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TITLE: Effectiveness of Acupuncture in the Treatment of Gulf War Illness

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Effectiveness of Acupuncture in the Treatment of Gulf War Illness

The goals of the first year/phase of the DOD funded research, GW080059, have been accomplished. We successfully gained IRB and administrative regulatory approval created our databases, instruments, and tested our procedures on mock volunteers which consisted of SurveyMonkey, the acupuncturists; initiated our advertising and most recently, our participant recruitment. The initial year of funding was spent primarily in extensive human subject review boards by NESA's contracted IRB, the New England Research Institute (NEIRB); IRB review for our biomarker collection and analysis through the Human Subjects Program Office of the Beth Israel Deaconess Hospital (BIDMC IRB); and the United States Army Medical Research and Materiel Command (USAMRMC IRB). All final approvals were granted this past month (July 2010), therefore advertising and recruitment has just begun. Upon completion of this project we should have important clinical information that will illustrate our outcome to increase the quality of life for veterans.
## Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>4</td>
</tr>
<tr>
<td>Body</td>
<td>4</td>
</tr>
<tr>
<td>Key Research Accomplishments</td>
<td>5</td>
</tr>
<tr>
<td>Reportable Outcomes</td>
<td>6</td>
</tr>
<tr>
<td>Conclusion</td>
<td>6</td>
</tr>
<tr>
<td>References</td>
<td>6</td>
</tr>
<tr>
<td>Appendices</td>
<td>6</td>
</tr>
</tbody>
</table>
INTRODUCTION: This project is a single-blind randomized controlled clinical trial with a wait list control evaluating the effectiveness of individualized acupuncture treatment on subjects' overall health and disease burden. This three-year project collects main outcomes after 2 months of biweekly acupuncture treatment. Longer-term effectiveness will be measured with a 6 month follow-up. Our objectives are to find: a successful treatment of GWI, by gathering data to better understand: 1) the efficacy of acupuncture in treating GWI, 2) the mechanisms of how GWI may be helped by acupuncture. Our specific aim is to evaluate in a sample of veterans with GWI, the effectiveness of an individualized acupuncture treatment protocol on the subjects' GWI symptoms.

The study design utilizes a randomized controlled trial design with a wait-list-control. Volunteers will be randomly assigned to treatment or wait list arm using computer assignment. Our primary outcome is quality of life. In an effort to better understand this disease and its treatment we are considering psychosocial variables (quality of life, depression, anxiety, mood), fatigue, sleep quality, and pain. All of the measurement instruments used in this trial have been used before and published on in peer reviewed scientific journals. All have shown good validity and reliability.

BODY: The initial year of funding was spent simultaneously on extensive IRB review by NESA’s contracted IRB, the New England Research Institute (NEIRB); IRB review for our biomarker collection and analysis through the Human Subjects Program Office of the Beth Israel Deaconess Hospital (BIDMC IRB); and the United States Army Medical Research and Materiel Command (USAMRCM IRB). Final IRB approval was granted just this month (July, 2010) by all three human subject review boards; therefore screening has just begun. We also recruited experienced study staff and study practitioners that successfully completed our study training. Concurrently we focused on the start up activities which included the formation of our final measurement procedure and instruments, the design of our databases and the testing of these procedures. A relational database was built for the purpose of intakes, screenings, and tracking. Our instrumentation package was created and placed onto SurveyMonkey, the WEB-based data collection interface. This interface was successfully created and tested on mock volunteers.

Since a single measure of severity that addresses all possible presentations of GWI does not exist we chose to use as the main outcome a general measure of health. Our primary outcome, the SF-36 is a 36-item measure of global health. It is well recognized with good reliability and validity; Items address multiple aspects of
physical and mental health as well as functionality. Almost 400 randomized controlled clinical trials suggest that the SF-36 is also a useful tool for evaluating the benefits of alternative treatments.

