**Presentation 13 – John Ottenweller**

## Proposal for Gulf War RFA and Deployment-Related REAP

Proposals discussed earlier

Copeland – "Process evaluation of the PTSD clinical practice guideline for veterans"

Ciccone – "Telemedicine treatment for veterans with Gulf War illness"

## Process Evaluation of the PTSD clinical practice guideline for veterans

- Principal Investigator: H. Liesel Copeland
- Co-Investigators:
  - WRIISC: Drew Helmer
  - National Center for PTSD: Josef Ruzek
  - Washington DC VA: Robin Peck
  - Indianapolis VA: Matt Bair
  - Columbia MO VA: Ayyasamy Panneerselvam
- Proposal to Gulf War RFA

## Rationale

- Gulf War veterans have a three-fold higher incidence of PTSD than veterans of the same era not deployed to the gulf. Prevalence is similar to Vietnam veterans.
- PTSD is under-recognized in primary care.
- The VA recently released an evidence-based clinical practice guideline for PTSD
- Adoption of the guideline could improve clinical care.
- There is a need to evaluate the extent of implementation (awareness and adoption) of the guideline in primary care settings

## Specific Aims

- Elucidate primary care providers' knowledge, needs, attitudes, beliefs, and intentions about he CPG for PTSD
- Describe patients' responses to assessment of key components of the PTSD CPG
- Identify documentation of diagnosis and care of patients with PTSD in the medical records
- Compare the three perspectives (clinician, patient, chart documentation) of need and utility for the PTSD CPG

## Data Collection

- Multi-method data collection with triangulation of sources
  - **Interviews of Primary Care providers**
    - Knowledge, perceptions, use
  - **Questionnaires of Primary Care providers**
    - Knowledge, perceptions, use
  - **Questionnaires of Patients**
    - Symptoms, provider communication, recall of screening
  - **Medical Record review**
    - Implementation – diagnosis, key guideline steps

## On-Line Treatment for Veterans with War-Related Multisymptom Illness

Principal Investigator: Donald S. Ciccone, Ph.D.
Co-Investigator: Helena K. Chandler, Ph.D.

## Background

- As far back as the American Civil War, soldiers have reported nonspecific ailments that could not be attributed to an underlying medical cause.
- The prevalence of GWI or similar symptom-based illness may be as high as 45% to 60% in deployed personnel. (Fukuda et al, 1998; Baker et al, 1997, Wolfe et al, 2002)

## Background (continued)

- Despite an uncertain etiology, GWI and other symptom-based ailments have substantial consequences for veteran health:
- Frequent VA medical visitation
- Physical disability
- Psychological distress/psychiatric morbidity.

## Study Rationale

- In order to address the anticipated increase in GWI, new and more efficient treatments are urgently needed to augment or replace standard VA care.

## Rationale for Telemedicine

- Fortunately, an effective treatment using cognitive-behavioral techniques (CBT) has been developed to ameliorate symptom-related distress and reduce unnecessary healthcare utilization.
- Despite evidence of CBT efficacy provided by RCTs, a major limitation is that patients are often nonadherent. Only 38% were adherent in a recent large scale trial of CBT.
- Clinical effectiveness of CBT is undermined if fewer than half of those who need treatment are likely to attend.

## A Randomized Trial of Telemedicine

- The proposed study will address this public health problem by testing a novel treatment for GWI-On-Line CBT using instant voice messaging (voice stream technology).
- Treatment is administered over the Internet and allows veterans to speak with CBT practitioners in real time just as they would on the telephone.

## Study Aims

**Aim 1.** **Determine the efficacy of On-Line CBT for veterans with GWI who are frequent consumers of ambulatory medical care.**

**Aim 2.** **Determine whether CBT for veterans with GWI leads to a reduction in the cost of VA healthcare**

## Study Design

150 High utilizing veterans will be assigned to one of three study conditions:

I On- Line CBT + Customary Medical Care (N=50)

II In-Person CBT + Customary Medical Care (N=50)

III Customary Medical Care Only (N=50)

## Study Design

•Intent-To-Treat Strategy

•Primary Outcome: Utilization of VA medical services

•Assessment Protocol: Electronic chart review 1 yr before and 1 yr after treatment

## VA Significance

•The proposed study is intended to reduce unnecessary VA utilization while preserving or improving physical function, patient satisfaction and other quality of life indicators.

•Treatment can be made readily available to veterans regardless of their geographic location.

## Long Term VA Benefits

Long-term benefits may also include:

•Lower costs for medical care

•Improved allocation of VA resources

•Improved quality of life for GWI veterans

•Less psychiatric morbidity

•Lower risk of iatrogenic injury.

## Proposals from Other Investigators

Kevin Beck, PhD – "Interoceptive stressor conditioning: a model for Gulf War Illness"

Shelley Weaver, PhD – "Early life determinants of vulnerability to pyridostigmine bromide"

## Cytokine Levels in Gulf War Veterans, their Spouses and Era Veterans

Principal Investigator:

John Ottenweller

Co-Investigators:

Clare Mahan

Joel Karlinsky

Nicholas Ponzio and William Gause

Rosemary Toomey

## Key Questions

Do GVs show signs of immune activation compared with NGVs or civilians?

