Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI) — PubMed Research Citations for October, November, December 2022

Prepared by Staff of the RACGWVI

RACGWVI: Gulf War Illness — PubMed Citations for October, November, December 2022

The following is a list of published research projects that focus on Gulf War Illness (GWI) for the months of October, November, December 2022.

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Hyperlinks Guide:

Table of Contents: Each title in the table of contents is linked to that corresponding abstract. Click on the desired title to go to that page (e.g., Impact of gulf war toxic exposures after mild traumatic brain injury, page 3).

Article Title: The title on each page (excluding table of contents), links to the abstract at PubMed.

DOI: Selecting the digital object identifier (DOI) will link to the article publication website.

Table of Contents

Randomized, Double-Blind Placebo-Controlled Trial to Assess the Effect of Probiotics on Irritable Bowel Syndrome in Veterans With Gulf War Illness

Ashok K. Tuteja, MD, MPH Nicholas J. Talley, MD, PhD Maureen A. Murtaugh, PhD Catherine M. Loc-Carrillo, MSc, PhD Gregory J. Stoddard Gary L. Anderson, PhD

Affiliations

George E. Whalen Veterans Affairs Medical Center, Salt Lake City, Utah

University of Utah, Salt Lake City

University of Newcastle, Callaghan, New South Wales, Australia

Lawrence Berkeley National Laboratory, Berkeley, California

Background: Many veterans who served in Operation Desert Storm (August 1990 to March 1991) experienced a complex of symptoms of unknown etiology called Gulf War illness (GWI), which significantly impacts the health and quality of life (QOL) and may have contributed to irritable bowel syndrome (IBS).

Methods: We performed a prospective, double-blind placebo-controlled study to determine the efficacy of the multistrain De Simone Formulation probiotic containing 8 strains of bacteria on symptoms of IBS and GWI. Veterans of Operation Desert Storm who had IBS and ≥ 2 nonintestinal symptoms of GWI were included. The primary study endpoint was change in bowel symptom score. The secondary endpoints were mean change in symptoms, QOL, and extra-intestinal and posttraumatic stress disorder (PTSD) symptoms.

Results: A total of 101 Gulf War veterans with IBS and GWI were screened at the Veteran Affairs Medical Center in Salt Lake City, Utah. The study was completed by 53 veterans; 47 (89%) were male with a mean (SD) age of 55 (8) years. The probiotic did not improve IBS symptoms or other extra-intestinal symptoms common to IBS and GWI.

Conclusions: Our study did not demonstrate statistically significant improvement in IBS symptoms or QOL after treatment with the probiotic. We also did not find any improvement in symptoms of GWI or PTSD.

Combinations of classical and non-classical voltage dependent potassium channel openers suppress nociceptor discharge and reverse chronic pain signs in a rat model of Gulf War illness

B Y Cooper 1, T J Nutter 2, L D Flunker 3, C M Bowers 4

Affiliations

1Division of Neuroscience, Dept. of Oral and Maxillofacial Surgery, JHMHC, University of Florida College of Dentistry, Box 100416, Gainesville, FL 32610, USA. Electronic address: bcooper@dental.ufl.edu.

2Division of Neuroscience, Dept. of Oral and Maxillofacial Surgery, JHMHC, University of Florida College of Dentistry, Box 100416, Gainesville, FL 32610, USA. Electronic address: t_nutter@msn.com.

3Division of Neuroscience, Dept. of Oral and Maxillofacial Surgery, JHMHC, University of Florida College of Dentistry, Box 100416, Gainesville, FL 32610, USA. Electronic address: linda.flunker@gmail.com.

4Division of Neuroscience, Dept. of Oral and Maxillofacial Surgery, JHMHC, University of Florida College of Dentistry, Box 100416, Gainesville, FL 32610, USA. Electronic address: clarissa.m.bowers@vanderbilt.edu.

Abstract

In a companion paper we examined whether combinations of Kv7 channel openers (Retigabine and Diclofenac; RET, DIC) could be effective modifiers of deep tissue nociceptor activity; and whether such combinations could then be optimized for use as safe analgesics for pain-like signs that developed in a rat model of GWI (Gulf War Illness) pain. In the present report, we examined the combinations of Retigabine/Meclofenamate (RET/MEC) and Meclofenamate/Diclofenac (MEC/DIC). Voltage clamp experiments were performed on deep tissue nociceptors isolated from rat DRG (dorsal root ganglion). In voltage clamp studies, a stepped voltage protocol was applied (-55 to -40 mV; Vh=-60 mV; 1500 msec) and Kv7 evoked currents were subsequently isolated by Linopirdine subtraction. MEC greatly enhanced voltage dependent conductance and produced exceptional maximum sustained currents of 6.01 ± 0.26 pA/pF (EC50: 62.2 ± 8.99 µM). Combinations of RET/MEC, and MEC/DIC substantially amplified resting currents at low concentrations. MEC/DIC also greatly improved voltage dependent conductance. In current clamp experiments, a cholinergic challenge test (Oxotremorine-M, 10 µM; OXO), associated with our GWI rat model, produced powerful action potential (AP) bursts (85 APs). Optimized combinations of RET/MEC (5 and 0.5 µM) and MEC/DIC (0.5 and 2.5 µM) significantly reduced AP discharges to 3 and 7 Aps, respectively. Treatment of pain-like ambulatory behavior in our rat model with a RET/MEC combination (5 and 0.5 mg/kg) successfully rescued ambulation deficits, but could not be fully separated from the effect of RET alone. Further development of this approach is recommended.

Impact of gulf war toxic exposures after mild traumatic brain injury

Scott Ferguson # 1, Robyn McCartan # 1, Mackenzie Browning 1, Coral Hahn-Townsend 1, Arissa Gratkowski 1, Alexander Morin 1, Laila Abdullah 1 2, Ghania Ait-Ghezala 1, Joseph Ojo 1, Kimberly Sullivan 3, Michael Mullan 1, Fiona Crawford 1 2, Benoit Mouzon 4 5

Affiliations

1Roskamp Institute, 2040 Whitfield Ave, Sarasota, FL, 34243, USA.

2James A. Haley Veterans' Hospital, Tampa, FL, USA.

3Department of Environmental Health, School of Public Health, Boston University, 715 Albany St. T4W, Boston, MA, 02118, USA.

4Roskamp Institute, 2040 Whitfield Ave, Sarasota, FL, 34243, USA. bmouzon@roskampinstitute.org.

