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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

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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.

KEYWORDS: Insulin, clinical trial, novel therapeutics, inflammation, cortisol, chronic fatigue, multi-symptom illness, malaise, deployment.

OVERALL PROJECT SUMMARY:

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.

KEY RESEARCH ACCOMPLISHMENTS:

As of September 2019, we have closed our study to patient accrual and will begin data analysis in 2020. Since the onset of this project we have accomplished the following:

- Screened numerous Gulf War Veterans to determine if they meet eligibility criteria for study participation
- Obtain fully informed consent from potentially eligible veterans
- Comprehensively assess subjects by obtaining demographics, medical history, and self-report questionnaires
- Complete medical evaluation and assess severity of symptoms of CMI and functional impairments
- Monitor adverse events

Total enrollment to-date at James J. Peters VA: 16
Total enrollment to-date at VA Boston Healthcare system: 12

REPORTABLE OUTCOMES

Currently trial is closed to patient accrual and undergoing data analysis, therefore there are no reportable outcomes now.

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