


## Presentation 7 – Nelda Wray



**GULF WAR ILLNESS  
RESEARCH INITIATIVES**

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**ORD FOCUSED AREAS OF INVESTIGATION**

- Explore the etiology and underlying pathology of Gulf War Illness (GWI)
- Develop and test therapies to mitigate symptoms of GWI
- Develop understanding of other illnesses that may have resulted from Gulf War service

**ORD STRATEGIC APPROACH TO GWVI**

**I. Call for Proposals In Deployment Health Research Issued in October '02**

- Several exciting new projects pertaining to GWM were funded by the VA (\$8,866,433 funded in FY03)
- In response to this ongoing RFP, 6 proposals were submitted to VA research this fall for funding consideration

**ORD STRATEGIC APPROACH TO GWVI**

**II. ORD has commitment to proactively advancing research on Gulf War Veterans' Illnesses (GWVI)**

- Soreq Study - Neurotransmitter dysfunction
- Weiner Study - Neuroimaging
- RFP for Neuroimaging Research Centers to be issued Fall '03
- Military Service and Parkinson's Disease

### **ORD STRATEGIC APPROACH TO GWVI**

#### **III. ORD to Reorganize Gulf War Research Office**

- Hiring of new scientific staff
- New staff will work with the RAC to catalog VA and non-VA research in Gulf War illness
- New staff will proactively seek out research aimed at enhancing diagnosis, treatment and delineation of GWVI mechanisms

### **ORD STRATEGIC APPROACH TO GWVI**

- **Understanding the etiology and underlying pathogenesis of GWI will lead to effective treatments**
- **VA research is focusing on**
  - Abnormalities of cholinergic neurotransmission
  - Neuroendocrine abnormalities
  - Neuroimaging techniques

### **ABNORMALITIES OF CHOLINERGIC NEUROTRANSMISSION**

- **Documented exposures to anti-AChE agents in the Gulf War**
  - Pyridostigmine bromide treatment
- **Abnormal AChE activity in animal model**
  - May lead to a depletion in cholinergic neurotransmitters producing symptoms such as memory loss and fatigue

### **ACETYLCHOLINESTERASE DYSFUNCTION**

- **Neurochemical and Neurobehavioral impact of Pyridostigmine Bromide Treatment**
  - East Orange VAMC (Funding for 5 years: \$1,113,800)
  - Study will determine the nature and functional significance of reduced acetylcholinesterase (AChE) activity in the brain of rodents when administered pyridostigmine bromide (PB) under conditions of intense stress

### **ACETYLCHOLINESTERASE DYSFUNCTION**

- **Acetylcholinesterase Activity in Gulf War Deployed and Era Veterans**
  - Iowa City VAMC (Funding for 2 years: \$150,000)
  - Dr. Brad Doebbeling at the Iowa City VAMC and Dr. Soreq of Hebrew University will collaborate on a research study based on Dr. Soreq's preliminary findings that pyridostigmine bromide may have led to chronic abnormalities in neurotransmitter systems and may be a cause of symptoms of illnesses in some Gulf War veterans

### **ACETYLCHOLINESTERASE DYSFUNCTION**

- **Differential Gene Expression in Pathologies Associated with: Links to Gulf War Illness**
  - Durham VAMC (Funding for 6 years: \$1,375,000)
  - This project will study differential gene expression in pathologies associated with 'neuronal hyper excitability'
  - This condition may be linked to pathologies associated with exposure to acetylcholinesterase inhibitors, such as organophosphates and carbamates (e.g., pyridostigmine bromide), potentially implicated in Gulf War illnesses

### **NEUROENDOCRINE DYSFUNCTION**

- **Hypothalamic-Pituitary-Adrenal Axis Alterations in Gulf War and Vietnam Veterans**
  - Bronx VAMC (Funding for 4 years: \$347,400)
  - This study will explore the hypothesis that ACTH levels may be reduced in patients with GWVI, which could reflect inhibition of the HPA axis or enhanced negative feedback
  - Elevated cortisol levels are associated with a number of diseases of the nervous system, such as memory disorders, and can be toxic to the hippocampus

### **NEUROIMAGING**

- **State-of-the-art diagnostic techniques**
- **Assess brain function as well as brain structures**
- **Potentially will be key in assessing the underlying pathology of neurological problems in GWW**

### NEUROIMAGING

- **Effects of Gulf War Illnesses on Brain Structure and Function (Pilot Study)**
  - San Francisco VAMC (currently undergoing Merit Review)
  - Neuroimaging study proposed to examine structural changes in basal ganglia and pons of healthy and ill Gulf War Veterans
  - This pilot project will attempt to confirm previous findings in a much larger population
  - Two recent manuscripts suggest a relationship between central nervous system abnormalities seen in GWI and ALS, and this pilot will also investigate this issue

### NEUROIMAGING

- **Neuroimaging Resource Centers RFP**
  - Neuroimaging Center - \$1,000,000, Future Consortia - \$5,000,000
  - Goal: Establishment of a coordinating center to guide efforts in developing, validating & standardizing neuroimaging research methodologies and metrics for GWVI
  - Development of consortia of sites

### UNDERSTANDING OTHER ILLNESSES THAT RESULT FROM GULF WAR EXPOSURE

- **ALS**
  - Epidemiology of ALS
  - Mechanisms of Injury due to ALS
  - Treatment for ALS

