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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.

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:

Our sites have enrolled 11 individuals in the previous year, and recruitment has increased significantly during the conduct of the last 6 months. Specifically, from June 2012 to May 2015 0 participants were enrolled; with all 11 participants having been enrolled from June 2015 to present. This significant boost in enrollment can be attributed to our team's new advertisements, and networking with other VA facilities within the New York City area. Furthermore, new recruitment strategies have recently been developed, and will be implemented at the beginning of November. We thereby anticipate even further recruitment gains over the next year. Our Boston site has met with some setbacks, as the site coordinator was activated for deployment to Afghanistan, and is no-longer on-site. The team in the Bronx is currently waiting to schedule training for a recently hired replacement site coordinator in Boston, who will remain in Boston until the previous coordinator returns from deployment. In summary, our team intends to enact our new recruitment initiatives, push forward with our existing initiatives, and continue to enroll Desert Storm/Desert Shield Veterans.

In addition to our team's focus on recruitment, we continue to refine the RedCap system; which is utilized for electronic data capture. Thus far, the system has been functioning with few issues.

For our enrolled participants the medication/placebo has been tolerated with no major issues. Moreover, the curve device being utilized for medication administration has also been functioning properly.

Our study team has submitted for a 1-year no-cost extension, to continue recruitment and boost enrollment in this study.

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