5James A. Haley Veterans' Hospital, Tampa, FL, USA. bmouzon@roskampinstitute.org.

Abstract

Chemical and pharmaceutical exposures have been associated with the development of Gulf War Illness (GWI), but how these factors interact with the pathophysiology of traumatic brain injury (TBI) remains an area of study that has received little attention thus far. We studied the effects of pyridostigmine bromide (an anti-nerve agent) and permethrin (a pesticide) exposure in a mouse model of repetitive mild TBI (r-mTBI), with 5 impacts over a 9-day period, followed by Gulf War (GW) toxicant exposure for 10 days beginning 30 days after the last head injury. We then assessed the chronic behavioral and pathological sequelae 5 months after GW agent exposure. We observed that r-mTBI and GWI cumulatively affect the spatial memory of mice in the Barnes maze and result in a shift of search strategies employed by r-mTBI/GW exposed mice. GW exposure also produced anxiety-like behavior in sham animals, but r-mTBI produced disinhibition in both the vehicle and GW treated mice. Pathologically, GW exposure worsened r-mTBI dependent axonal degeneration and neuroinflammation, increased oligodendrocyte cell counts, and increased r-mTBI dependent phosphorylated tau, which was found to colocalize with oligodendrocytes in the corpus callosum. These results suggest that GW exposures may worsen TBI-related deficits. Veterans with a history of both GW chemical exposures as well as TBI may be at higher risk for worse symptoms and outcomes. Subsequent exposure to various toxic substances can influence the chronic nature of mTBI and should be considered as an etiological factor influencing mTBI recovery.

Low glutamate diet improves working memory and contributes to altering BOLD response and functional connectivity within working memory networks in Gulf War Illness

Mackenzie T Langan # 1, Anna E Kirkland # 2, Laura C Rice 1, Veronica C Mucciarone 3, James Baraniuk 4, Ashley VanMeter 3, Kathleen F Holton 5 6 7 8

Affiliations

1Department of Neuroscience, American University, Washington, DC, USA.

2Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA.

3Department of Neurology, Center for Functional and Molecular Imaging, Georgetown University, Washington, DC, USA.

4Department of Medicine, Georgetown University, Washington, DC, USA.

5Department of Neuroscience, American University, Washington, DC, USA. holton@american.edu.

6Department of Health Studies, American University, Washington, DC, USA. holton@american.edu.

7Center for Neuroscience and Behavior, American University, Washington, DC, USA. holton@american.edu.

8Nutritional Neuroscience Lab, American University, 4400 Massachusetts Ave NW, Washington, DC, 20016, USA. holton@american.edu.

Abstract

Gulf War Illness is a chronic multi-symptom disorder with severe cognitive impairments which may be related to glutamate excitotoxicity and central nervous system dysfunction. The low glutamate diet has been proposed as a comprehensive intervention for Gulf War Illness. We examined the effects of the low glutamate diet on verbal working memory using a fMRI N-back task. Accuracy, whole-brain blood oxygen level dependency (BOLD) response, and task-based functional connectivity were assessed at baseline and after 1 month on the diet (N = 24). Multi-voxel pattern analysis identified regions of whole-brain BOLD pattern differences after the diet to be used as seeds for subsequent seed-to-voxel functional connectivity analyses. Verbal working memory accuracy improved after the diet (+ 13%; p = 0.006). Whole-brain BOLD signal changes were observed, revealing lower activation within regions of the frontoparietal network and default mode network after the low glutamate diet. Multi-voxel pattern analysis resulted in 3 clusters comprising parts of the frontoparietal network (clusters 1 and 2) and ventral attention network (cluster 3). The seed-to-voxel analyses identified significant functional connectivity changes post-diet for clusters 1 and 2 (peak p < 0.001, cluster FDR p < 0.05). Relative to baseline, clusters 1 and 2 had decreased functional connectivity with regions in the ventral attention and somatomotor networks. Cluster 2 also had increased functional connectivity with regions of the default mode and frontoparietal networks. These findings suggest that among veterans with Gulf War Illness, the low glutamate diet improves verbal working memory accuracy, alters BOLD response, and alters functional connectivity within two networks central to working memory.

The low glutamate diet improves cognitive functioning in veterans with Gulf War Illness and resting-state EEG potentially predicts response

Anna E Kirkland 1, Michael Baron 2, John W VanMeter 3, James N Baraniuk 4, Kathleen F Holton 5 6

Affiliations

1Behavior, Cognition and Neuroscience Program, American University, Washington, DC, USA.

2Mathematics & Statistics Department, American University, Washington, DC, USA.

3Department of Neurology, Center for Functional & Molecular Imaging, Georgetown University, Washington, DC, USA.

4Department of Medicine, Georgetown University, Washington, DC, USA.

5Department of Health Studies, American University, Washington, DC, USA.

6Center for Behavioral Neuroscience, American University, Washington, DC, USA.

Abstract

Objectives: Gulf War Illness (GWI) is a chronic, multi-symptom disorder with underlying central nervous system dysfunction and cognitive impairments. The objective of this study was to test the low glutamate diet as a novel treatment for cognitive dysfunction among those with GWI, and to explore if baseline resting-state electroencephalography (EEG) could predict cognitive outcomes.

Methods: Cognitive functioning was assessed at baseline, after one-month on the diet, and across a two-week double-blind, placebo-controlled crossover challenge with monosodium glutamate (MSG) relative to placebo.

Results: Significant improvements were seen after one-month on the diet in overall cognitive functioning, and in all other domains tested (FDR $p < 0.05$), except for memory. Challenge with MSG resulted in significant inter-individual response variability ($p < 0.0001$). Participants were clustered according to baseline resting-state EEG using k-means clustering to explore the inter-individual response variability. Three distinct EEG clusters were observed, and each corresponded with differential cognitive effects during challenge with MSG: cluster 1 had cognitive benefit (24% of participants), cluster 2 had cognitive detriment (42% of participants), and cluster 3 had mild/mixed effects (33% of participants).

Discussion: These findings suggest that the low glutamate diet may be a beneficial treatment for cognitive impairment in GWI. Future research is needed to understand the extent to which resting-state EEG can predict response to the low glutamate diet and to explore the mechanisms behind the varied response to acute glutamate challenge.

