Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI) — PubMed Research Citations for January, February, March 2023

Prepared by Staff of the RACGWVI.

RACGWVI: Gulf War Illness — PubMed Citations for Jan, Feb, March 2023

The following is a list of published research projects that focus on Gulf War Illness (GWI) for the months of January, February and March 2023.

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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.

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

Autonomic dysfunction and gastroparesis in Gulf War veterans

J Investig Med. 2023 Jan;71(1):7-10. doi: 10.1136/jim-2021-002291.

Zachary Thomas Verne 1, Jeremy Z Fields 2, Benjamin Buyi Zhang 2, QiQi Zhou 2 3

Affiliations

1Biology, Texas A&M University System, College Station, Texas, USA.

2Department of Medicine, The University of Tennessee Health Science Center College of Medicine, Memphis, Tennessee, USA.

3Memphis VA Medical Center, Memphis, Tennessee, USA.

Abstract

Over 25% of veterans with Gulf War illness developed chronic gastrointestinal (GI) symptoms of unknown etiology after they returned from deployment to the Persian Gulf. To determine the prevalence of delayed gastric emptying and its association with autonomic dysfunction in returning Gulf War (GW) veterans with chronic GI symptoms, we prospectively studied 35 veterans who were deployed to the Persian Gulf and developed chronic nausea, vomiting, postprandial abdominal pain, and bloating during their tour of duty and 15 asymptomatic controls. All veterans underwent 5 standardized cardiovascular tests to assess autonomic function. Each test was scored from 0 (normal) to 5 (severe disease) and the mean was calculated. A composite score >1.5 was considered abnormal, with 5 representing severe autonomic dysfunction. A standardized gastric emptying test with a solid phase was performed in each veteran. A gastric retention of >50% at 100 minutes was considered abnormal. The composite autonomic score was 3.7 in veterans with GI symptoms (vs 1.3 in controls) ($p<0.01$). The mean solid phase retention at 100 minutes was 72.6% in the symptomatic veterans versus 24.6% in controls ($p<0.001$). Our results suggest that autonomic dysfunction and delayed gastric emptying are common in returning GW veterans with GI symptoms. Autonomic dysfunction was positively correlated with the severity of delayed gastric emptying and may account for the GI symptoms of nausea, vomiting, postprandial abdominal pain, and bloating. These new findings are important for an increasing number of veterans who are serving in the Persian Gulf and are at a high risk of developing GI disorders while deployed.

Unexplained dyspnea linked to mitochondrial myopathy following military deployment to Southwest Asia and Afghanistan

Physiol Rep. 2023 Jan;11(2):e15520. doi: 10.14814/phy2.15520.

Claudia Daniela Onofrei 1, Eva Brigitte Gottschall 2 3 4, Lauren Zell-Baran 2 4, Cecile Stephanie Rose 2 3 4, Richard Kraus 2, Kathy Pang 2, Silpa Dhoma Krefft 2 3 4 5

Affiliations

1Division of Pulmonary and Critical Care Medicine, Department of Medicine, National Jewish Health, Denver, Colorado, USA.

2Division of Environmental and Occupational Health Sciences, Department of Medicine, National Jewish Health, Denver, Colorado, USA.

3Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Colorado Anschutz Medical Campus, Colorado, Aurora, USA.

4Department of Environmental and Occupational Health, Colorado School of Public Health, Colorado, Aurora, USA.

5Division of Pulmonary and Critical Care Medicine, Department of Medicine, Veterans Administration Eastern Colorado Health Care System, Colorado, Aurora, USA.

Abstract

We identified a case of probable mitochondrial myopathy (MM) in a soldier with dyspnea and reduced exercise tolerance through cardiopulmonary exercise testing (CPET) following Southwest Asia (SWA) deployment. Muscle biopsy showed myopathic features. We compared demographic, occupational exposure, and clinical characteristics in symptomatic military deployers with and without probable MM diagnosed by CPET criteria. We evaluated 235 symptomatic military personnel who deployed to SWA and/or Afghanistan between 2010 and 2021. Of these, 168 underwent cycle ergometer maximal CPET with an indwelling arterial line. We defined probable MM based on five CPET criteria: arterial peak exercise lactate >12 mEq/L, anaerobic threshold (AT) ≤50%, maximum oxygen consumption (VO2max) <95% predicted, oxygen (O2) pulse percent predicted (pp) at least 10% lower than heart rate pp, and elevated ventilatory equivalent for O2 at end exercise (VE/VO2 ≥ 40). We characterized demographics, smoking status/pack-years, spirometry, and deployment exposures, and used descriptive statistics to compare findings in those with and without probable MM. We found 9/168 (5.4%) deployers with probable MM. Compared to symptomatic deployers without probable MM, they were younger ($p = 0.0025$) and had lower mean BMI ($p = 0.02$). They had a higher mean forced expiratory volume (FEV1)pp ($p = 0.02$) and mean arterial oxygen partial pressure (PaO2) at maximum exercise ($p = 0.0003$). We found no significant differences in smoking status, deployment frequency/duration, or inhalational exposures. Our findings suggest that mitochondrial myopathy may be a cause of dyspnea and reduced exercise tolerance in a subset of previously deployed military personnel. CPET with arterial line may assist with MM diagnosis and management.