Do they show a shift to a Th2 pattern?

Are plasma cytokine levels associated with specific diseases, symptoms, signs or disabilities in GVs?

Are plasma cytokine levels associated with specific exposures in the Gulf, particularly vaccines?

## Preliminary Results

Both Mark Peakman and I presented evidence of immune dysfunction in sick GVs at the last meeting of your committee.

Our group has reported evidence of persistent immune activation in GVs that is associated with cognitive impairments and lower levels of physical functioning.

## Experimental Plan

Plasma levels of ten cytokines (IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13, IFN-γ and TNF-α) will be measured in about 1,000 GVs, 1,000 NGVs and 1,000 spouses of these veterans who participated in Phase III of the NHS.

Multivariate statistical models will corporate other data from Phases I/II (e.g., demographics, military conditions, environmental exposures, vaccinations) and Phase III (e.g., medical conditions, illness characteristics, cognitive function, cortisol levels, functional status) of the NHS.

We will determine the demographic, military characteristics and Gulf exposures (including vaccines) that are associated with cytokines levels.

We will determine whether cytokine levels along with other variables are associated with specific diseases, health outcomes or functional outcomes in GVs.

We will determine whether these associations are unique to GVs or whether they also occur in NGVs or civilians.

## Multidimensional Predictors and Outcomes of Unexplained Gulf War Illness

**Principal Investigator:** John Ottenweller

**Co-Investigators:**

**NJ WRIISC:**
Benjamin Natelson,
Donald Ciccone
Usha Sambamoorthi

**Hines CSP:**
Domenic Reda
Kwan Hur
Renee Alpern

**DC WRIISC:**
Clare Mahan

**St. Louis VA:**
Seth Eisen
Melvin Blanchard

**Harvard:**
Rosemary Toomey

## Rationale

Analysis of NHS data has so far been divided into niches that looked at a limited number of variables in one domain.

There needs to be a broader, overall analysis that incorporates all the information collected in the NHS.

However, funding has essentially run out for further analyses of NHS data.

## Key Questions

Are there subgroups of sick GVs with distinctive illness patterns?

Are there subgroups of sick GVs with different outcomes, i.e. different patterns in their functional impairments?

Can GVs be subdivided into groups based on the different health consequences of their illness?

Can either the illness subgroups or outcomes be related to specific military conditions or exposures in the Gulf?

## Analytic Design

Data from all three phases of the NHS will be merged with physiological data and maybe immune data.

Factor analysis will be performed on 10 domains in these data: demographic/deployment, general physical health, neurologic, dermatologic, laboratory chemistry, psychological/cognitive, fatigue, pain, immune and quality of life.

The primary outcomes will come from factors derived from the quality of life domain.

Data from the other domains (except the demographic domain) will be used to define characteristics of illness subgroups (current manifestations of illness) and the consequences of these illnesses.

Multivariate regression models will be used to see whether different outcomes can be associated with illness subgroups, different consequences of illness, or demographic and military antecedents.

## Research Center for Deployment-Related Illnesses

Principal Investigator: Thomas W. Findley, M.D., Ph.D.

Co-Director: John E. Ottenweller, Ph.D.

Other Participants: WRIISC Faculty

## Background

The Research Enhance Award Program (REAP) provides infrastructure support and funds for pilot experiments to groups of VA-funded researchers at one site working on the same problem.

REAPs are generally funded at $250,000/yr with $100,000 for Equipment

Call for Proposals listed "Gulf War Illnesses" and "Deployment-Related Conditions" as areas of interest for new REAPs

- But included "other collaborative initiatives … with relevancy to veterans health"

Our application on July 1 will be competing with 32 currently funded REAPs on Cancer, Diabetes, Neurodegenerative Diseases and Molecular Medicine, etc.

## Plan for NJ REAP on Deployment-Related Illnesses

Multidisciplinary Approach to Studies

MDs:

- Physiatry, Neurology, Internal Medicine, Occupational Medicine, Pulmonology, Endocrinology and Infectious Diseases

PhDs:

- Neuroscience, Neuroendocrinology, Psychology, Functional Imaging, Exercise Science, Pain, Statistics, Public Health and Health Economics

## Research Focus

Improving Clinical Research on Gulf War Illnesses and Deployment Health Problems

Hyporeactivity to stimuli may be a general problem in unexplained deployment-related illnesses.

Clinical trials in those with unexplained illnesses present particular challenges.

## Overall Research Plan

Stress reactivity and other measures will be assessed before and after two treatment arms

- One-on-One Cognitive Behavioral Therapy
- Individualized Exercise Therapy

## Pilot 1: Acute Stress Reactivity in Gulf War Veterans with CMI

Key Questions:

- Does the hyporeactivity we have seen so far extend to other stimuli and responses?
- Are there subgroups that respond differently to physical and psychological stressors?
  - Both in the stressors they respond to and the stress systems that react to the stressors
- How is reactivity in the various stress response systems related?

