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The effectiveness of acupuncture in the treatment of Gulf War Illness

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ABSTRACT

Introduction: It can be challenging to study complex and novel health states within the parameters of a RCT. This report describes the use of an unblinded Phase II Clinical Trial design to investigate the effectiveness of acupuncture in the treatment of Gulf War Illness (GWI). GWI is a complex illness found among veterans of the first Gulf War, and is characterized by multiple symptoms, including fatigue, sleep and mood disturbances, cognitive dysfunction, and musculoskeletal pain. No published trials of acupuncture for the treatment of GWI exist. This trial is designed to both answer questions of the effectiveness of acupuncture for our entire sample, as well as subgroups with of individual presentations of GWI.

Materials and methods: Our primary outcome is quality of life as measured by the SF-36. In an effort to better understand this complex disease and its treatment, our multi-level measurement plan examines psychosocial variables, fatigue, sleep quality, pain, and biomarkers of inflammation and immune status. All of the measurement instruments used in this trial show good validity and reliability.

Results: This study is ongoing and clinical results are not available. We have achieved good feasibility of our recruitment, treatment, and data collection procedures.

Conclusions: Low constraint RCT designs are an appropriate choice when investigating conditions in which the causes and mechanisms of disease are poorly understood. This naturalistic RCT includes individualized protocols, a clinically supported length and dose of treatment, a wait list control arm, and the ethical benefit that all subjects receive treatment during the study.

1. Introduction

Upon their return, a significant number of veterans of the first Gulf War (Operation Desert Shield/Storm, years 1990–1991), presented with medical complaints. Clinical and registry programs [1] indicate that of the 700,000 service personnel deployed to the Persian Gulf, 100,000 are affected by clusters of symptoms and co-morbid medical diagnoses including chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, arthralgia, digestive complaints, and mood-related psychiatric disorders, including depression, posttraumatic stress disorder (PTSD), and other anxiety disorders [2,3]. First defined by the Centers for Disease Control and Prevention (CDC) [4], Gulf War Illness (GWI) is a complex, poorly understood illness commonly seen with a highly individualistic presentation, and symptoms difficult for conventional medicine to treat effectively; GWI has been shown to be remarkably stable at 5- and 10-year follow-ups [5,6]. GWI is twice as prevalent in deployed veterans, and seen in 15% of non-deployed veterans [7] (p. 71). Acupuncture is likely to be helpful in treating GWI as published work suggests it can successfully reduce many key symptoms including pain [8,9], musculoskeletal disorders [10–12], both acute and chronic pain after amputation in military contexts [13,14], fatigue [15] state, trait and situational anxiety [16], and depression [17–19]. Further, there is evidence that acupuncture may be effective in the treatment of other complex diseases such as irritable bowel syndrome [20,21], fibromyalgia [22], and post-traumatic stress disorder [23].

Chinese medicine, on which acupuncture is based, uses diagnostic and treatment procedures that are complex [24]

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and tailored to each individual's specific symptoms. Although this individualized treatment ideal is often replaced in clinical research with standardized protocols for the purposes of reliability and simplicity, the complexity of the medicine is a core concept and strength of traditional acupuncture and can be maintained successfully in a RCT format [25–28]. This study is designed to allow for individualized treatment protocols which allow veterans to receive care that is directed specifically at their most distressing symptoms. Numerous studies have shown acupuncture is well tolerated by patients, safe, and cost-effective compared to routine care [29].

Using questionnaires, physician assessment and medical histories, we are measuring the severity of symptoms before treatment, and every 2 months until the treatment period is completed at 6 months. One group of patients will receive acupuncture evaluation and treatment twice per week for 6 months. The wait-list comparison group will continue usual care from baseline for 2 months, at which point they will begin weekly treatments for 4 months. Based on the clinical experience of our expert practitioners we expect this length of treatment will be enough for subjects to receive significant benefit. Along with survey measures at baseline, 2, 4 and 6 months, we are also sampling blood from our subjects to help identify possible disease mechanisms for the illness and track the effects of treatment.

Table 1
CDC symptom clusters for Gulf War Illness.