The low glutamate diet reduces blood pressure in veterans with Gulf War Illness: A CONSORT randomized clinical trial

Medicine (Baltimore). 2023 Jan 27;102(4):e32726. doi: 10.1097/MD.0000000000032726.

Prairie R Fiebel 1, Shalini S Ramachandra 2 3, Kathleen F Holton 1 2 4

Affiliations

1Department of Neuroscience, American University, WA DC.

2Department of Health Studies, American University, WA DC.

3Department of Mathematics and Statistics, American University, WA DC.

4Center for Neuroscience and Behavior, American University, WA DC.

Abstract

Background: Gulf War Illness is a multi-symptom condition affecting veterans of the 1990 to 1991 Gulf War, which often presents with comorbid hypertension. The purpose of this study was to analyze the effects of the low glutamate diet, as well as an acute challenge of monosodium glutamate (MSG)/placebo, on resting heart rate, blood oxygenation level, and blood pressure (BP) in this population.

Methods: These data were measured at 4 time points: baseline, after 1 month on the low glutamate diet, and during each challenge week, where subjects were randomized into a double-blind, placebo-controlled, crossover challenge with MSG/placebo over 3 days each week. Pre-post diet changes were analyzed using paired t tests, change in the percentage of veterans meeting the criteria for hypertension was compared using chi-square or Fisher exact tests, and crossover challenge results were analyzed using general linear modeling in SAS® 9.4.

Results: There was a significant reduction in systolic BP (sitting and recumbent; both $P < .001$) and diastolic BP (sitting; $P = .02$) after 1 month on the diet. The percentage meeting the criteria for hypertension was also significantly reduced ($P < .05$). Challenge with MSG/placebo did not demonstrate an acute effect of glutamate on blood pressure.

Conclusion: Overall, these findings suggest that the low glutamate diet may be an effective treatment for lowering blood pressure in veterans with Gulf War Illness. This dietary effect does not appear to be driven by reduced consumption of free glutamate, but rather, by an increase in consumption of non-processed foods.

Dysbiosis in gastrointestinal pathophysiology: Role of the gut microbiome in Gulf War Illness

J Cell Mol Med. 2023 Jan 30. doi: 10.1111/jcmm.17631. Online ahead of print.

Elise Slevin 1 2, Sachiko Koyama 1 2, Kelly Harrison 3, Ying Wan 4, James E Klaunig 5, Chaodong Wu 6, Ashok K Shetty 7, Fanyin Meng 1 2

Affiliations

1Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA.

2Richard L. Roudebush VA Medical Center, Indianapolis, Indiana, USA.

3Department of Transplant Surgery, Baylor Scott & White Memorial Hospital, Temple, Texas, USA.

4Department of Pathophysiology, School of Basic Medical Science, Southwest Medical University, Luzhou, China.

5Laboratory of Investigative Toxicology and Pathology, Department of Environmental and Occupational Health, Indiana School of Public Health, Indiana University, Bloomington, Indiana, USA.

6Department of Nutrition, Texas A&M University, College Station, Texas, USA.

7Department of Molecular and Cellular Medicine, Institute for Regenerative Medicine, Texas A&M College of Medicine, College Station, Texas, USA.