Several outlets have been utilized for recruitment of veteran volunteers for this study. Due to privacy regulations, the Veterans Administration (VA) was unable to provide the research team with the names of patients registered with the GWI registry. The Boston and Bedford VA systems were able however, to provide research staff with frequencies of GWI cases by zip code. By obtaining the frequency of GWI cases by zip code, the research team was able to identify cities and towns with large numbers of GWI cases, and therefore, the research team was able to select study acupuncturists practicing in close proximity to these potential subjects.

Additionally, outreach was performed to local veteran organizations and professional associations that are specific to veterans. Outreach efforts announcing the study to professional organizations included outreach to Dr. Roberta White and her staff at the Department of Environmental Health at Boston University. Her advice proved valuable to our recruitment efforts. Other professionals in the GWI field contacted included Dr. Robert Haley of Southwestern University, Dr. Gordon Broderick of the University of Alberta, Dr. Douglas Dockery of Harvard University, Dr. Harold Sox of Dartmouth University. We also contacted local veteran organizations including the U.S. Veterans Outreach Center; American Legion Department of MA; Veteran’s of Foreign Wars of the U.S.; South Boston VFW Post 6536; Disabled American Veterans; Veteran’s Up and Running, and Gulf War Vets of New England. IRB approved advertisement flyers were sent to these organizations as well as information sheets about the study. An IRB approved advertisement was placed in the local paper Boston Metro on 7/13/10. Additionally, a press release announcing the grant was distributed on 6/23/10 by NESA’s public relations agency, Bishoff Communications, whom NESA has on monthly retainer. Several veterans contacted the research team expressing their interest as a result of press garnered from the release.

KEY RESEARCH ACCOMPLISHMENTS:

- Poster presentation at Southwest Symposium, April 2010 in Austin, TX on Methodological Challenges in Designing Research Protocols to Evaluate Acupuncture in the Treatment of Complex Medical Diseases: the Case of Gulf War Illness (please see attached slides).
- Poster presentation at The Society of Acupuncture Research, March 2010, Chapel Hill, NC. Methodological Challenges in Designing Research Protocols to Evaluate Acupuncture in the Treatment of Complex Medical Diseases: the Case of Gulf War Illness (please see attached poster).

REPORTABLE OUTCOMES:

- We have yet to publish any results as recruitment has just begun. Our hope is that once the study is underway it may represent a reportable outcome in year 2 of the funded work.
CONCLUSION:

We have just begun recruitment and our first medical screening day is scheduled for August 21st. We have our data collection and reporting systems in place and a well-trained experienced staff in operation. We hope to have reportable outcomes in the coming year.

REFERENCES:


APPENDICES: See attached
Effectiveness of Acupuncture in Treating Gulf War Illness

Practitioner Training
Sunday, January 31, 1999
New England School of Acupuncture
Newton, MA

Presenters:
Lisa Cebiky, MA MS ScD
Director of Research
Principal Investigator

Melissa Stobbe, MAC LAc
Academic Dean
Co-Investigator

Definition

- A chronic, multi-symptom illness (CMI)
- Affects more than one fourth of the nearly 700,000 U.S. military personnel who served in the first Gulf War Operation Desert Shield/Storm (1990-1991)
- CMI symptoms also studied in veterans in the United Kingdom, Canada, & Australia
- No disease-specific treatment identified as helpful

Symptoms in 3 clusters

<table>
<thead>
<tr>
<th>Cluster A</th>
<th>Cluster B</th>
<th>Cluster C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Mood &amp; Cognition</td>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>Headache 24 hrs or more after exertion</td>
<td>Feeling disconnected</td>
<td>Joint pain/muscle pain</td>
</tr>
<tr>
<td>Feeling irritable</td>
<td>Feeling worried, tense, or anxious</td>
<td></td>
</tr>
<tr>
<td>Difficulty thinking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Problems finding words</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Problems sleeping</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gulf War Illness (GWI)

- Definition
- Epidemiology
- Study Methodology
- History
- Exposures to neurotoxins
- GWI characterized by Traditional Chinese Medicine (TCM)
- First person accounts
- Clinical Partners
- Citations

Study Methodology

- Objectives: To find a successful treatment for GWI, by gathering data to better understand: 1) the effectiveness of acupuncture in treating GWI; 2) the mechanisms of this disease.
- Specific Aim: In a sample of veterans with GWI, evaluate the effectiveness of an individualized acupuncture treatment protocol on the volunteers' most distressing GWI symptom.