A-Fatigability
- fatigue 24 hours or more after exertion

B-Mood and Cognition
- feeling depressed or
- feeling irritable or
- difficulty thinking or concentrating or
- feeling worried, tense, anxious or
- problems finding words or
- problems getting to sleep

C-Musculoskeletal
- joint pain or muscle pain

Exclusion:

Potential subjects will be excluded if they are:
- Currently enrolled in another clinical trial
- Have another disease that likely could account for the symptoms, as determined by our Medical Monitor
- Severe psychiatric illness (in the last 2 years psychiatric hospitalization, suicidal attempt, alcohol or substance abuse, use of antipsychotic medication) as measured by our primary screening instrument the Primary Care Evaluation of Mental Disorder (Prime MD) [49].
- Unable to complete the protocol on based on the evaluation of the Medical Monitor
- Participants will not be excluded due to age, race, ethnicity, or gender limitations.

Since this study is limited to United States veterans with Gulf War Syndrome, we do not expect subjects to be minors, illiterate, or unable to speak or understand English.

2. Materials and methods

All of our study processes are approved and oversight is provided by: 1) The New England Institutional Review Board (http://www.neirb.com/), 2) United States Army Human Research Protection Office (https://mrmc-www.**army**.mil/rodorp**hrpo**.asp).

2.1. Inclusion/exclusion

The study results will be generalizable to individuals with Gulf War Illness as determined by responses on the Gulf War Illness Symptom Checklist [30] and who also meet the following inclusion/exclusion criteria set forth in the federal definition of Gulf War Illness as used for the Gulf War Registry: 1) deployed to the "*Gulf Theater of operations, as defined by 38 CFR 3.317, includes Iraq, Kuwait, Saudi Arabia, Bahrain, Qatar, the United Arab Emirates, Oman, the Gulf of Aden, the Gulf of Oman, the Persian Gulf, the Arabian Sea, the Red Sea, and the airspace above all of these locations*" in the years 1990–1991, 2) they have at least 2 of the following symptoms from the 3 CDC clusters of symptoms [31] that have lasted for more than 6 months. Each symptom cluster must be characterized as "mild-moderate" or "severe" with at least one symptom in each cluster required to be severe. Please see Table 1.

2.2. Recruitment and consent

We are recruiting via local advertisements and direct mailing to veterans on the Defense Manpower Data Center (http://www.virec.research.va.gov/Non-VADataSources/DMDC.htm). Because the demographics of GWI veterans are unpublished, we could not guarantee a sufficient population of GWI veterans in the Boston area. Thus we designed the study to include treatment sites around the state, and built in a mechanism to add treatment sites in areas that GWI veterans are found to be clustered. Thirty treatment sites are currently operational. This design has the added benefit of allowing veterans to attain treatments near where they live and work; a technique which should bolster adherence. Further, subjects are encouraged (but not required) to remain with the same acupuncturist for the whole study period to allow for a fuller development of patient–practitioner rapport.

The informed consent process occurs in two stages. Verbal informed consent is requested prior to the initial telephone screening, and written informed consent is administered in person, at the start of the screening visit. Please see Fig. 1.

2.3. Measurement

To better understand GWI and how acupuncture may be effective, we are using validated instruments to collect information on baseline and study-related changes that may occur in the subjects': 1) biology, such as inflammatory cytokines associated with GWI manifestation [32], 2) psychosocial attitudes and functioning such as perceived social support and improvements in social functioning, 3) symptomatology such as medical history and other symptoms. See Table 2.

Correlations between disease factors (such as main GWI symptom) and treatment factors (such as specific acupuncture diagnosis and practitioners' prognosis for each case) will also be considered in order to understand how acupuncture might work in the treatment of GWI. Last, toward the aim of better understanding this disease and its treatment, correlational analyses of symptom expression and treatment

