS®) Adult Short Form v1.0 – Pain Interference; PSS = Perceived Stress Scale; SF-MPQ-2 = Short-form McGill Pain Questionnaire; VR-36 = Veterans RAND 36-Item Health Survey. Estimated marginal means (standard errors) were obtained for each outcome separately using linear mixed models comprised of treatment group, time, treatment-by-time interaction, age, and gender. P-values were adjusted for multiple comparisons using the Dunn-Šidák correction. Hedges' *g* was calculated as a measure of effect size for between-group differences at endpoint and follow-up for each primary and secondary outcome measure.
[a]The Intention-to-Treat models for MCS and BSI also controlled for the effects of missing data patterns by including a dummy variable that identified participants with that specific pattern of missingness. No patterns of missingness were observed to be related to these outcomes in the "completer" analyses.
[b]Indicates that the specified time point was significantly different from baseline (within-group difference; $P < .05$).
[c]Indicates that the specified time point was significantly different from endpoint (within-group difference; $P < .05$).

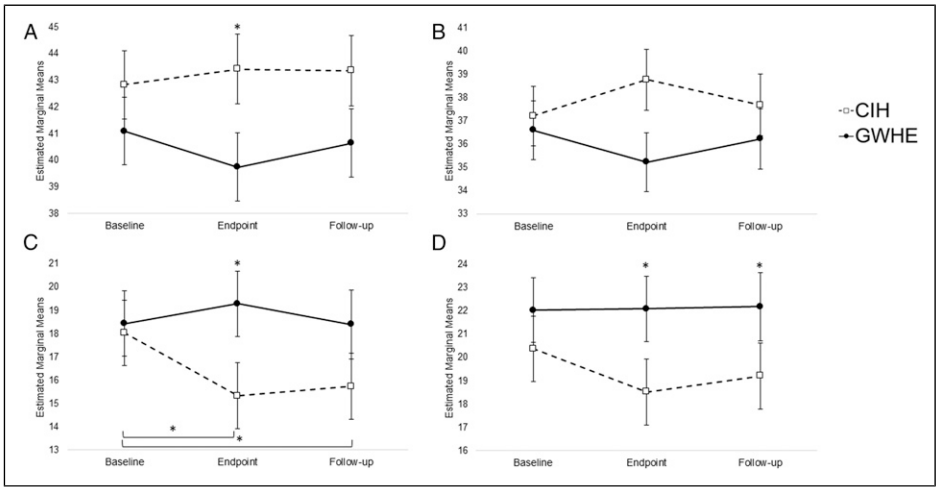

Figure 2. Plots of the estimated marginal means (± standard error) for each primary outcome by time and treatment (Completer Analysis). (A): Veterans RAND 36-Item Health Survey (VR-36) Mental Component Summary scale; (B): VR-36 Physical Component Summary scale; (C): Patient-Reported Outcomes Measurement Information System® (PROMIS®) – Pain Interference (PROMIS-PI); (D): PROMIS® Fatigue (PROMIS-F). *$P \leq .05$ for statistical significance of between- and within-group differences. P-values were adjusted for multiple comparisons using the Dunn-Šidák correction.

Completer Analyses

When limiting the sample to those who attended at least 4 sessions ("completers"), the results for the primary and secondary outcomes were similar to the ITT analysis, with a few exceptions that are discussed (see Table 2 and Figure 2).

Primary outcomes. **Pain interference**. There was a significant treatment-by-time interaction for PROMIS-PI ($F_{2,\ 190.16} = 5.36$, $P < .01$). Examination of the pairwise comparisons revealed a significant between-group difference at endpoint for the PROMIS-PI scale in which the CIH "completers" had significantly lower pain interference at endpoint compared to GWHE "completers" ($P = .03$, Hedges' g = .41; see Figure 2).

Fatigue. For the PROMIS-F scale, the treatment-by-time interaction was not significant ($P > .05$), but the pairwise comparisons revealed 2 significant between-group differences at endpoint and follow-up in which the CIH "completers" had significantly less fatigue at those 2 timepoints compared to the GWHE "completers" ($P = .03$, Hedges' $g = .44$; $P = .05$, Hedges' $g = .36$, respectively; see Figure 2).