Abstract

Gulf War Illness (GWI) has been reported in 25%-35% of veterans returned from the Gulf war. Symptoms of GWI are varied and include both neurological and gastrointestinal symptoms as well as chronic fatigue. Development of GWI has been associated with chemical exposure particularly with exposure to pyridostigmine bromide (PB) and permethrin. Recent studies have found that the pathology of GWI is connected to changes in the gut microbiota, that is the gut dysbiosis. In studies using animal models, the exposure to PB and permethrin resulted in similar changes in the gut microbiome as these found in GW veterans with GWI. Studies using animal models have also shown that phytochemicals like curcumin are beneficial in reducing the symptoms and that the extracellular vesicles (EV) released from gut bacteria and from the intestinal epithelium can both promote diseases and suppress diseases through the intercellular communication mechanisms. The intestinal epithelium cells produce EVs and these EVs of intestinal epithelium origin are found to suppress inflammatory bowel disease severity, suggesting the benefits of utilizing EV in treatments. On the contrary, EV from the plasma of septic mice enhanced the level of proinflammatory cytokines in vitro and neutrophils and macrophages in vivo, suggesting differences in the EV depending on the types of cells they were originated and/or influences of environmental changes. These studies suggest that targeting the EV that specifically have positive influences may become a new therapeutic strategy in the treatment of veterans with GWI.

Impact of Tumor Necrosis Factor Receptor 1 (TNFR1) Polymorphism on Dry Eye Disease

Biomolecules. 2023 Jan 31;13(2):262. doi: 10.3390/biom13020262.

Kelly Acuna 1 2, Anjalee Choudhary 1 2, Elyana Locatelli 1 2, Daniel A Rodriguez 1 2, Eden R Martin 3 4, Roy C Levitt 2 3 4 5, Anat Galor 1 2

Affiliations

1Department of Ophthalmology, Miami VA Medical Center, Miami, FL 33136, USA.

2Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami, Miami, FL 33136, USA.

3John T. MacDonald Foundation Department of Human Genetics, University of Miami Miller School of Medicine, Miami, FL 33136, USA.

4John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, FL 33136, USA.

5Department of Anesthesiology, Perioperative Medicine and Pain Management, University of Miami Miller School of Medicine, Miami, FL 33136, USA.

Abstract

The goal of the study was to examine whether a genetic polymorphism in tumor necrosis factor receptor 1 (TNFR1) gene impacted the dry eye disease (DED) phenotype and response to anti-inflammatory therapy. The prospective study included 328 individuals with various dry eye (DE) symptoms and signs recruited from the Miami Veterans Hospital eye clinic between October 2013 and October 2017. The population underwent genetic profiling for a polymorphism within the TNFR1 gene (rs1800693 [TT, TC, CC]). The study examined the genotype distribution and relationships between the genotype, phenotype, and response to anti-inflammatory therapy. The mean age of the population was 61.7 ± 9.8 years. Here, 92% self-identified as male, 44% as White, and 21% as Hispanic; 13% (n = 42) of individuals had a CC genotype. DED symptoms and signs were similar across the three genotype groups. Thirty individuals (four with CC) were subsequently treated with an anti-inflammatory agent. There was a non-significant trend for individuals with CC genotype to have a partial or complete symptomatic response to treatment compared with the other two groups (100% for CC vs. 40% for TT and 36.4% for TC, p = 0.22). In conclusion, the presence of homozygosity of minor allele C (CC genotype) in a single nucleotide polymorphism (SNP) within TNFR1 was noted in a minority of individuals with various aspects of DED, but did not impact the DED phenotype. Our findings suggest that the current phenotyping strategies for DED are insufficient to identify underlying disease contributors, including potential genetic contributors.

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

Contemp Clin Trials. 2023 Feb;125:107045. doi: 10.1016/j.cct.2022.107045. Epub 2022 Dec 6.

Barbara L Niles 1, Stephanie Grossman 2, Maria McQuade 2, Daniel 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, 2700 N. Highway A1A, 2-101, Indialantic, FL 32903, United States of America.

4Yang Martial Arts Association Boston, 756 South Street, Roslindale, MA, 02131, United States of America.

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.

Prevalence of amyotrophic lateral sclerosis in the United States using established and novel methodologies, 2017

Amyotroph Lateral Scler Frontotemporal Degener. 2023 Feb;24(1-2):108-116. doi: 10.1080/21678421.2022.2059380. Epub 2022 Apr 15.

Paul Mehta 1, Jaime Raymond 1, Reshma Punjani 1, Moon Han 1, Theodore Larson 1, Wendy Kaye 2, Lorene M Nelson 3, Barbara Topol 3, Oleg Muravov 1, Corina Genson 1, D Kevin Horton 1

Affiliations

1Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry, National ALS Registry (CDC/ATSDR), Atlanta, GA, USA.

2McKing Consulting Corporation, Atlanta, GA, USA and.

3Department of Epidemiology and Population Health, Stanford University School of Medicine, Stanford, CA, USA.