- Unblinded randomized controlled trial design with a wait-list-control.
- Individualized treatments
- Active group: 6 months of biweekly treatment
- Waitlist group: 2 months of waiting then 4 months of weekly treatments
Study Methodology: How we measure improvement

Measure general symptoms in Quality of Life and most distressing symptoms
- Painfulness
  - fatigue 24 hours or more after exertion
- Mood and Cognition
  - feeling depressed or
  - feeling anxious or
  - difficulty thinking or concentrating or
  - feeling worn out, tense, anxious or
  - problems falling asleep or
- Musculoskeletal
  - joint pain or muscle pain

Study Methodology: How do we record TCM improvement

Recording TCM symptoms, diagnosis, prognosis, expectations for treatment, alliance with subject
- OM intake-baseline
- Health History Questionnaire-baseline
- Monthly progress TCM (baseline and monthly for 6 months of study)

Study Methodology: Patient Safety

- An adverse event is any health change (or side-effect) that happens to a volunteer while he/she is participating in the study.
- The PI has the primary responsibility of reporting adverse events to our Army safety team.
- Please contact study staff of any negative health change no matter how small.
- Please utilize 911 or suicide prevention hotline per your usual clinical protocol.

Study Methodology: Practitioner Safety

- Safety issues treating trauma survivors
- Safety Resources
  - Suicide Prevention Hotline
    1-800-273-8255 (TALK)
  - VA Boston
    24-hour nurse available to provide telephone care for veterans
    1-800-865-3384
  - National Veterans Helpline
    1-800-223-8255

Recruitment/Randomization

- Recruitment materials
  - Written informed consent
  - Study information
  - Study requirements
  - Study randomization

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  - Study information
  - Study requirements
  - Study randomization
**Bombing of Baghdad**

**Persian Gulf**

**History**

In the first Gulf War (Operation Desert Shield/Storm, 1990-1991), more troops were harmed by our own technology than by the enemy.

**US Casualties**

<table>
<thead>
<tr>
<th>US Casualties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Killed: fiction: 140</td>
</tr>
<tr>
<td>Non-battle deaths: 145</td>
</tr>
<tr>
<td>Wounded: 20</td>
</tr>
</tbody>
</table>

**Gulf War losses**

- 20,000 - 175,000 people affected

**Operation Desert Storm**

**Summary of the Offensive in the 4-Day Ground War**

**Timeline:**

- **1990-1991**
  - US bomb attack on Kuwait (Operation Desert Shield)
  - US invasion of Kuwait (Operation Desert Storm)
- **1991-1992**
  - US begins 40-day war (Operation Desert Storm)
  - US forces begin withdrawal
  - **3/29/1991**
    - US begins 120-hour ground war
  - **4/29/1991**
    - US ends the war
Operation Desert Storm

"Iraq went from the fourth-largest army in the world to the second-largest army in Iraq in 100 hours"

Lieutenant General Tom Kelly

Gulf War Illness

Many deadly harms of modern, technological warfare:
- Medication
- Pesticides
Exposures

US troops in protective gear

PB Exposure

Pyridostigmine Bromide (PB)
Numerous first person accounts provide details of side effects of PB that surfaced after the medication was discontinued or the dosage reduced:

- Fever
- Diarrhea, gas, abdominal cramps, vomiting
- Weakness, muscle twitches, and aches
- Fatigue
- Confusion, poor concentration
- Burning nose
- Burned vision

PB Continued

Risk vs Harm
- Safe use for myasthenia gravis
- Investigational drug for pre-treatment for exposure to soman nerve agent
- High cost associated with possible chemical warfare

Dosage/exposure
- Dose-dependent relationship between use of PB and much milder symptoms in ground troops serving in forward areas. Warning in open desert.