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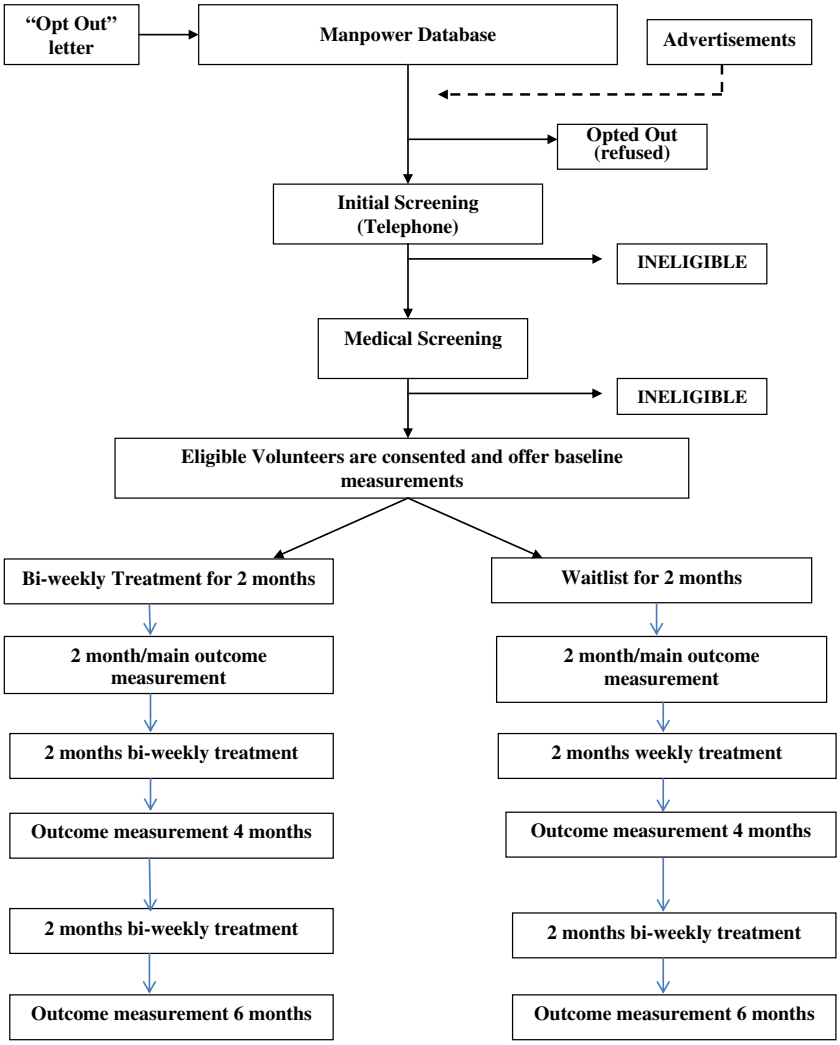

Fig. 1. Recruitment/randomization flowchart: the effectiveness of acupuncture in the treatment of Gulf War Illness.

effectiveness by socioeconomic status, ethnicity, race, and co-morbidities will also be conducted.

Because GWI is a complex illness with multiple manifestations, we have chosen to design our treatment plan to offer subjects tailored individualized treatments. Our treatment protocol is based on published effective protocols in similar disease, for example PTSD [33] as well as clinical experience. Due to the individualized nature of the treatments, systematic detailed records will be kept by practitioners of each treatment visit including: symptom presentation and consequent diagnosis, dose of acupuncture (measured as number of needles used and techniques applied), treatment effects. Additional clinical observations will be solicited qualitatively using an open response question format. This information is critical to best understand how acupuncture might be work and how the most effective treatment schedules can be designed. This treatment level data will also be examined for trends to better understand which specific types of treatment are most effective in the treatment of GWI.

Due to its novelty, complexity, and variability a single measure of severity that addresses all possible presentations of GWI does not exist. Thus we chose to use a general measure of health as the main outcome. Our primary outcome, the SF-36 [34] is a 36-item measure of global health. It is

Table 2
GWI measurements.

- The SF-36 [50]
- Multidimensional Assessment of Fatigue [51]
- The Profile of Mood States [52]
- Pittsburg Sleep Quality Index [53]
- Measure Your Medical Outcomes Profile111 [54]
- Beck Anxiety Inventory [55]
- McGill Pain Scale [56]
- Carroll Depression Scale [57]
- Social support, Social Networks, and Stress [58,59]
- Medication use and Expectations for Treatment
- Blood draw to examine levels of selected markers of inflammation, stress, and immune function
- Standardized practitioner recorded accounts of effects of Acupuncture Treatment

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well recognized with good reliability and validity. Items address multiple aspects of physical and mental health as well as functionality. Experience to date from nearly 400 randomized controlled clinical trials suggests that the SF-36 is also a useful tool for evaluating the benefits of alternative treatments [35].