### ALS

- **Mechanisms of Injury**
  - **The Role of Oxidative injury in Spongiform Neurodegeneration**
    - Funding: \$171,420, FY' 03
    - Using a rat model, this VA investigator aims to determine the pathogenic mechanism by which free radicals produce spongiform vacuolation and degeneration of neurons that result in a progressive neurodegenerative disorder

## ALS

- **Mechanisms of Injury (continued)**
  - **Early Gene Triggers of Neurodegeneration**
  - Funding: \$163,963, FY'03
  - VA is investigating the hypothesis that thrombin signaling, which may have neuroprotective effects, is recapitulated in neurodegenerative diseases involving neuronal cell death; the outcome of this study may be a new treatment strategy.

## ALS

- **Treatment**
  - **Clinical Trials: Treating the primary disease**
    - **Clinical Trials – Albuterol to increase muscle mass**
    - Dr. Robert Ferrante, Bedford VAMC and colleges have published an article ([Science](#) Oct 3, 2003, Wild-Type Nonneuronal Cells Extend Survival of Superoxide Dismutase deficient (SOD1) Mutant Motor Neurons in ALS Mice).
    - This study shows that nonneuronal cells that do not express mutant superoxide dismutase delay degeneration and significantly extend survival of abnormal motor neurons.

## ALS

- **Clinical Trials: Treating the primary disease (continued)**
  - **Clinical Trials – Ginkgo Biloba (Antioxidant)**
  - Dr. Robert Ferrante, Bedford VAMC
  - The SOD system is an intracellular enzymatic system that protects against oxidative stress which can lead to neuronal death. Animals with an abnormality in this protective mechanism develop a disease very similar to ALS, and serve as a model for studying the disease. Dr. Robert Ferrante is also studying many antioxidant agents in the mouse (superoxide dismutase) model. VA has recently patented and licensed a Ginkgo Biloba treatment for ALS. Phase 1 trial will begin in 2004.

## ALS

- **Clinical Trials: Treating the Complications**
  - **Dysphagia Research, Madison VAMC**
    - Some therapeutic trials are geared toward increasing muscle mass (reversing sarcopenia) through focused exercise.
    - In a study conducted at the Madison VAMC, muscles involved in the swallowing process are strengthened. MRI imaging has shown an increase in muscle mass, and clinical responses have been encouraging in terms of more effective swallowing and decreased aspiration.

### ALS

- **Clinical Trials: Treating the Complications (continued)**
  - **A Phase II Study: Escalating Dose Response Trial of Tamoxifen Therapy on Mean Percent Predicted Isometric Strength in ALS, Madison VAMC**
  - Dr Benjamin Brooks, a VA Madison neurologist and researcher, is studying the impact of adding medications such as albuterol (known for increasing muscle mass in animals and humans) and tamoxifen (theoretically because of its testosterone effects) to exercise to reverse sarcopenia and increase functional strength.

### OTHER POST-DEPLOYMENT HEALTH RESEARCH INITIATIVES

- **Combat Trauma**
  - **Prazosin Treatment for Combat Trauma PTSD Nightmares and Sleep Disturbance, Seattle VAMC (Funded for 5 years:\$582,000)**
  - This placebo-controlled trial investigates possible mechanisms involving alpha-1 adrenergic receptor-mediated effects on sleep physiology, corticotropin releasing hormone secretion, and disruption of cognitive processing.

### OTHER POST-DEPLOYMENT HEALTH RESEARCH INITIATIVES

- **Parkinson's Disease**
  - **Examining Possible Associations between Military Service during the Vietnam Era and Parkinson's Disease: A Feasibility Study, West Haven VAMC & Houston VAMC (Possible Funding for 1 year: \$235,296)**
  - This one-year initiative determines the feasibility and design of an epidemiologic investigation examining the link between service in Vietnam and risk of Parkinson's Disease (PD).

### OTHER POST-DEPLOYMENT HEALTH RESEARCH INITIATIVES

- **Pre and Post Deployment Study**
  - **Prospective Assessment of Neurocognition in Future Gulf-Deployed and Gulf-Non Deployed Military Personnel, New Orleans VAMC (This study will be funded by DoD for 2 years at \$495,140 and by VA for 2 years at \$55,700)**
  - The VA and the Department of Defense (DoD) are jointly funding a first-of-its-kind study to ascertain whether or not deployment can lead to a deterioration in military service members' ability to function normally.

### **OTHER POST-DEPLOYMENT HEALTH RESEARCH INITIATIVES**

- **PTSD in Women**
  - **A Randomized Clinical Trial for Cognitive-Behavioral Treatment for PTSD in Women, White River Junction VAMC**
  - VA investigators are examining differences between a "Prolonged Exposure" therapy and a "Present-Centered Therapy" at 3 months post treatment for post traumatic stress disorder.

### **ORD'S COMMITMENT TO GWVI**

- **ORD is dedicated to furthering the knowledge to understand GWI and its health consequences, and to develop effective treatments**
- **ORD is also dedicated to working closely with the Gulf War Veterans' Illnesses Research Advisory Committee to achieve our common goal**



**Today's VA Research,  
Leading Tomorrow's Health Care**