Pesticide Exposures

Pesticide Exposures

- Organophosphates
  - DEET, Dichlorvos pest strip
  - Chlorpyrifos, Diazinon, Malathion used in surface spraying, environmental fogging
**Pesticide Exposures**

Organophosphates a likely cause of GWI

- Result in delayed neuropathy (OPDN) after acute poisoning episodes
- Subacute CNS effects from repeated low dose exposure even without acute episode
- Low level use linked to chronic neurodegenerative disease and chronic multisymptoms illness
- Role of biological variability of protective enzymes (paraoxonase, or PON1) under investigation

**Sarin Exposures**

Sarin is classified as a nerve agent

- 100,000 troops exposed at Khamisiyah, Iraq
- Onset of symptoms after observing explosions of Iraqi missiles (Multiple Chemical Sensitivity)

**Other Exposures**

- Depleted uranium (DU) used in munitions and tank armor
- Oil field and smoke
- Vaccines
- Sand and particulates
- Petrochemicals (tent heaters, jet fuel, solvents)
- Chemical agent resistant coating (CARC) paint
- Contaminated food and water
- Psychological stress

**How TCM Characterizes GWI**

TCM's individualized diagnosis and treatment strategy appropriate for heterogeneous presentation

- TCM Neurology
  - Wei-zhang (Fascicly Syndrome) - treatment of organophosphate poisoning from TCM perspective
- Autonomic Nervous System (ANS)
- Bi Syndrome

**TCM Treatments**

Veterans with GWI will receive individualized TCM diagnosis and treatment strategy directed at their most distressing symptom and at any additional symptoms, as well as all their co-morbid conditions. Full intake will include medical history and exposure to known or suspected neurotoxins during the war.

Treatments provided by senior practitioners in private offices, may include:
- Needling with or without manipulation
- Acupuncture (face, neck, chest, back, and extremities)
- Thermal therapies, including far infrared, cupping, deep tissue manipulation, known to be effective for its analgesic and anti-inflammation effects
- Treatment for musculoskeletal pain
- Chinese herbal medicine (CHM)
- Supplements

Not within the scope of this study, excluded treatments are:
- Chinese Herbal Medicine (CHM)
- Supplements
**Biomedical Treatments**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Fatigue Syndrome (CFS)</td>
<td>Exercise, cognitive-behavioral therapy (CBT)</td>
</tr>
<tr>
<td>Depression</td>
<td>Antidepressants; psychotherapy; exercise</td>
</tr>
<tr>
<td>Fibromyalgia (FM)</td>
<td>No therapy identified as beneficial</td>
</tr>
<tr>
<td>M sailing</td>
<td>Immediate medical care, psychosocial care</td>
</tr>
<tr>
<td>Irritable bowel syndrome (IBS)</td>
<td>Antidepressants, antipsychotics, cognitive-behavioral therapy (CBT)</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>Selective serotonin reuptake inhibitors (SSRIs) / tricyclic antidepressants (TCAs) / benzodiazepines (BZPs) / CBT</td>
</tr>
<tr>
<td>Posttraumatic stress disorder (PTSD)</td>
<td>GABA, CBT</td>
</tr>
</tbody>
</table>

**Biomedical Treatments**

Medically unexplained physical symptoms (MUPS)
- Conservative diagnostic testing
- Judicious use of medications
- Collaborative goals
- Physical and role reactivation to reduce disability
- Social support
- Coordination of care
- Psychiatric care only when specifically indicated
- Intensive multimodal care.

**Clinical Partners**

We invite practitioners of acupuncture and OM to collaborate with us and contribute to our knowledge base about GWI by sharing treatment results. If you have treated patients with GWI, please consider writing case reports to share with us.