2.4. Acupuncture intervention

Subjects are randomized to one of two groups: (1) one group of patients will receive acupuncture evaluation and treatment twice per week for 6 months, (2) the wait-list comparison group will continue usual care from baseline for 2 months, at which point they will begin weekly treatments for 4 months. We chose to offer weekly treatment after the first 2 months of wait list in order to offer treatment to all subjects, as well as gather data to begin to consider questions of dose of acupuncture; such as is biweekly treatment more effective than weekly treatment.

Licensed acupuncturists with at least 5 years of clinical experience, who have received additional training concerning GWI, will provide the acupuncture treatments. During the first session, the acupuncturist will conduct an interview reviewing the subject's medical history and presenting symptoms. Generally, during the physical examination, the practitioner evaluates areas of pain and aspects of diagnosis from the perspective of Traditional Chinese Medicine (TCM), including condition of the tongue, pulse, meridians, and acupoints. The subject's most distressing and other significant symptoms are identified and evaluated for TCM diagnosis. Each subject will receive an individualized treatment protocol that specifically addresses his or her unique pattern of symptoms. Individualized treatment is especially well suited for the highly variable presentation of Gulf War Illness (GWI) because the practitioner can alter the treatment plan based on how the patient is presenting at the moment; acupuncture treatment trials with pragmatic designs have shown effectiveness for pain [36].

Individualized treatment was also chosen because the specific mechanisms and most appropriate acupuncture treatment protocols for GWI are not yet known; that is GWI is still poorly understood by both Western and East Asian Medicine. Our study investigators have previously and with success used a technique of diagnosis and treatment called manualization [37]; this technique shapes providers' choices when best practice evidence is available allowing for improved replicability of treatments. However, while the symptoms of GWI have been successfully treated with acupuncture, a best practice evidence base is not yet available for GWI; thus the use of a manualized approach would be premature.

Each treatment session lasts about an hour. Brief interviews begin each subsequent session to review progress, prioritize symptoms, and identify any questions or concerns. After needle insertion, subjects can expect to rest comfortably or nap. From 10 to 35 sterile, disposable needles will be inserted, with a technique characteristic of TCM known as "obtaining *de qi*," an elicited response felt by both the patient and the acupuncturist. The needling sensation, adjusted for the comfort and safety of each patient, may be experienced as a pinch that rapidly subsides, or a sense of spreading pressure, dull ache, or warmth. Several types of needles, including from 32 to 38 gauge, and lengths from 15 mm to 50 mm, will be used on various parts of the body. Insertion depths vary by location, from subcutaneous to about 25 mm. Needles are retained 30–45 minutes. Choice of acupoints may vary during subsequent treatments to improve results.

A number of co-interventions will be used to supplement manual needling, usually 1 or 2 in each session, at the discretion of the acupuncturist. Electroacupuncture will be used for its efficacy in reducing pain and inflammation [38]. Heat therapies will be used when appropriate, including heat lamp and moxibustion, a process in which a topical herbal product is heated on the needle or skin. Tui na, cupping and gua sha will be used, massage techniques in which rubbing, pressing, and scraping are applied to the body with the hands or with instruments. To prolong effects of treatment, tiny metallic balls, tacks or magnets may be applied to points after needling. The initial dose of acupuncture is twice per week for the main treatment group. The wait-list group receives treatment once per week beginning after the 2-month waiting period.

Numerous studies have shown that acupuncture is safe when provided by professionally trained practitioners. Minor adverse effects of acupuncture may include needling pain, hematoma, and slight bleeding at the needle sites, as well as transient dizziness or drowsiness [39]. Serious adverse events are extremely rare. In a systematic review of 12 prospective studies scrutinizing over a million treatments, the very low risk of serious adverse event, mostly trauma from needle puncture or infection, was estimated at 0.05 per 10,000 treatments, a risk below that of many common medical treatments [40].