Secondary outcomes. **Secondary pain measure.** For the secondary pain measure (SF-MPQ-2), there was a significant treatment-by-time interaction ($F_{2,\ 98.98} = 3.49$, $P = .03$). Examination of the pairwise comparisons revealed a significant between-group difference at endpoint ($P = .04$, Hedges' $g = .42$), in which CIH group "completers" had significantly fewer pain characteristics at endpoint compared to GWHE.

Table 3. Participants meeting the Kansas Research Case Definition and report at least 1 moderate to severe symptom in each domain, by treatment group before and after the intervention.

	Baseline	Endpoint
Kansas research case definition [n (%)]		
CIH	73 (97.3)	45 (88.2)
GWHE	72 (97.3)	56 (93.3)
At least 1 moderate to severe symptom in each domain [n (%)]		
Fatigue/sleep problems		
CIH	75 (100.0)	45 (88.2)
GWHE	71 (95.9)	53 (88.3)
Somatic pain		
CIH	67 (89.3)	42 (82.4)
GWHE	65 (87.8)	52 (86.7)
Neurological/cognitive/mood		
CIH	75 (100.0)	48 (94.1)
GWHE	68 (91.9)	56 (93.3)
Skin		
CIH	32 (42.7)	15 (29.4)
GWHE	31 (41.9)	28 (46.7)
Gastrointestinal		
CIH	30 (40.0)	12 (23.5)
GWHE	28 (37.8)	26 (43.3)
Respiratory		
CIH	30 (40.0)	17 (33.3)
GWHE	30 (40.5)	24 (40.0)

Note. CIH = Complementary and integrative health; GWHE = Gulf War Health Education. The denominator used to calculate percentages corresponds with the number of participants who completed the assessments at each time point (baseline: CIH:75, GWHE: 74; endpoint: CIH: 51, GWHE: 60).

Other Secondary Outcomes. Although, the treatment-by-time interaction terms were not significant (all $P > .05$), examination of the pairwise comparisons revealed significant between-group differences at endpoint for depression symptoms (PHQ-9; $P = .02$, Hedges' $g = .47$), PTSD symptoms (PCL-C; $P = .03$, Hedges' $g = .43$), and psychological distress (BSI; $P = .02$, Hedges' $g = .45$). Specifically, CIH "completers" had significantly lower scores for these measures compared to the GWHE "completers." Additional between-group differences were observed for depressive symptoms ($P = .04$, Hedges' $g = .39$), perceived stress ($P = .05$, Hedges' $g = .37$), and psychological distress ($P = .03$, Hedges' $g = .41$) at follow-up in which the CIH "completers" had significantly lower scores for these measures compared to the GWHE "completers".

Kansas Case Definition

For the full sample, the percentage of participants meeting the Kansas case definition for CMI was similar for the treatment groups at baseline (see Table 3). There was an observed decrease in the percentage of participants meeting the Kansas case definition at endpoint for the CIH group. A decrease was also noted for each of the symptom domains at endpoint for the CIH group, in which fewer participants were self-reporting at least 1 moderate to severe symptom within each domain.

Discussion

To our knowledge, this is the first RCT designed to examine the effectiveness of a CIH treatment, combining mindfulness meditation and acupuncture, compared to an active control group receiving a GWHE program among Veterans with GWI. In the intention-to-treat analyses, a significant between-group difference was observed for 1 of our primary outcomes in which the CIH group had greater mental health-related functioning (higher MCS scores) at endpoint compared to the GWHE group. There were also significant differences between groups for the secondary fatigue scale (MFSI-SF), depression symptoms, and Kansas total severity score, suggesting that the CIH group had less fatigue, lower depression symptoms, and lower total severity scores for GW symptoms at endpoint compared to the GWHE group. Additionally, there were several within-group changes observed for our primary and secondary pain measures. Specifically, the CIH group had significant reductions in pain interference (PROMIS-PI), whereas no significant changes were observed in the GWHE group. For the secondary pain scale (SF-MPQ-2), the GWHE group was observed to have significantly higher scores at endpoint compared to baseline indicating a worsening of pain characteristics, while no change was observed in the CIH group.