Complementary/integrative healthcare utilization in US Gulf-War era veterans: Descriptive analyses based on deployment history, combat exposure, and Gulf War Illness

Katherine Kelton 1, Jonathan R Young 2, Mariah K Evans 3, Yasmine M Eshera 3, Shannon M Blakey 4, Adam J D Mann 5, Mary Jo Pugh 6, Patrick S Calhoun 7, Jean C Beckham 2, Nathan A Kimbrel 7

Affiliations

1South Texas Veteran Health Care System, Audie L. Murphy Veteran Hospital San Antonio, TX, USA; National Center for Homelessness Among Veterans, USA. Electronic address: katherine.kelton@va.gov.

2Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, NC, USA; Durham Veterans Affairs Health Care System, Durham, NC, USA; Mid-Atlantic Mental Illness Research, Education, And Clinical Center (MIRECC), Durham, NC, USA.

3Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, NC, USA; Durham Veterans Affairs Health Care System, Durham, NC, USA.

4Durham Veterans Affairs Health Care System, Durham, NC, USA; Mid-Atlantic Mental Illness Research, Education, And Clinical Center (MIRECC), Durham, NC, USA.

5Department of Psychology, University of Toledo, Toledo, OH, USA.

6VA Salt Lake City Health Care System and IDEAS Center of Innovation, Salt Lake City UT, USA; University of Utah School of Medicine, Department of Medicine, Salt Lake City UT, USA.

7Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, NC, USA; Durham Veterans Affairs Health Care System, Durham, NC, USA; Mid-Atlantic Mental Illness Research, Education, And Clinical Center (MIRECC), Durham, NC, USA; Durham HSRD Center (ADAPT), USA.

Abstract

Complementary and integrative health (CIH) approaches have gained empirical support and are increasingly being utilized among veterans to treat a myriad of conditions. A cluster of medically unexplained chronic symptoms including fatigue, headaches, joint pain, indigestion, insomnia, dizziness, respiratory disorders, and memory problems, often referred to as Gulf War Illness (GWI) prominently affect US Gulf War era (GWE) veterans, yet little is known about CIH use within this population. Using data collected as part of a larger study (n = 1153), we examined the influence of demographic characteristics, military experiences, and symptom severity on CIH utilization, and utilization differences between GWE veterans with and without GWI. Over half of the sample (58.5%) used at least one CIH modality in the past six months. Women veterans, white veterans, and veterans with higher levels of education were more likely to use CIH. GWE veterans with a GWI diagnosis and higher GWI symptom severity were more likely to use at least one CIH treatment in the past six months. Over three quarters (82.7%) of veterans who endorsed using CIH to treat GWI symptoms reported that it was helpful for their symptoms. Almost three quarters (71.5%) of veterans indicated that they would use at least one CIH approach if it was available at VA. Results provide a deeper understanding of the likelihood and characteristics of veterans utilizing CIH to treat health and GWI symptoms and may inform expansion of CIH modalities for GWE veterans, particularly those with GWI.

Symptom attribution to a medically unexplained syndrome is associated with greater perceived severity and bothersomeness of symptoms in US military veterans

L Alison Phillips 1, Lisa M McAndrew 2 3, Benjamin Laman-Maharg 4

Affiliations

1Department of Psychology, Iowa State University, Ames, IA, USA.

2War Related Illness and Injury Study Center (WRIISC), Veterans Affairs New Jersey Healthcare System, East Orange, NJ, USA.

3Department of Educational and Counseling Psychology EDU220, University at Albany, Albany, NY, USA.

4Department of Psychology, Northern Illinois University, DeKalb, IL, USA.

Abstract

Objective: Medically unexplained symptoms (MUS) are prevalent among veteran and non-veteran populations. Current biopsychosocial theory implicates a multitude of factors in MUS development and perpetuation. The current study tests whether physical symptom attribution to MUS is associated with perceived symptom severity and bothersomeness and thereby might function to perpetuate MUS, as suggested by existing theory.

Design and main outcome measures: Military combat veterans (n = 243) answered postal-mail questions about their physical symptoms, severity of experienced symptoms, and attributions of these symptoms to MUS (e.g. Gulf War Illness) versus non-MUS conditions.

Results: Independent t-tests showed support for the first hypothesis-that those who experience the symptom and attribute it to MUS will perceive it to be more severe and bothersome than those who experience the symptom but do not attribute it to MUS. Paired-sample t-tests showed support for the second hypothesis-that experienced symptoms attributed to MUS by an individual will be perceived as more severe and bothersome than experienced symptoms the individual does not attribute to MUS.

Conclusions: Results highlight a potential role of symptom attribution in MUS perpetuation, through greater perceived severity and bothersomeness of MUS-attributed symptoms. Possible intervention targets may include behavior ramifications, such as coping strategies; more research is needed.

Complementary/integrative healthcare utilization in US Gulf-War era veterans: Descriptive analyses based on deployment history, combat exposure, and Gulf War Illness

Katherine Kelton 1, Jonathan R Young 2, Mariah K Evans 3, Yasmine M Eshera 3, Shannon M Blakey 4, Adam J D Mann 5, Mary Jo Pugh 6, Patrick S Calhoun 7, Jean C Beckham 2, Nathan A Kimbrel 7

Affiliations

1South Texas Veteran Health Care System, Audie L. Murphy Veteran Hospital San Antonio, TX, USA; National Center for Homelessness Among Veterans, USA. Electronic address: katherine.kelton@va.gov.

2Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, NC, USA; Durham Veterans Affairs Health Care System, Durham, NC, USA; Mid-Atlantic Mental Illness Research, Education, And Clinical Center (MIRECC), Durham, NC, USA.

3Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, NC, USA; Durham Veterans Affairs Health Care System, Durham, NC, USA.

4Durham Veterans Affairs Health Care System, Durham, NC, USA; Mid-Atlantic Mental Illness Research, Education, And Clinical Center (MIRECC), Durham, NC, USA.

5Department of Psychology, University of Toledo, Toledo, OH, USA.

6VA Salt Lake City Health Care System and IDEAS Center of Innovation, Salt Lake City UT, USA; University of Utah School of Medicine, Department of Medicine, Salt Lake City UT, USA.

7Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, NC, USA; Durham Veterans Affairs Health Care System, Durham, NC, USA; Mid-Atlantic Mental Illness Research, Education, And Clinical Center (MIRECC), Durham, NC, USA; Durham HSRD Center (ADAPT), USA.