2.5. Data analysis

Our study is designed to give us adequate power to detect clinically meaningful differences between treatment groups. Previous acupuncture research using our main outcome, the SF-36, in pain conditions [41,42] show a consistent standard deviation of 20 points in the Physical Component Summary score of the SF-36 for both baseline values and change scores. Sixty individuals per group (total $n = 120$) would offer us a power of 80% to detect the difference between groups of 7 points. Using Cohen's d estimation of effect size [43]:

$$d = \frac{\text{mean}_1 - \text{mean}_2}{\sqrt{(\text{SD}_1^2 + \text{SD}_2^2)/2}}$$

A sample size of 60 will allow us to see a moderate effect. In further support of our main outcome a 7 unit improvement has been shown to be clinically relevant [44–46] .

Although we do not expect attrition to be large, we expect a dropout rate of no more than 10% by the 8-week endpoint. The length of the treatment window could increase drop-out rate. Still a veteran's population may have fewer other options for care, a factor that should increase adherence. Thus we plan to oversample to a target sample size of 67 subjects per group (total $n = 134$) to assure that our power to detect effects is maintained. For our calculations, we will use the normal distribution assumption and explore this using a

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normal plot and goodness of fit test. If violations are found, non-parametric tests or transformations will be utilized. Variance equivalence will be tested using the *F*-test. Our protocol is designed to assure sample independence and adherence will be closely monitored. Before beginning the main statistical analyses, baseline variable levels across groups will first be considered to assess group equivalence. If the groups are not balanced on any baseline characteristics, these factors will be considered as variables in later multivariate regressions.

Comparisons between the treatment and wait-list groups will be based on improvement on our main outcome, SF-36 scores. We are considering the primary outcome to be the Physical Component Summary score of the SF-36. We chose to use the SF-36 in order to show general health related quality of life in this population with very diverse complaints. The Physical component subscale was chosen because it focuses on 2 of the three Centers for Disease Control GWI clusters (fatigue and musculosketal complaints). An intention to treat analysis will consider mean differences between groups following 2 months of treatment using Student's *t*-tests at an alpha = 0.05. Analyses of secondary outcomes will include a test for mean differences between groups using two-sided Student's *t*-tests at an alpha = 0.05.

3. Results

This study is still ongoing thus we do not have clinical results to report. We are finding the protocols to be highly feasible and have strong anecdotal evidence that treatments are enjoyable. First, many of our subjects have told us that they want to continue with treatments and a few have tried to re-enroll in the study. Second, many of our new subjects have been referred by subjects already enrolled in the study. That is, the subjects are telling their friends. This word of mouth advertising is also a good indicator that the vets are enjoying the process and want their friends to have the benefits too. Last, as of this writing our drop-out rate is less than 5% ($n = 2$); these two subjects were upset that they were not randomized to the immediate treatment and this did not begin the protocol.

4. Conclusions

Twenty years following deployment in the first Persian Gulf War, widespread and sometimes severe symptoms have been remarkably persistent in an estimated 100,000 US military personnel who first became ill following their service. This study is designed to find an effective treatment for the management of GWI symptoms as well as for individuals with similar exposures. Numerous studies have shown that acupuncture is a widely available [47] safe, effective, and cost-effective in the treatment of other diseases and syndromes with similar presentations to GWI. Given this research, it is likely that acupuncture treatment may benefit veterans with persistent symptoms who are still injured due to their service, as well as other military and civilian populations impacted by chronic multi-symptom illness and its co-morbidities.

This study is also designed to gather data on the mechanisms of healing in GWI and of acupuncture; this information can be generalized toward the development of treatments of other diseases and disorders associated with military service, and improving the health and quality of life of active service personnel as well as veterans. Our multiple-measurement package allows for depth and breadth in the usability of findings; we can better understand the specific disease in question, and our results can be directly usable by researchers in other health research specialties. In a military context, this is an important consideration as use of Veterans Affairs mental health services have greatly increased, by Persian Gulf-era veterans, and also returning Iraq/Afghanistan veterans as well as Vietnam era veterans [48]. Acupuncture may be an effective, safe, low-cost treatment option for our returning military.

Little is known about GWI and the specific mechanisms of acupuncture in the treatment of GWI making a low-constraint design the appropriate choice. This naturalistic RCT includes individualized protocols, a clinically supported length and dose of treatment, and a wait list control arm, which offers the ethical benefit that all subjects receive treatment during the study.

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