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Award Number: W81XWH-12-1-0585

TITLE: Intranasal Insulin: A Novel Treatment for Gulf War Multisymptom Illness

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REPORT DATE: October 2013

TYPE OF REPORT: Annual Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2013	Annual Report	30September2012-29September2013

4. TITLE AND SUBTITLE
Intranasal Insulin: A Novel Treatment for Gulf War Multisymptom Illness

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-12-1-0585

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER
W81XWH-12-1-0585

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Bronx Veterans Medical Research Foundation Inc.
Bronx, NY 10468

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Following their deployment to the 1991 Gulf War, many veterans (GWV) reported a constellation of unexplained health symptoms; common among them were attention and memory difficulties, fatigue, joint pain, headaches, gastrointestinal complaints, and mood and sleep problems (Proctor et al., 1998; Sullivan et al., 2003). Despite the passage of time, the symptom complex persists for many veterans. Indeed, it is estimated that at least 25 percent of GWV (nearly 170,000 veterans) have a persistent form of chronic multisymptom illness (CMI) (Kang et al., 2009; Gulf War Research Advisory Committee (RAC), 2008; IOM, 2010). GW deployed veterans are also developing significantly more chronic diseases such as diabetes, hypertension, arthritis, and coronary heart disease than their non-deployed veteran peers (Toomey et al., 2009; Chao et al., 2010; Chao et al., 2011; Li et al., 2011) putting these individuals at risk for accelerated aging-related diseases of the peripheral and central nervous system (CNS). Over the years it has been found that cognitive complaints have been particularly troublesome to GWV. Recent studies have shown a slowing of response speed that affects mental flexibility across multiple cognitive domains (memory, attention, visuospatial functions) especially on tests that were timed and computerized and where small differences in cognitive reaction times could be measured (Anger et al., 1999; RAC, 2008; Krengel and Sullivan, 2008; Toomey et al., 2009; Chao et al., 2011). Recent studies also have suggested that the response inhibition deficits shown in GWV may reflect executive system dysfunction (Tillman et al., 2010) as reflected by slower motor responses across multiple cognitive domains (RAC, 2008). To date, there are no treatments that have been shown to substantially improve cognitive impairments or health symptoms of GWVs. Thus, it is of paramount importance to identify effective, safe, and tolerable treatments for Gulf War CMI.

15. SUBJECT TERMS
none provided

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	6	19b. TELEPHONE NUMBER *(include area code)*

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INTRODUCTION:

Background: Following their deployment to the 1991 Gulf War, many veterans (GWV) reported a constellation of unexplained health symptoms; common among them were attention and memory difficulties, fatigue, joint pain, headaches, gastrointestinal complaints, and mood and sleep problems (Proctor et al., 1998; Sullivan et al., 2003). Despite the passage of time, the symptom complex persists for many veterans. Indeed, it is estimated that at least 25 percent of GWV (nearly 170,000 veterans) have a persistent form of chronic multisymptom illness (CMI) (Kang et al., 2009; Gulf War Research Advisory Committee (RAC), 2008; IOM, 2010). GW deployed veterans are also developing significantly more chronic diseases such as diabetes, hypertension, arthritis, and coronary heart disease than their non-deployed veteran peers (Toomey et al., 2009; Chao et al., 2010; Chao et al., 2011; Li et al., 2011) putting these individuals at risk for accelerated aging-related diseases of the peripheral and central nervous system (CNS). Over the years it has been found that cognitive complaints have been particularly troublesome to GWV. Recent studies have shown a slowing of response speed that affects mental flexibility across multiple cognitive domains (memory, attention, visuospatial functions) especially on tests that were timed and computerized and where small differences in cognitive reaction times could be measured (Anger et al., 1999; RAC, 2008; Krengel and Sullivan, 2008; Toomey et al., 2009; Chao et al., 2011). Recent studies also have suggested that the response inhibition deficits shown in GWV may reflect executive system dysfunction (Tillman et al., 2010) as reflected by slower motor responses across multiple cognitive domains (RAC, 2008). To date, there are no treatments that have been shown to substantially improve cognitive impairments or health symptoms of GWVs. Thus, it is of paramount importance to identify effective, safe, and tolerable treatments for Gulf War CMI.