Abstract

Complementary and integrative health (CIH) approaches have gained empirical support and are increasingly being utilized among veterans to treat a myriad of conditions. A cluster of medically unexplained chronic symptoms including fatigue, headaches, joint pain, indigestion, insomnia, dizziness, respiratory disorders, and memory problems, often referred to as Gulf War Illness (GWI) prominently affect US Gulf War era (GWE) veterans, yet little is known about CIH use within this population. Using data collected as part of a larger study (n = 1153), we examined the influence of demographic characteristics, military experiences, and symptom severity on CIH utilization, and utilization differences between GWE veterans with and without GWI. Over half of the sample (58.5%) used at least one CIH modality in the past six months. Women veterans, white veterans, and veterans with higher levels of education were more likely to use CIH. GWE veterans with a GWI diagnosis and higher GWI symptom severity were more likely to use at least one CIH treatment in the past six months. Over three quarters (82.7%) of veterans who endorsed using CIH to treat GWI symptoms reported that it was helpful for their symptoms. Almost three quarters (71.5%) of veterans indicated that they would use at least one CIH approach if it was available at VA. Results provide a deeper understanding of the likelihood and characteristics of veterans utilizing CIH to treat health and GWI symptoms and may inform expansion of CIH modalities for GWE veterans, particularly those with GWI.

A review of chemical warfare agents linked to respiratory and neurological effects experienced in Gulf War Illness

Angela Cruz-Hernandez 1, Andrew Roney 2, Dinesh G Goswami 2, Neera Tewari-Singh 2, Jared M Brown 1

Affiliations

1Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, The University of Colorado, Anschutz Medical Campus, Aurora, CO, USA.

2Department of Pharmacology and Toxicology, College of Osteopathic Medicine, Michigan State University, East Lansing, MI, USA.

Abstract

Over 40% of veterans from the Persian Gulf War (GW) (1990-1991) suffer from Gulf War Illness (GWI). Thirty years since the GW, the exposure and mechanism contributing to GWI remain unclear. One possible exposure that has been attributed to GWI are chemical warfare agents (CWAs). While there are treatments for isolated symptoms of GWI, the number of respiratory and cognitive/neurological issues continues to rise with minimum treatment options. This issue does not only affect veterans of the GW, importantly these chronic multisymptom illnesses (CMIs) are also growing amongst veterans who have served in the Afghanistan-Iraq war. What both wars have in common are their regions and inhaled exposures. In this review, we will describe the CWA exposures, such as sarin, cyclosarin, and mustard gas in both wars and discuss the various respiratory and neurocognitive issues experienced by veterans. We will bridge the respiratory and neurological symptoms experienced to the various potential mechanisms described for each CWA provided with the most up-to-date models and hypotheses.

Fatigue and Pain Severity in Gulf War Illness Is Associated With Changes in Inflammatory Cytokines and Positive Acute Phase Proteins

Kathleen S Hodgin 1, Chloe L Jones, Jarred W Younger

Affiliation

1From the Department of Psychology, University of Alabama at Birmingham, Birmingham, Alabama.

Abstract

Objective: The aim of the study is to investigate relationships between inflammatory analytes and symptoms of pain and fatigue in Gulf War illness (GWI).

Methods: In this preliminary study, 12 male veterans meeting GWI criteria provided daily blood samples and symptom ratings over 25 days. Linear mixed models were used to analyze associations between symptoms and sera concentrations of cytokines, acute phase proteins, insulin, and brain-derived neurotropic factor.

Results: Analyses included 277 days with both blood draws and self-reports. Days with worse fatigue severity were associated with higher C-reactive protein and serum amyloid A, and lower eotaxin 1. Muscle pain and joint pain were associated with leptin, monocyte chemoattractant protein 1, and interferon γ-induced protein. Joint pain was further associated with serum amyloid A and eotaxin 3.

Conclusions: Gulf War illness involves fatigue and pain associated with inflammation. Conventional and novel anti-inflammatories should be further explored for the treatment of GWI.

Evaluation of delayed LNFPIII treatment initiation protocol on improving long-term behavioral and neuroinflammatory pathology in a mouse model of Gulf War Illness

Jessica M Carpenter 1 2, Kyle A Brown 1, Lukas Veltmaat 1, Helaina D Ludwig 1, Kendall B Clay 2, Thomas Norberg 3, Donald A Harn 4, John J Wagner 1 2, Nikolay M Filipov 1 2

Affiliations

1Department of Physiology and Pharmacology, University of Georgia, Athens, GA, United States.

2Neuroscience Program, University of Georgia, Athens, GA, United States.

3Department of Chemistry, University of Uppsala, Uppsala, Sweden.

4Department of Infectious Diseases and Center for Tropical and Emerging Diseases, University of Georgia, Athens, GA, United States.

Abstract

Chemical overexposures and war-related stress during the 1990-1991 Gulf War (GW) are implicated in the persisting pathological symptoms that many GW veterans continue to endure. These symptoms culminate into a disease known as Gulf War Illness (GWI) and affect about a third of the GW veteran population. Currently, comprehensive effective GWI treatment options are unavailable. Here, an established GWI mouse model was utilized to explore the (1) long-term behavioral and neuroinflammatory effects of deployment-related GWI chemicals exposure and (2) ability of the immunotherapeutic lacto-N-fucopentaose III (LNFPIII) to improve deficits when given months after the end of exposure. Male C57BL6/J mice (8-9 weeks old) were administered pyridostigmine bromide (PB) and DEET for 14 days along with corticosterone (CORT; latter 7 days) to emulate wartime stress. On day 15, a single injection of the nerve agent surrogate diisopropylfluorophosphate (DFP) was given. LNFPIII treatment began 7 months post GWI chemicals exposure and continued until study completion. A battery of behavioral tests for assessment of cognition/memory, mood, and motor function in rodents was performed beginning 8 months after exposure termination and was then followed by immunohistochemcal evaluation of neuroinflammation and neurogenesis. Within tests of motor function, prior GWI chemical exposure led to hyperactivity, impaired sensorimotor function, and altered gait. LNFPIII attenuated these motor-related deficits and improved overall grip strength. GWI mice also exhibited more anxiety-like behavior that was reduced by LNFPIII; this was test-specific. Short-term, but not long-term memory, was impaired by prior GWI exposure; LNFPIII improved this measure. In the brains of GWI mice, but not in mice treated with LNFPIII, glial activation was increased. Overall, it appears that months after exposure to GWI chemicals, behavioral deficits and neuroinflammation are present. Many of these deficits were attenuated by LNFPIII when treatment began long after GWI chemical exposure termination, highlighting its therapeutic potential for veterans with GWI.

