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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:

The Bronx team plans to continue recruiting Gulf War Veteran's by visiting other VA hospitals and vet centers in the surrounding areas and working with veterans' service organizations. In the last year study recruitment has been slow-moving due to several logistical issues. Primarily we encountered several manufacture issues with our research medication device. Resolving this issue was difficult and time consuming, however we now have new up-to-date devices ready to be used in our research study. Additionally, since June 2018 our study has been paused by our local IRB. We were informed by our information security officer that we need a data use agreement before being able to proceed with our study. Preparing and having all parties review, revise and sign the DUA has taken several months. As a result, we have not been able to recruit or perform any work at all with this study since June 2018. A newly agreed-to DUA has been signed by the PI at the Bronx and Boston University's legal representative as of December 17, 2018 and we are awaiting concurrence from the Information Security. Once approved we will resubmit to our IRB. Ideally this study will be running smoothly after January 2019. We are confident that after overcoming these setbacks and utilizing our DOD approved two year no-cost extension, study recruitment will increase as it did during 2017. We are also in the process of amending the protocol so that Data Analytics will consider a request from us to access patient data for recruiting.

The team will continue to work through issues through established weekly conference calls and further training. Additionally, we are in the process of hiring a new research coordinator which will strengthen our team's ability to increase study recruitment and enrollment.

Total enrollment to-date at James J. Peters VA: 39 subjects
Total enrollment to-date at VA Boston Healthcare system: 12

REPORTABLE OUTCOMES

(*none). Trial is still open.*

REFERENCES:

Anger WK, Storzbach D, Binder LM, Campbell KA, Rohlman DS, McCauley L, Kovera CA, Davis KL. (1999) Neurobehavioral deficits in Persian Gulf veterans: evidence from a population-based study. Portland Environmental Hazards Research Center. *J Int Neuropsychol Soc*, *5*(3):203-12.

Chao LL, Abadjian L, Hlavin J, Meyerhoff DJ, Weiner MW. (2011, June 29). Effects of low -level sarin and cyclosarin exposure and Gulf War Illness on Brain Structure and Function: A study at 4T. *Neurotoxicology*.

Chao LL, Rothlind JC, Cardenas VA, Meyerhoff DJ, Weiner MW. (2010). Effects of low-level exposure to sarin and cyclosarin during the 1991 Gulf War on brain function and brain structure in US veterans. *Neurotoxicology*, *31*(5):493-501.

Institute of Medicine (IOM). (2010). Gulf War and Health: Volume 8. Health Effects of Serving in the Gulf War. Washington, DC: *National Academies Press*.

Kang H, Li B, Mahan C, Eisen S, Engel C. (2009). Health of US Veterans of 1991 Gulf War: A follow up Survey in 10 years. *JOEM*, *51*(4): 1-10.

Krengel M, Sullivan K. (2008). Neuropsychological Functioning in Gulf War veterans exposed to pesticides and pyridostigmine bromide. Fort Detrick, MD: *US Army Medical Research and Material Command*.

Li B, Mahan CM, Kang HK, Eisen SA, Engel CC. (2011, July 27). Longitudinal Health Study of US 1991 Gulf War Veterans: Changes in Health Status at 10-Year Follow-up. *Am J Epidemiol.*

Proctor SP, Heeren T, White RF, Wolfe J, Borgos MS, Davis JD, Pepper L, Clapp R, Sutker PB, Vasterling JJ, Ozonoff D. (1998). Health status of Persian Gulf War veterans: self-reported symptoms, environmental exposures and the effect of stress. *Int J Epidemiol*, *27*(6):1000-10.

Research Advisory Committee (RAC) on Gulf War Veterans' Illnesses. (2008). Gulf War illness and the Health of Gulf War Veterans: Scientific Findings and Recommendations. Washington, DC: US GPO.

Sullivan K, Krengel M, Proctor SP, Devine S, Heeren T, White RF. (2003). Cognitive functioning in treatment-seeking Gulf War veterans: pyridostigmine bromide use and PTSD. *Journal of Psychopathology and Behavioral Assessment*. *25*(2):95-103.

Tillman GD, Green TA, Ferree TC, Calley CS, Maguire MJ, Briggs R, Hart J Jr, Haley RW, Kraut MA. (2010, Oct 15). Impaired response inhibition in ill Gulf War veterans. *J Neurol Sci*, *297*(1-2):1-5.

Toomey R, et al. (2009). Neuropsychological functioning of U.S. Gulf War veterans 10 years after the war. *Journal of the International Neuropsychological Society*, *15*(5):717-29.