

Complementary and Alternative Medicine (CAM) for Sleep, Health Functioning, and Quality of Life in Veterans with Gulf War Veterans' Illnesses

Study Protocol and Statistical Analysis Plan

NCT #: NCT02180243

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Specific Aims and Hypotheses

Aim 1. To test the efficacy of combined auricular acupuncture and iRest® Yoga Nidra (CAM) treatment compared to Gulf War Health Education (GWHE) for improving health-related functioning and multiple symptoms among Veterans with Gulf War Illnesses (GWI).

- Hypothesis 1.1 - Veterans in the CAM group will report improvement in physical and mental health functioning
- Hypothesis 1.2 - Veterans in the CAM group will report greater reductions in fatigue, cognitive deficits, pain symptoms compared to GWHE.

Aim 2. To test the efficacy of combined auricular acupuncture and iRest® Yoga Nidra (CAM) treatment for reducing sleep disturbance among Veterans with GWI (secondary aim).

- Hypothesis 2.1 - Veterans in the CAM group will report greater improvement in sleep disturbance compared to GWHE (secondary).
- Hypothesis 2.2 Veterans in the CAM group will show greater improvement in objective measures of sleep initiation and maintenance measured by actigraphy compared to GWHE (secondary).

Aim 3. (Exploratory) To determine treatment acceptance and the unique and personal “fit” of auricular acupuncture and iRest® Yoga Nidra (CAM) with the day-to-day needs of Gulf War-deployed Veterans.

- Using qualitative analysis of interview data collected from Veterans, the team will assess treatment preferences, outcomes and personal goals. These findings will help to explore the hypothesis that auricular acupuncture and iRest® Yoga Nidra together are acceptable and meaningful to Veterans.

Research Design and Methods

Research Design

A two-arm, single-masked RCT will be used to evaluate the efficacy of a CAM intervention (iRest® Yoga Nidra with auricular acupuncture) for increasing health-related functioning and specific symptoms (fatigue, pain, cognitive deficits, sleep disturbance) compared to GWHE. Assessments will occur at baseline, midpoint, endpoint and 3-, 6-, and 12- months follow-up with a combination of in-person activity (completed at DC VAMC) and tablet information.

Our decision to compare CAM to an active control group (GWHE) was based on several factors. First, current empirical evidence shows that both mindfulness interventions and acupuncture have been shown to be effective for a wide range of health conditions, but not in GWI specifically. Thus, it is first important simply to detect a clinically and statistically significant effect of CAM interventions in comparison to an active control. Second, intervention research for GWI is in its early stages, which suggests that employing more active comparison conditions are premature at this stage of research.

Inclusion/Exclusion Criteria

Participants will include both male and female Veterans of any race who are current or new patients of the DC VAMC. We expect that participants will reflect the distribution of race and ethnicity throughout the DC VAMC: African American, 65%; Caucasian, 35%; Hispanic 4%.

Inclusion Criteria

- a) > 18 years of age (self-report)
- b) U.S. Veteran who was deployed to the 1990-1991 Gulf War
- c) Self-report 2 of 3 symptom types (fatigue, pain and cognitive) of GWI using the Fukuda et al. (1998) case definition.

Exclusion Criteria

- a) Moderate to severe substance abuse/dependence in the past 6 months (Structured Clinical Interview for DSM Disorders, or SCID)
- b) History of psychotic symptoms, schizophrenia, or bipolar disorder (SCID screening questions)
- c) Suicide attempt within the past year OR is currently experiencing suicidal ideation
- d) Hearing impairment that would prevent participation in a group intervention
- e) Current involvement in meditation or acupuncture, although prior (greater than 6 months) meditation or acupuncture treatments are acceptable, as long as the potential participant meets other eligibility criteria

Screening Procedures

A two-step screening process will include a pre-screening checklist administered over the phone

followed by a more in-depth screening performed in person to make sure each participant is eligible for the study. If the potential participant meets the pre-screening checklist criteria, in-person screening assessment will be completed by appointment in a private location at the DC VAMC.

Randomization

Randomization codes will be generated in advance in fixed blocks of 20 and stored in a list in a file saved on a network drive. Following informed consent and baseline assessment, once it is determined that a participant is eligible, he or she will be randomized to either the CAM or the GWHE group in a 1:1 allocation.

Interventions

CAM group

Two modalities of treatment with the potential to address multiple symptoms domains of GWI simultaneously are iRest® Yoga Nidra and auricular acupuncture; each approaches the Veteran as a whole person and do not segment a complex symptom picture into distinct symptom compartments, but rather see all symptoms as interrelated. In this study, we will combine the therapeutic effects of these two distinct CAM therapies while maintaining their clinical integrity. Each modality will be run by the respective providers as separate sessions administered one directly after the other on the same day. These interventions will, however, take place in the same room and the same environmental conditions.

Integrative Restoration iRest® Yoga Nidra Meditation (iRest®): iRest® Yoga Nidra is a guided meditation practice that is used clinically at numerous VA Medical Centers nationwide. A standardized 10-step iRest® protocol and study manual has been developed for use in clinical research. iRest® meditation practice consists of weekly 20- to 30-minute group sessions administered over the course of 8 weeks. The weekly group sessions will be conducted by two experienced iRest ® instructors who have undergone extensive training under the developer of this meditation technique, Dr. Richard Miller. This meditation practice is designed to increase moment-to-moment awareness of kinesthetic, emotional, energetic, and cognitive experiences. Standardized scripts will be administered over the course of the eight sessions.