A pilot reverse virtual screening study suggests toxic exposures caused long-term epigenetic changes in Gulf War Illness

Modeline Jean-Pierre 1 2, Lindsay T Michalovicz 3, Kimberly A Kelly 3, James P O'Callaghan 3, Lubov Nathanson 2 4, Nancy Klimas 2 4 5, Travis J A Craddock 1 2 4 6

Affiliations

1Department of Psychology & Neuroscience, Nova Southeastern University, Ft. Lauderdale, FL, United States.

2Institute for Neuro-Immune Medicine, Nova Southeastern University, Ft. Lauderdale, FL, United States.

3Health Effects Laboratory Division, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Morgantown, WV, United States.

4Department of Clinical Immunology, Nova Southeastern University, Ft. Lauderdale, FL, United States.

5Miami Veterans Affairs Medical Center, Miami, FL, United States.

6Department of Computer Science, Nova Southeastern University, Ft. Lauderdale, FL, United States.

Abstract

Gulf War Illness (GWI) is a chronic illness that affects upward of 32% of deployed Veterans to the 1991 Gulf War (GW). The symptoms are medically unexplained, ranging across cognitive deficits, fatigue, gastrointestinal problems, and musculoskeletal pain. Research indicates that chemical warfare agents play a key role in the onset and progression of GWI. The Khamisiyah ammunition storage that housed chemical warfare agents such as sarin, an acetylcholinesterase (AChE) inhibitor, was demolished during the GW, releasing toxicants into the atmosphere affecting deployed troops. Exposure to other chemical agents such as pyridostigmine bromide, N,N-diethyl-m-toluamide, permethrin and chlorpyrifos, were also prevalent during the war. These additional chemical agents have also been shown to inhibit AChE. AChE inhibition induces an acetylcholine build-up, disrupting signals between nerves and muscles, which in high doses leads to asphyxiation. Little is known about low dose exposure. As bioactive compounds tend to interact with multiple proteins with various physiological effect, we aimed to identify other potential shared targets to understand the extent in which these chemicals could lead to GWI. We followed a reverse screening approach where each chemical is computationally docked to a library of protein targets. The programs PharmMapper and TargetNet were used for this purpose, and further analyses were conducted to mark significant changes in participants with GWI. Previously published work on DNA methylation status in GWI was reanalyzed focusing specifically on the predicted shared targets indicating significant changes in DNA methylation of the associated genes. Our findings thus suggest that exposure to GWI-related agents may converge on similar targets with roles in inflammation, neurotransmitter and lipid metabolism, and detoxification which may have impacts on neurodegenerative-like disease and oxidative stress in Veterans with GWI.

A review of chemical warfare agents linked to respiratory and neurological effects experienced in Gulf War Illness

Angela Cruz-Hernandez 1, Andrew Roney 2, Dinesh G Goswami 2, Neera Tewari-Singh 2, Jared M Brown 1

Affiliations

1Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, The University of Colorado, Anschutz Medical Campus, Aurora, CO, USA.

2Department of Pharmacology and Toxicology, College of Osteopathic Medicine, Michigan State University, East Lansing, MI, USA.

Abstract

Over 40% of veterans from the Persian Gulf War (GW) (1990-1991) suffer from Gulf War Illness (GWI). Thirty years since the GW, the exposure and mechanism contributing to GWI remain unclear. One possible exposure that has been attributed to GWI are chemical warfare agents (CWAs). While there are treatments for isolated symptoms of GWI, the number of respiratory and cognitive/neurological issues continues to rise with minimum treatment options. This issue does not only affect veterans of the GW, importantly these chronic multisymptom illnesses (CMIs) are also growing amongst veterans who have served in the Afghanistan-Iraq war. What both wars have in common are their regions and inhaled exposures. In this review, we will describe the CWA exposures, such as sarin, cyclosarin, and mustard gas in both wars and discuss the various respiratory and neurocognitive issues experienced by veterans. We will bridge the respiratory and neurological symptoms experienced to the various potential mechanisms described for each CWA provided with the most up-to-date models and hypotheses.

Sarin: a never-ending story

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Hermann M Bolt 1

Affiliation

1Leibniz Research Centre for Working Environment and Human Factors at TU Dortmund (IfADo), Ardeystr. 67, 44579, Dortmund, Germany. bolt@ifado.de.

No abstract available

Combinations of classical and non-classical voltage dependent potassium channel openers suppress nociceptor discharge and reverse chronic pain signs in a rat model of Gulf War illness

B Y Cooper 1, T J Nutter 2, L D Flunker 3, C M Bowers 4

Affiliations

1Division of Neuroscience, Dept. of Oral and Maxillofacial Surgery, JHMHC, University of Florida College of Dentistry, Box 100416, Gainesville, FL 32610, USA. Electronic address: bcooper@dental.ufl.edu.

2Division of Neuroscience, Dept. of Oral and Maxillofacial Surgery, JHMHC, University of Florida College of Dentistry, Box 100416, Gainesville, FL 32610, USA. Electronic address: t_nutter@msn.com.

3Division of Neuroscience, Dept. of Oral and Maxillofacial Surgery, JHMHC, University of Florida College of Dentistry, Box 100416, Gainesville, FL 32610, USA. Electronic address: linda.flunker@gmail.com.

4Division of Neuroscience, Dept. of Oral and Maxillofacial Surgery, JHMHC, University of Florida College of Dentistry, Box 100416, Gainesville, FL 32610, USA. Electronic address: clarissa.m.bowers@vanderbilt.edu.

Abstract

In a companion paper we examined whether combinations of Kv7 channel openers (Retigabine and Diclofenac; RET, DIC) could be effective modifiers of deep tissue nociceptor activity; and whether such combinations could then be optimized for use as safe analgesics for pain-like signs that developed in a rat model of GWI (Gulf War Illness) pain. In the present report, we examined the combinations of Retigabine/Meclofenamate (RET/MEC) and Meclofenamate/Diclofenac (MEC/DIC). Voltage clamp experiments were performed on deep tissue nociceptors isolated from rat DRG (dorsal root ganglion). In voltage clamp studies, a stepped voltage protocol was applied (-55 to -40 mV; Vh=-60 mV; 1500 msec) and Kv7 evoked currents were subsequently isolated by Linopirdine subtraction. MEC greatly enhanced voltage dependent conductance and produced exceptional maximum sustained currents of 6.01 ± 0.26 pA/pF (EC50: 62.2 ± 8.99 μM). Combinations of RET/MEC, and MEC/DIC substantially amplified resting currents at low concentrations. MEC/DIC also greatly improved voltage dependent conductance. In current clamp experiments, a cholinergic challenge test (Oxotremorine-M, 10 μM; OXO), associated with our GWI rat model, produced powerful action potential (AP) bursts (85 APs). Optimized combinations of RET/MEC (5 and 0.5 μM) and MEC/DIC (0.5 and 2.5 μM) significantly reduced AP discharges to 3 and 7 Aps, respectively. Treatment of pain-like ambulatory behavior in our rat model with a RET/MEC combination (5 and 0.5 mg/kg) successfully rescued ambulation deficits, but could not be fully separated from the effect of RET alone. Further development of this approach is recommended.