## Protocol

Veterans with unexplained CMI and healthy controls will be exposed to 3 stressors:

- Physical Stressor - Maximal Exercise Test
- Psychological Stressors - Mental Arithmetic and Speech Task

Stress Response Systems:

- Hormones, Cardiovascular, Respiratory, Metabolic

Other Variables:

- Psychiatric Conditions, Cognitive Performance, Balance, Sensory Testing, Activity Levels

## Analytic Plan

Compare responses of those with and without Axis I psychopathology

Determine whether there are predictors that can separate high and low responders to each stressor

Determine the relationships between the magnitudes of the responses in the different stress systems

The results from Pilot I will be used as pre-measures for treatment trials.

In addition, we will collect data using validated questionnaires for depression, anxiety, physical health, coping, functional status, fatigue, pain, activities of daily living and quality of life.

## Pilot 2: Cognitive Behavioral Therapy of Gulf Veterans with CMI

CBT proved somewhat effective in VA trial

- But there was very poor compliance and the group CBT used was not the best protocol

Pilot will determine if delivering CBT over the telephone will be improve compliance and health, decrease healthcare utilization, and alter psychological and physiological measures.

- First use of laboratory measures in such a trial

## Protocol

90 GVs with CMI will go through the protocol for Pilot I.

60 will be randomly assigned to the CBT group
30 will served as ordinary care controls

One hour weekly CBT sessions for10 weeks

- Treatment manuals based on "Personal Health Improvement Program" and modifications to protocol used in VA trial.

Pre-treatment measures repeated 6, 12 and 24 months after end of treatment. Other questionnaires include patient satisfaction survey and coping skills questionnaire.

Chart abstraction used to determine healthcare utilization over 24 months and cost effectiveness.

## Pilot 3: An Individualized Exercise Prescription for the Treatment of Gulf War Illnesses

Compliance with the exercise protocol in the VA trial was also very poor. And exercise was ineffective.

Compliance should be better when exercise prescription is individualized to each veteran's needs and capabilities.

## Protocol

90 GVs with CMI will go through protocol for Pilot I.

60 will be randomly assigned to Exercise Group
30 will be randomly assigned to Standard Care

Evaluation of each subject's endurance, strength and flexibility

Devise an individualized 12 weeks exercise program that addresses specific areas of weaknesses for each veteran.

Post-treatment measures at 6, 12 and 24 months

Measures of exercise capacity, stress reactivity, balance and cognition provide objective measures of improvement

## Exercise Treatment

Based on gradual progression in the frequency, intensity and duration of exercises.

Exercises to deal with cardiorespiratory fitness, muscle strength and endurance, functional movement and flexibility

Compliance will be monitored with weekly phone calls and an "ecological momentary assessment" watch that records activity levels and exercises.

Additional measure will be the Occupational and Leisure Time Physical Activity Questionnaires

## Advantages of Combined Pilots

Same measures in Pilot 1 on 180 veterans with CMI to provide power for its analyses

Evaluate which measures in battery of tests are best for assessing improvement in trials

Objective biobehavioral measures of improvement

Can evaluate whether variables from Pilot 1 can predict who will benefit from CBT or Exercise

## REAP Training Mission

It is expected that some REAP funds be used to hire and train fellows, but that cuts into pilot funds.

Applied for VA Clinical Research Center of Excellence to prepare young physicians for studying deployment-related health problems.

Size of program cut. We did very well, but not funded.

We have been awarded a **Special Fellowship Program** in Deployment Related Illnesses that will provide 2 slots for 5 years. For training clinicians to care for Gulf veterans and to do deployment-related health research

First fellow is MD/PhD physiatrist starting 7/1
Second fellow is clinical psychologist starting 9/1

## Clinical Databases and Computer Guided Workup for Gulf Veterans

WRIISC Clinicians have developed a standardized intake protocol we will share with DC WRIISC.

We are implementing secure databases to store the same clinical data at the two WRIISCs so they can be merged for research purposes.

We are developing a computer interface for both clinicians and veterans to input data that will be stand alone and could be used anywhere.

Ultimate goal is combine this software with the VA/DOD Clinical Practice Guidelines for Post-Deployment Illnesses to produce computerized aide for evaluating Gulf Veterans.

## Future Directions for Gulf War Research

Clinical Research

- Multidisciplinary research projects and teams
  - Identifying subgroups of GVs with distinctive problems
  - Comorbid physical and psychological conditions
  - Brain Imaging for neurologic problems
  - Animal Studies on subclinical neurotoxicity
  - Implementation Research - education of VA clinicians
  - Risk Perception/Communication for Military/Veterans

## Small Clinical Trials

Subgroups that may respond differently
Better outcome measures
Improving compliance

CBT – which components work
Exercise – which components work
Low-dose cortisol