Auricular Acupuncture: Acupuncture affects interacting mechanisms that may be involved in GWI. For example, acupuncture is known to have effects on the autonomic nervous system and the pre-frontal cortex which are involved in the pathophysiology of pain as well as emotional and cognitive dysfunctions of GWI. The points which have been selected for this study address symptoms commonly seen in Veterans with Gulf War related illnesses:

- (a) Shen Men: quiets the mind; connects to one's inner self; decreases pain, anxiety, depression, insomnia.
- (b) Point Zero: promotes homeostasis of energy, hormones and brain activity
- (c) Sympathetic: balances sympathetic and parasympathetic nervous system functions
- (d) Thalamus: modulates pain signal transmission; also affects hypothalamic autonomic regulation
- (e) Master Cerebral: affects pre-frontal cortex; stimulation, decreases anxiety, pessimism, and dream-disturbed sleep
- (f) San Jiao: regulates circulatory, respiratory, digestive, sexual and excretory functions
- (g) Brain C: decreases metabolic effects of stress and quiets the mind
- (h) Adrenal C: regulates cortisol and adrenaline production
- (i) Kidney C: strengthens willpower and vitality; relieves fear
- (j) Cingulate gyrus: modulates this cortical structure, which is part of the limbic system, and is associated with emotions, learning, and memory
- (k) Vitality Point: strengthens the immune system
- (l) Liver: improves blood circulation, affects tendons, sinews and ligaments; used to heal sprains, strains, spasms, soft tissue injuries and digestive disturbance, mediates anger and relieves frustration.

Gulf War Health Education Group

The Gulf War Health Education Group is modeled after commonly offered educational courses provided at VAMC's. The group is aimed specifically at providing health education to Gulf War Era Veterans with chronic medical conditions. It provides information to these Veterans on various health topics of common interest among this era's Veterans. The educational group consists of a weekly, one hour long, group-oriented session that meets for 8 consecutive weeks. Handouts with information about each topic will be on the tablet for participants to review on their own after in person meetings. Courses

will be taught by WRIISC-DC staff with expertise in each of the specific content areas.

Gulf War Health Education		
Week	Topic	Description
1	Course Introduction	<ul style="list-style-type: none">• Introduction to the course – what to expect• Gulf War – What we know?• Important research findings about Gulf War Veterans• Gulf War related VA benefits• Resources
2	Fatigue Management and Pacing	<ul style="list-style-type: none">• Fatigue introduction• Techniques to manage chronic fatigue• Important guidelines for fatigue• Emotions of chronic fatigue
3	Insomnia-Sleep Hygiene	<ul style="list-style-type: none">• Sleep introduction and importance of sleep• Contributors to sleep difficulties• Sleep and pain• Sleep hygiene theory and techniques• <i>Homework:</i> 7-day sleep diary
4	Nutritional Psychology	<ul style="list-style-type: none">• Introduction - How food impacts mood• Nutrient depletion• Mood disorders• Foods to control mood• Eating tips
5	Chronic Pain Management	<ul style="list-style-type: none">• Chronic pain introduction- Models of pain• Pain myths• Techniques to manage chronic pain• Thoughts/emotions and chronic pain• Energy and activity and chronic pain• Relationships and sex and chronic pain• Chronic pain and nutrition
6	Cognitive Health	<ul style="list-style-type: none">• Cognition introduction• Medical conditions contributing to cognitive difficulties• Mental health disorders contributing to cognitive difficulties• Nutrition and cognition• Brain health activities

7	Coping with Chronic Illness	<ul style="list-style-type: none"> • Chronic illness introduction • Effects of chronic illness • Techniques to cope • Resources available
8	Environmental Exposures and Gulf War	<ul style="list-style-type: none"> • Gulf War exposures • Risk factors • Related illnesses • Registry exam • Resources

Statistical Plan and Data Analysis

PASS (Power Analysis and Sample Size Software, Kaysville, UT) 2008 was used for the power calculation. The power calculations were based on the primary hypothesis (RAND VR-36) using two-sample t-test. We set α at 0.05 and power at 80%. A sample size of 64 in each study arm for a total 128 will provide 80% power to detect a mean difference of 5 with SD=10 (an effect size of 0.5) using a t-test with an α of 0.05. Anticipating a study loss to follow-up rate of 25%, we plan to recruit 86 participants in each study arm for a total of 172 participants.

All analysis will be performed by using SPSS software (IBM SPSS Statistics for Windows, IBM Corp., Armonk, N.Y., USA). Descriptive statistics will be presented for the full study population and will be broken down by treatment condition. The demographics and baseline values will be compared between treatment groups using Chi-square for categorical variables, and t-tests for continuous variables. Data analysis for the primary and secondary outcomes will be conducted based on the intent-to-treat principle. Mixed models will be used to assess differences between the CAM treatment group and GW Health Education group over time adjusted for age and gender. Mixed models take account of the correlation among the repeated measures and is an ideal approach for the data that will be collected. The interaction of time with treatment will be included in all models.