Effect of Problem-solving Treatment on Self-reported Disability Among Veterans With Gulf War Illness: A Randomized Clinical Trial

Lisa M McAndrew 1, Karen S Quigley 2 3, Shou-En Lu 4, David Litke 1 5, Joseph F Rath 5, Gudrun Lange 1, Susan L Santos 1, Nicole Anastasides 1, Beth Ann Petrakis 2, Lauren Greenberg 1 6, Drew A Helmer 1 7, Wilfred R Pigeon 8 9

Affiliations

1War Related Illness and Injury Study Center, Veterans Affairs (VA) New Jersey Health Care System, East Orange.

2Bedford VA Medical Center, Bedford, Massachusetts.

3Department of Psychology, Northeastern University, Boston, Massachusetts.

4Department of Biostatistics and Epidemiology, Rutgers School of Public Health, Piscataway, New Jersey.

5Department of Rehabilitation Medicine, New York University School of Medicine, New York.

6VA Palo Alto Health Care System, Palo Alto, California.

7Center for Innovations in Quality, Effectiveness and Safety at Michael E. DeBakey VA Medical Center and Baylor College of Medicine, Houston, Texas.

8Center of Excellence for Suicide Prevention, Canandaigua VA Medical Center, Canandaigua, New York.

9Department of Psychiatry, University of Rochester Medical Center, Rochester, New York.

Abstract

Importance: Few evidence-based treatments are available for Gulf War illness (GWI). Behavioral treatments that target factors known to maintain the disability from GWI, such as problem-solving impairment, may be beneficial. Problem-solving treatment (PST) targets problem-solving impairment and is an evidence-based treatment for other conditions.

Objective: To examine the efficacy of PST to reduce disability, problem-solving impairment, and physical symptoms in GWI.

Design, setting, and participants: This multicenter randomized clinical trial conducted in the US Department of Veterans Affairs compared PST with health education in a volunteer sample of 511 Gulf War veterans with GWI and disability (January 1, 2015, to September 1, 2019); outcomes were assessed at 12 weeks and 6 months. Statistical analysis was conducted between January 1, 2019, and December 31, 2020.

Interventions: Problem-solving treatment taught skills to improve problem-solving. Health education provided didactic health information. Both were delivered by telephone weekly for 12 weeks.

Main outcomes and measures: The primary outcome was reduction from baseline to 12 weeks in self-report of disability (World Health Organization Disability Assessment Schedule). Secondary outcomes were reductions in self-report of problem-solving impairment and objective problem-solving. Exploratory outcomes were reductions in pain, pain disability, and fatigue.

Results: A total of 268 veterans (mean [SD] age, 52.9 [7.3] years; 88.4% male; 66.8% White) were randomized to PST (n = 135) or health education (n = 133). Most participants completed all 12 sessions of PST (114 of 135 [84.4%]) and health education (120 of 133 [90.2%]). No difference was found between groups in reductions in disability at the end of treatment. Results suggested that PST reduced problem-solving impairment (moderate effect, 0.42; P = .01) and disability at 6 months (moderate effect, 0.39; P = .06) compared with health education.

Conclusions and relevance: In this randomized clinical trial of the efficacy of PST for GWI, no difference was found between groups in reduction in disability at 12 weeks. Problem-solving treatment had high adherence and reduced problem-solving impairment and potentially reduced disability at 6 months compared with health education. These findings should be confirmed in future studies.

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Clinical Normative Data for Gulf War Veterans

Mathew J Reinhard 1, Nathaniel Allen 1, Lucas E Crock 1, Kelly K McCarron 2, Gladys M Veltkamp 3, Ryan C Brewster 1

Affiliations

1War Related Illness and Injury Study Center at the Washington DC VA Medical Center (WRIISC-DC), Washington, DC, United States of America.

2War Related Illness and Injury Study Center at the VA New Jersey Healthcare System (WRIISC-NJ), East Orange, NJ, United States of America. The work for this article was conducted during my work as an employee of the Department of Veterans Affairs.

3War Related Illness and Injury Study Center at the VA Palo Alto Health Care System (WRIISC-CA), Palo Alto, CA, United States of America.

Abstract

Objective: Heterogenous test batteries and methods applied in neurocognitive research on Gulf War Veterans (GWVs) limit the translation of findings to clinical practice. A clinical data set is necessary.

Methods: Neurocognitive screening data from treatment-seeking GWVs were collected from multiple sites and compiled, informed by consideration of performance validity.

Results: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) scores revealed the cognitive profile for GWVs (n = 189) as poorer across multiple domains when compared to similarly educated, non-veteran peers. However, mean scores generally remained within normal clinical limits. Data tables are presented to establish a comparison group for use in clinical care.

Conclusions: When assessing cognitive symptoms in GWVs, attention to education level and interpretation of subtle deficits is warranted. Current results highlight the importance of nuanced translation of neurocognitive research findings into clinical practice with GWVs.

Study protocol for a revised randomized trial: Remotely delivered Tai Chi and wellness for Gulf War illness

Barbara L Niles 1, Stephanie Grossman 2, Maria McQuade 2, Dan Grossman 2, Anica Pless Kaiser 2, Brian Muccio 3, Ben Warner 4, Chenchen Wang 5, DeAnna L Mori 6

Affiliations

1National Center for PTSD, VA Boston Healthcare System and Boston University School of Medicine, Boston, MA, United States of America. Electronic address: Barbara.Niles@va.gov.

2National Center for PTSD, VA Boston Healthcare System and Boston University School of Medicine, Boston, MA, United States of America.

3Body Movement Solutions.

4Yang Martial Arts Association Boston.