Objective: To test whether insulin, administered intranasally, improves the health and functioning of GWV with CMI.

Specific Aims: (1) To assess the efficacy of two different doses (10 IU BID and 20 IU BID) of daily intranasal insulin for eight weeks on memory and attention functioning in GWV with CMI. (2) To assess the efficacy of two different doses of intranasal insulin on overall physical health and mood in GWV with CMI. (3) To characterize the effect of two different doses of intranasal insulin on other symptoms that are characteristic of or associated with CMI (e.g., fatigue, pain, sleep quality, subjective cognitive function). (4) To assess the safety of two different doses of self-administered intranasal insulin in GWV with CMI.

Study Design: 114 eligible GWVs with CMI will be randomly assigned in parallel groups to treatment with 20 IU (i.e., 10 IU BID (after breakfast and dinner)), 40 IU (i.e., 20 IU BID (after breakfast and dinner)), or placebo for eight weeks and assessed for clinical outcomes at treatment endpoint. The treatment groups will self-administer 10 IU insulin or 20 IU insulin through a nasal infusion pump twice daily through the nose. The placebo group will administer saline through a nasal infusion pump twice daily as well. The primary outcome measure will be neuropsychological outcome (verbal memory and selective attention). As this will be the first trial of intranasal insulin in Gulf War veterans, a dose-finding clinical trial is proposed using two doses within the range that has been shown to be effective and safe in cognitively impaired older adults. Treatment duration of eight weeks was chosen in order to assess the effect of sustained intranasal treatment on cognition, mood, and overall health; a post-treatment follow-up assessment will be performed to characterize the sustainability of treatment effects.

BODY:

We have worked to obtain the authorizations necessary to initiation of human subjects' research. In September 2012 an Investigational Device Exemptions (IDE) application (#G120209) was submitted to the Food and Drug Administration. We were later informed that an IND must be submitted instead to the Center for Drug Evaluation and Research (CDER). On April 5, 2013 the FDA approved the IND (#117950) and concluded that the study may proceed.

Following several submissions and resubmission, the study received contingent IRB approval from the James J Peters VAMC (Bronx site) in January 2013, and we obtained the local pharmacy and laboratory agreements. IRB approval following the FDA IND approval was obtained, contingent upon an update on data collection security measures. A protocol amendment for data security at the Boston University School of Public Health was then approved by the IRB. Study protocol, consent form and drug were also approved by the Human Research Protection Office after the assignment of Eran Chemerinski, MD of the Bronx VA as study research monitor. The Bronx VA and Boston VA are now in process for IRB resubmission of the revised study documents. A Certificate of Confidentiality is now also being obtained at the request of the Boston VA R&D office.

Procurement of study insulin and intranasal device is in process through continued communication with Novo Nordisk and Kurve Technologies. Kurve Technologies was unable to deliver the intranasal devices as originally planned in the fall of 2012 but now report they will deliver them before the end of 2013. A purchase order was sent to Kurve Technologies on March 28th, 2013 for the ViaNase intranasal devices. There has been ongoing collaboration with the study pharmacist in an effort to finalize the logistics related to ordering and preparing study medication, and delivery of the intranasal device. Arrangements have been made to obtain an insulin-diluent, which is required to properly blind the study, and will be provided to us as no cost. The research pharmacist has also collaborated with Boston VA's pharmacist in order to ensure uniformity.

Both VA sites have reviewed and established the neuropsychological testing measures for the study, and obtained the testing materials. A change has been made in the planned method for electronic data capture. The team plans to use REDCap software instead of Teleform, and is currently reviewing the budgetary implications of this change with local budgetary staff representatives. All data will now be entered into the database by participants in real time. This will ensure the completeness of the data and reduce human error.

All study staff, including a new clinical psychologist and two recently hired research coordinators, have completed research and HIPPA related trainings. All study issues will continue to be discussed by the study team during bimonthly conference calls.

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