When the analysis was limited to those who attended at least 4 sessions, there were additional between-group differences observed at endpoint and follow-up. These outcomes included pain interference (PROMIS-PI), fatigue (PROMIS-F), pain characteristics (SF-MPQ-2), PTSD symptoms (PCL-C), perceived stress (PSS), and psychological distress (BSI) in which Veterans who attended at least 4 sessions of the CIH intervention had significantly lower scores at endpoint and/or follow-up compared to those who attended at least 4 sessions of the GWHE intervention. Additional research is needed to confirm these findings in a larger sample. Overall, the results from both the ITT and "completer" analyses suggest a possible beneficial effect of combining 2 CIH therapies, mindfulness meditation and auricular acupuncture, on the overall total severity of symptoms and individual symptom domains of fatigue, musculoskeletal, and mood/cognition in Veterans with GWI.

Although individuals often engage in multiple wholistic methods to improve their chronic conditions, most investigations of GWI compare individual therapies to a control group or another established therapy. Given that this RCT combined 2 CIH therapies, comparison with other GWI studies that isolate CIH therapies is challenging. However, there are some noted similarities with previous CIH interventions that used mind-body approaches or acupuncture for GWI.[8-11,35] Specifically, participants within the CIH group were observed to have lower total severity scores for GWI symptoms compared to the active control group at endpoint, demonstrating a moderate effect for improvement in GWI symptoms. This corresponded with a decrease in the percentage of participants meeting the Kansas case definition at endpoint for the CIH group. Nakamura et al.[10] also observed in their RCT that there was a greater percentage of participants in their mindfulness-based intervention that endorsed improvement in overall sleep/GWI symptoms compared to the control group at endpoint. Additionally, fatigue improved significantly within the CIH group as demonstrated by an 8 point decrease from baseline to endpoint on our secondary measure of fatigue (MFSI-SF), which falls within the range for clinical significance defined as a change between 4.50 and 10.79.[36] This corroborates findings from other CIH intervention studies including 1 mindfulness-based stress reduction intervention that also saw improvements in fatigue among Veterans with GWI.[9] In other clinical populations (e.g., cancer survivors, somatization disorders), several studies with a mindfulness-based intervention demonstrated a reduction in fatigue,[37,38] suggesting a reliable impact on this symptom domain.

Previous research has also demonstrated the effectiveness of mindfulness-based interventions and auricular acupuncture in reducing pain intensity.[39,40] However, 1 noted difference between our RCT and other CIH intervention studies using mindfulness-based approaches or acupuncture was the lack of significant improvement in our secondary pain scale, SF-MPQ-2, within the CIH group. We did observe a significant difference between the CIH and GWHE groups when limiting our analysis to those who

completed at least 4 sessions. This between-group difference at endpoint likely resulted from the significant changes occurring within the GWHE group, in which pain characteristics significantly worsened at endpoint compared to baseline. Regarding the CIH group, the significant improvement on the PROMIS-PI scale but not on the SF-MPQ-2 scale may seem counterintuitive, however, these questionnaires measure different domains of pain. The SF-MPQ-2 has been defined as a measure of "pain quality and location" while PROMIS-PI measures "pain interference and function".[41] Although we did not observe a significant improvement in SF-MPQ-2, there was a greater percentage of participants in the CIH group with a clinically significant improvement, defined as a 20% or greater improvement,[42] at endpoint compared to the GWHE group (41% vs 18%, respectively). Our combined CIH approach may show particular efficacy for improving mental aspects of pain, such as diminishing focus on current pain and increasing ability to accomplish daily tasks.

There are several hypothesized mechanisms through which mindfulness practice may influence fatigue and pain including improving self-regulation and attentional processes, sleep, body awareness, and cognitive reappraisal, as well as by reducing comorbid depression and stress that indirectly may reduce these symptoms.[43,44] Auricular acupuncture also has analgesic effects and is used clinically in the treatment of different types of pain; however, the exact mechanisms are not fully understood.[45,46] Most of the auricular acupuncture points are in areas innervated by a mixture of cervical nerves and the auricular branch of the vagal nerve, and the transcutaneous stimulation of those points may be behind the analgesic effects of auricular acupuncture.[40] Although auricular therapy (e.g., auricular acupuncture, acupressure, and electroacupuncture stimulation) has been found to provide immediate pain relief, there is evidence that the effect may be limited to the first 24 to 48 hours after a session,[47] suggesting that auricular treatments may be more efficacious for short-term pain relief or combined with other therapies. Furthermore, we saw a diminished effect for the CIH intervention at follow-up for the secondary measure of fatigue, which is a common observation for mindfulness-based interventions.[37,48,49] This may warrant the inclusion of booster sessions after completion of the intervention or suggests that a longer or continuous treatment may be necessary for sustained improvement. Future research should determine the effectiveness of booster sessions and clarify the optimal treatment length to maximize sustainable improvements.