5Center for Integrative Medicine, Division of Rheumatology, Tufts Medical Center, Tufts University School of Medicine, Boston, MA, United States of America.

6VA Boston Healthcare System and Boston University School of Medicine, Boston, MA, United States of America.

Abstract

Background: Many of the 700,000 American military personnel deployed to the Persian Gulf region in 1990 and 1991 have since reported health symptoms of unknown etiology. This cluster of symptoms has been labeled Gulf War Illness and include chronic musculoskeletal pain, fatigue, headaches, memory and attention difficulties, gastrointestinal complaints, skin abnormalities, breathing problems, and mood and sleep problems [1,2]. There have been few high-quality intervention trials and no strong evidence to support available treatments [3]. Tai Chi is an ancient Chinese martial art with benefits that include enhancing physical and mental health and improving quality of life for those with chronic conditions.

Proposed methods: In this randomized controlled trial, GW Veterans are randomly assigned to either Tai Chi or a Wellness control condition, with both remotely delivered intervention groups meeting twice a week for 12 weeks. The primary aim is to examine if Tai Chi is associated with greater improvements in GWI symptoms in Veterans with GWI compared to a Wellness intervention. Participants will receive assessments at baseline, 12 weeks (post-intervention), and follow-up assessments 3- and 9-months post-intervention. The primary outcome measure is the Brief Pain Inventory that examines pain intensity and pain interference.

Conclusion: This trial will produce valuable results that can have a meaningful impact on healthcare practices for GWI. If proven as a helpful treatment for individuals with GWI, it would support the implementation of remotely delivered Tai Chi classes that Veterans can access from their own homes.

Effects of a diet low in excitotoxins on PTSD symptoms and related biomarkers

Sidney L Murray 1, Kathleen F Holton 1 2 3

Affiliations

1Department of Neuroscience, American University, Washington, DC, USA.

2Department of Health Studies, American University, Washington, DC, USA.

3Center for Neuroscience and Behaviour, American University, Washington, DC, USA.

Abstract

Post-traumatic stress disorder (PTSD) develops after trauma exposure and involves symptoms of avoidance, intrusive re-experiencing, mood and cognitive dysfunction, and hypervigilance. PTSD is often comorbid with Gulf War Illness (GWI), a neurological condition involving widespread pain, cognitive dysfunction, digestive problems, and other symptoms, in Gulf War veterans. PTSD tends to be more severe when comorbid with GWI. Low cortisol and elevated homocysteine levels have been found in PTSD, making them potential PTSD biomarkers. The low-glutamate diet, which aims to reduce excitotoxicity by eliminating the consumption of free glutamate and aspartate, has been shown to significantly reduce GWI and PTSD symptoms. This study examined whether changes in serum cortisol and homocysteine are associated with reduced PTSD severity in veterans with GWI after one month on the low-glutamate diet, and whether reducing the consumption of dietary excitotoxins was associated changes in PTSD and serum biomarkers. Data were analyzed for 33 veterans. No serum biomarkers significantly changed post-diet; however, cortisol increased as dietary excitotoxin consumption decreased, which held in a multivariable linear regression after adjustment for sex. Reduced dietary excitotoxin consumption was also associated with reduced hyperarousal symptoms, which held in a multivariable linear regression after adjustment for sex. Cortisol increase was associated with reduced avoidance symptoms after adjustment for change in BMI, and was marginally associated with overall PTSD reduction. Change in homocysteine was not significantly related to dietary adherence nor change in PTSD. Results suggest that reducing the consumption of dietary excitotoxins may normalize cortisol levels, which has been associated with alleviating PTSD.

Mental health of U.S. combat veterans by war era: Results from the National health and Resilience in veterans study

Peter J Na 1, Paula P Schnurr 2, Robert H Pietrzak 3

Affiliations

1VA Connecticut Healthcare System, West Haven, CT, USA; Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA. Electronic address: peter.na@yale.edu.

2National Center for PTSD, White River Junction, VT, USA; Department of Psychiatry, Geisel School of Medicine at Dartmouth, Hanover, NH, USA.

3Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA; National Center for PTSD, VA Connecticut Healthcare System, West Haven, CT, USA; Department of Social and Behavioral Sciences, Yale School of Public Health, New Haven, CT, USA.

Abstract

Combat exposure is associated with elevated risk for adverse psychiatric outcomes in military veterans. However, few studies have examined psychiatric characteristics of veterans who served in different war eras. We analyzed data from the 2019-2020 National Health and Resilience in Veterans Study, which surveyed a nationally representative sample of 1257 US combat veterans including World War II or Korean War veterans (n = 61, weighted 4.9%), Vietnam War veterans (n = 767, weighted 44.5%), Gulf War veterans (n = 168, weighted 14.5%), and Iraq/Afghanistan War veterans (n = 261, weighted 36.2%). Sociodemographic, military, and mental health factors were examined. Gulf and Iraq/Afghanistan War era veterans were comprised of younger veterans and included more women and racial/ethnic minorities relative to previous era veterans. Overall, Gulf and Iraq/Afghanistan War veterans endorsed greater trauma burden, and were more likely to screen positive for lifetime and current major depressive disorder and posttraumatic stress disorder (PTSD), as well as current suicidal ideation. Among all war era groups, Iraq/Afghanistan war veterans reported the greatest lifetime trauma and combat exposure severity, and were most likely to screen positive for lifetime PTSD (weighted 29.3%), current alcohol use disorder (weighted 17.2%), and current drug use disorder (weighted 12.4%). Specifically, more than 1-in-4 Iraq/Afghanistan War veterans (weighted 26.3%) reported current suicidal thoughts. Collectively, these findings provide war-era specific characterization of the psychiatric status of US combat veterans, which may help inform era-specific assessment, monitoring, and treatment of psychiatric disorders in the combat veteran population.