Please submit your case reports to:

dodgw@gmail.com

**Clinical Partners**

Suggested format of case report:
- Abstract
- Description of case – presenting symptoms, history, prior treatments & their effects, diagnosis, treatment strategy, treatment points, adjunctive techniques, effects of treatment
- Literature
- Discussion
- Summary or conclusions

**Gulf War Illness**

Special thanks & acknowledgements:

New England School of Acupuncture
120 California Street
Newton, MA 02458

US Department of Defense
MEDCRA-CCMP-901-95-0004

**GW1 Study Staff**

- Lisa Codrey, MA, MS, ScD - Principal Investigator
- Julie Daniels, PPhD - Data Analysis Coordinator
- Krista St. John, MAc - Acupuncture Coordinator
- Rosa Lucha, LICC - Senior Acupuncture Coordinator
- Marc Goldstein, MD - Medical Director
- Jessica Polsin, MD - Medical Director
- Elaine Simic, LICC - Project Coordinator
- Christina Noll, LICC - Research Assistant
- Matthew Hilton, MD - Research Assistant
- Dr. Kulkarni, MD - Biostatistician
- Roger Davis, Statistician
- Wadha C. - Work Study Student
- Marfa Maruca - Work Study Student
Thank you veterans!
Methodological Challenges in Designing Research Protocols to Evaluate Acupuncture in the Treatment of Complex Medical Diseases: the Case of Gulf War Illness
Lisa Conboy, MA MS ScD1,2, Meredith St. John, MAC. LicAc. 1, Rosa Schnyer, LicAc1, Julie Dunn, PhD1. 1New England School of Acupuncture, 2Osher Research Center, Harvard Medical School

Background
The first Gulf War (Operation Desert Shield/Storm, 1990-1991), was initially considered a dramatic success with very few combat casualties. More troops were harmed by our own technology than by the enemy (RAC 200B, p. 214-22B)*

Today Gulf War Illness (GWI) is a chronic, multi-symptom illness (CMI), which affects more than one fourth of the nearly 700,000 U.S. military personnel who served.*

Three symptom clusters:
- Fatigability – Fatigue 24 hours or more after exertion
- Mood and Cognition – Feeling depressed or feeling irritable, sleep problems, difficulty thinking or concentrating, feeling worried, tense anxious, problems finding words
- Musculoskeletal – joint or muscle pain

How TCM Characterizes GWI
- TCM’s individualized diagnosis and treatment strategy is appropriate for populations’ heterogeneous presentation
- GWI neurological presentations
- A new disease for TCM
- Wei-zhang (Flaccidity Syndrome) treatment of organophosphate poisoning
- Bi Syndrome
- Autonomic Nervous System (ANS) dysregulation

Study Methodology
Objectives: To find a successful treatment for GWI, by gathering data to better understand: 1) the effectiveness of acupuncture in treating GWI; 2) the mechanisms of this disease.

Specific Aim: Evaluate the effectiveness of an individualized acupuncture treatment protocol on the volunteers’ most distressing GWI symptom.

Design:
- Unblinded randomized controlled trial with wait-list control
- Individualized treatments
- Active group – 6 months of biweekly treatment
- Waitlist group – 2 months of waiting then 4 months of weekly treatment

Multilevel Outcome Measures
- The SF-36
- Multidimensional Assessment of Fatigue
- The Profile of Mood States
- Pittsburg Sleep Quality Index
- Measure Your Medical Outcomes Profile
- Beck Anxiety Inventory
- McGill Pain Scale
- Carroll Depression Scale
- Social Support, Social Networks, and Stress
- Medication use and Expectations for Treatment
- Biomarkers

Challenges:
- Unknown etiology
- Heterogeneous symptom presentation
- Individualized acupuncture treatments
- Appropriate control group

Clinical Partners
Practitioners: Do you treat veterans with GWI? Become our clinical partner by writing a short case report. Please contact Lisa Conboy lconboy@nesa.edu or Meredith St. John mstjohn@nesa.edu.

Thank you Veterans!!!

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US Department of Defense
MEDCOM CDMRP W81XWH-09-2-0064

NEW ENGLAND SCHOOL OF ACUPUNCTURE

Study Staff
Marc Goldstein, MD: Medical Screener; Jessica Wolin, MD: Medical Monitor; Elaine Scarmoutzos, Project Coordinator; Christina Noonan, MAC., LicAc.: Research Assistant; Matthew Hitron, MD: Research Assistant; Efik Kokotou, MD: Biomarker Coordinator; Roger Davis PhD: Statistical Consultant; Weihui Li PhD: Work Study Student; Kara Marquis: Work Study Student