Limitations

This study is not without limitations. First, we examined the combination of 2 CIH therapies which prevents us from examining the individual effect of each therapy separately. However, CIH approaches are often combined in real world settings with mindfulness meditation and acupuncture being widely available. Secondly, testing the effect of a combined treatment resulted in some additional contact time for Veterans in the intervention group. Thirdly, 14.5% of the CIH group (9/62) dropped out before treatment completion, which decreased available data for this group (Figure 1). This dropout rate is similar to another RCT study involving auricular acupuncture which had a dropout rate of 15%.[50] Future studies should consider increasing the ratio of acupuncture participants to maintain a balanced design. Additionally, the auricular acupuncture treatment was individualized for each participant which may lead to some variation in the treatment administered and therefore, may impact the overall effect of the CIH intervention on the outcomes of interest. Nevertheless, an individualized approach is likely more common in the community making our results more relevant in that regard.

Furthermore, this study was designed to test a combined CIH intervention against an active control which may have diminished the overall effect of the intervention on some of the outcomes of interest. In a recent systematic review, mindfulness-based interventions were found to have greater superiority over passive controls than they do with active controls in which effect sizes tended to be smaller and/or non-significant.[46] Our sample size also may not have been large enough to detect group differences for some of our outcomes including the PCS scale of the VR-36 which had a significant treatment-by-time interaction, but no significant between-group differences. Lastly, the completer analysis was a post-hoc subgroup analysis in which participants who completed at least 4 sessions of their assigned intervention arm were included and therefore, this reduced the sample size and possibly the statistical power. Additionally, this sub-group analysis may have resulted in some differences between the CIH and GWHE groups post-randomization. However, no differences were observed between the CIH and GWHE treatment "completers" for any of the baseline demographic characteristics.

Conclusions

The current study assessed the potential benefits of a CIH intervention combining mindfulness meditation and auricular acupuncture for Veterans with GWI and observed significant reductions in overall symptom severity and individual symptom domains of fatigue, musculoskeletal, and mood/cognition at endpoint. The current study adds support to the IHCC listing of evidence-based therapies, and the combination of 2 CIH therapies may represent a new approach for integrating multiple approved CIH therapies in conjunction with a Veteran's conventional care. For difficult to treat and chronic conditions such as GWI, even the potential for marginal improvement is

welcomed by patients and practitioners alike. It is notable that the results of the current study show that for those who completed treatment, there was a moderate effect for improvement in GWI symptoms as measured by the Kansas total severity score. This provides hope beyond a "weak" recommendation and may indicate that combination approaches are useful for those who can maintain adherence to integrative health practices such as meditation and acupuncture. Future research should examine if there is greater therapeutic effect of administering 2 or more CIH therapies in a multimodal approach within the same session vs either alone. Furthermore, additional research is needed in other demographic groups to assess effectiveness across diverse cultures from Veteran and non-Veteran populations.

Acknowledgements

The authors acknowledge Michael Knep, Jennifer J. Cho, and Thomas H. Nassif for administering the complementary and integrative health intervention; Rachel Stewart, Lauren Skalina, Chmaika Mills, Kayleigh Hale, and Stephanie Holliday for their clinical knowledge and professional delivery of the Gulf War Health Education program; and Richard Miller for developing the iRest® protocol for clinical research. Furthermore, we are indebted to Adil Alaoui and his colleagues at Georgetown University Medical Center for developing the mobile "study app" used for data collection.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The opinions presented in this article are those of the authors and do not reflect the views of any institution/agency of the U.S. government, the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., or Georgetown University.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the U.S. Department of Veterans Affairs (SPLD-013-13S).

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Supplemental Material

Supplemental material for this article is available online.

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