Veteran-derived cerebral organoids display multifaceted pathological defects in studies on Gulf War Illness

Philip L. Yates1‡ , Kendra Case1‡ , Xiaohuan Sun1 , Kimberly Sullivan2 , Peter W. Baas1† and Liang Qiang1*

Affiliations

1Department of Neurobiology and Anatomy, Drexel University College of Medicine, Philadelphia, PA, United States, 2Department of Environmental Health, Boston University School of Public Health, Boston, MA, United State

Abstract

Approximately 30% of the veterans who fought in the 1991 Gulf War (GW) suffer from a disease called Gulf War Illness (GWI), which encompasses a constellation of symptoms including cognitive deficits. A coalescence of evidence indicates that GWI was caused by low-level exposure to organophosphate pesticides and nerve agents in combination with physical stressors of the battlefield. Until recently, progress on mechanisms and therapy had been limited to rodent-based models. Using peripheral blood mononuclear cells from veterans with or without GWI, we recently developed a bank of human induced pluripotent stem cells that can be differentiated into a variety of cellular fates. With these cells, we have now generated cerebral organoids, which are three-dimensional multicellular structures that resemble the human brain. We established organoid cultures from two GW veterans, one with GWI and one without. Immunohistochemical analyses indicate that these organoids, when treated with a GW toxicant regimen consisting of the organophosphate diisopropyl fluorophosphate (a sarin analog) and cortisol (to mimic battlefield stress), display multiple indicators consistent with cognitive deficits, including increased astrocytic reactivity, enhanced phosphorylation of tau proteins, decreased microtubule stability, and impaired neurogenesis. Interestingly, some of these phenotypes were more pronounced in the organoids derived from the veteran with GWI, potentially reflecting a stronger response to the toxicants in some individuals compared to others. These results suggest that veteran-derived human cerebral organoids not only can be used as an innovative human model to uncover the cellular responses to GW toxicants but can also serve as a platform for developing personalized medicine approaches for the veterans.

Experiential Avoidance, Pain, and Suicide Risk in a National Sample of Gulf War Veterans

Jeremy L Grove, Jonathan R Young, Zhengxi Chen, Shannon M Blakey, Jean C Beckham, Patrick S Calhoun, Eric A Dedert, David B Goldston, Mary J Pugh, Nathan A Kimbrel

Abstract

Objective: Pain confers risk for suicidal thoughts and behaviors. Experiential avoidance (EA), which is relevant to both pain and suicide risk, has not been studied as a potential mechanism for this relationship. The present study tested the hypothesis that pain indirectly impacts suicide risk through EA in a national sample of Gulf War veterans.

Methods: Participants included a stratified random sample of United States veterans (N = 1,012, 78% male) who had served in the Gulf War region between August 1990 and July 1991. Validated scales were used to quantify levels of pain, EA, and suicide risk.

Results: Regression analyses indicated independent associations between pain, EA, and suicide risk; moreover, the association between pain and suicide risk was no longer significant once EA was included in model. Bootstrapping analyses confirmed that EA partially accounted for the cross-sectional association between pain and suicide risk, independent of common co-occurring problems, such as depression, PTSD, and alcohol use disorder symptoms.

Conclusions: EA could be a key modifiable risk factor to target in people experiencing pain.

Association of Gulf War Illness with Characteristics in Deployed vs. Non-Deployed Gulf War Era Veterans in the Cooperative Studies Program 2006/Million Veteran Program 029 Cohort: A Cross-Sectional Analysis

Linh M. Duong 1,2,*, Alice B. S. Nono Djotsa 3,4, Jacqueline Vahey 5,6, Lea Steele 7, Rachel Quaden 8,Kelly M. Harrington 8,9, Sarah T. Ahmed 3,4, Renato Polimanti 1,2, Elani Streja 1, John Michael Gaziano 8,10, John Concato 11,12, Hongyu Zhao 1,13, Krishnan Radhakrishnan 14, Elizabeth R. Hauser 5,15, Drew A. Helmer 3,4, Mihaela Aslan 1,11 and Elizabeth J. Gifford 5,16

Affiliations

1 Cooperative Studies Program Clinical Epidemiology Research Center (CSP-CERC), VA Connecticut Healthcare System 151B, West Haven, CT 06516, USA

2 Department of Psychiatry, Yale School of Medicine, Yale University, New Haven, CT 06511, USA

3 Center for Innovations in Quality, Effectiveness, and Safety (IQuESt), Michael E. DeBakey VA Medical Center, Houston, TX 77030, USA

4 Department of Medicine, Baylor College of Medicine, Houston, TX 77030, USA

5 VA Cooperative Studies Program Epidemiology Center—Durham, Department of Veterans Affairs, Durham, NC 27705, USA

6 Computational Biology and Bioinformatics Program, Duke University, Durham, NC 27705, USA

7 Veterans Health Research Program, Yudofsky Division of Neuropsychiatry, Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX 77030, USA

8 Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Healthcare System, Boston, MA 02130, USA

9 Department of Psychiatry, Boston University School of Medicine, Boston, MA 02118, USA

10 Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA

11 Yale School of Medicine, Yale University, New Haven, CT 06511, USA

12 Food and Drug Administration, Silver Spring, MD 20993, USA

13 Department of Biostatistics, Yale School of Public Health, New Haven, CT 06520, USA

14 National Mental Health and Substance Use Policy Laboratory, Substance Abuse and Mental Health Services Administration, Rockville, MD 20857, USA

15 Department of Biostatistics and Bioinformatics, Duke Molecular Physiology Institute, Duke University, Durham, NC 27705, USA

16 Center for Child and Family Policy, Duke Margolis Center for Health Policy, Duke University Sanford School of Public Policy, Durham, NC 27708, USA

* Correspondence: linh.duong@va.gov

Abstract: Gulf War Illness (GWI), a chronic multisymptom illness with a complex and uncertain etiology and pathophysiology, is highly prevalent among veterans deployed to the 1990–1991 GW. We examined how GWI phenotypes varied by demographic and military characteristics among GW-era veterans. Data were from the VA's Cooperative Studies Program 2006/Million Veteran Program (MVP) 029 cohort, Genomics of GWI. From June 2018 to March 2019, 109,976 MVP enrollees (out of a total of over 676,000) were contacted to participate in the 1990–1991 GW-era Survey. Of 109,976 eligible participants, 45,169 (41.1%) responded to the 2018–2019 survey, 35,902 respondents met study inclusion criteria, 13,107 deployed to the GW theater. GWI phenotypes were derived from Kansas (KS) and Centers for Disease Control and Prevention (CDC) GWI definitions: (a) KS Symptoms (KS Sym+), (b) KS GWI (met symptom criteria and without exclusionary health conditions) [KS GWI: Sym+/Dx−], (c) CDC GWI and (d) CDC GWI Severe. The

prevalence of each phenotype was 67.1% KS Sym+, 21.5% KS Sym+/Dx−, 81.1% CDC GWI, and 18.6% CDC GWI severe. These findings affirm the persistent presence of GWI among GW veterans providing a foundation for further exploration of biological and environmental underpinnings of this condition.