Abstract

Objective: To estimate the prevalence of amyotrophic lateral sclerosis (ALS) in the United States for 2017 using data from the National ALS Registry (Registry) as well as capture-recapture methodology to account for under-ascertainment. Established in 2010, the Registry collects and examines data on ALS patients in the US to better describe the epidemiology of ALS (i.e. risk factor exposures, demographics).

Methods: The Registry compiled data from national administrative databases (from the Centers for Medicare and Medicaid Services, the Veterans Health Administration, and the Veterans Benefits Administration) and a voluntary enrollment data through a web portal (www.cdc.gov/als). To estimate the number of missing cases, capture-recapture methodology was utilized.

Results: The Registry conservatively identified 17,800 adult persons (lower-bound estimate) who met the Registry definition of ALS for an age-adjusted prevalence of 5.5 per 100,000 US population. Using capture-recapture methodology, we obtained a "mean case count" of 24,821 ALS cases (prevalence of 7.7 per 100,000 U.S. population) and estimated the upper-bound estimate to be 31,843 cases (prevalence of 9.9 per 100,000 U.S. population). The pattern of patient characteristics (e.g. age, sex, and race/ethnicity) remained unchanged from previous Registry reports. Overall, ALS was most common among whites, males, and persons aged 60-69 years. The age groups with the lowest number of cases were persons aged 18-39 years. Males had a higher prevalence than females overall and across all data sources.

Conclusions: Existing Registry methodology, along with capture-recapture methodology, are being used to better describe the epidemiology and demographics of ALS in the US.

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

J Psychiatr Res. 2023 Feb;158:36-40. doi: 10.1016/j.jpsychires.2022.12.019. Epub 2022 Dec 20.

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.

Development and cross-validation of a veterans mental health risk factor screen

PLoS One. 2023 Feb 8;18(2):e0272599. doi: 10.1371/journal.pone.0272599. eCollection 2023.

Eve B Carlson 1 2, Patrick A Palmieri 3, Dawne Vogt 4 5, Kathryn Macia 1 2, Steven E Lindley 2 6

Affiliations

1Dissemination and Training Division, National Center for Posttraumatic Stress Disorder, VA Palo Alto Health Care System, Menlo Park, California, United States of America.

2Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California, United States of America.

3Traumatic Stress Center, Department of Psychiatry, Summa Health System, Akron, Ohio, United States of America.

4Women's Health Sciences Division, National Center for Posttraumatic Stress Disorder, VA Boston Healthcare System, Boston, Massachusetts, United States of America.

5Department of Psychiatry, Boston University School of Medicine, Boston, Massachusetts, United States of America.

6VA Palo Alto Health Care System, Palo Alto, California, United States of America.

Abstract

Background: VA primary care patients are routinely screened for current symptoms of PTSD, depression, and alcohol disorders, but many who screen positive do not engage in care. In addition to stigma about mental disorders and a high value on autonomy, some veterans may not seek care because of uncertainty about whether they need treatment to recover. A screen for mental health risk could provide an alternative motivation for patients to engage in care.

Method: Data from samples of veterans and traumatic injury survivors were analyzed to identify mental health risk factors that are characteristics of individuals or stressors or of post-trauma, post-deployment, or post-military service resources, experiences, or responses. Twelve risk factors were strongly related to PTSD ($r > .50$): current PTSD, depression, dissociation, negative thinking, and emotional lability symptoms, life stress, relationship stress, social constraints, and deployment experiences of a difficult environment, concerns about life and family, perceived threat, and moral injury. Items assessing each of these risk factors were selected and their validity to prospectively predict PTSD and/or depression 6 months later was assessed in a new sample of 232 VA primary care patients.

Results: Twelve items assessing dissociation, emotional lability, life stress, and moral injury correctly classified 86% of those who later had elevated PTSD and/or depression symptoms (sensitivity) and 75% of those whose later symptoms were not elevated (specificity). Performance was also very good for 110 veterans who identified as members of ethnic/racial minorities.

Conclusions: Mental health status was prospectively predicted in VA primary care patients with high accuracy using a screen that is brief, easy to administer, score, and interpret, and fits well into VA's integrated primary care. When care is readily accessible, appealing to veterans, and not perceived as stigmatizing, information about mental health risk may result in higher rates of engagement than information about current mental disorder status.

Exploring the acceptability of behavioral interventions for veterans with persistent "medically unexplained" physical symptoms

J Psychosom Res. 2023 Feb 14;167:111193. doi: 10.1016/j.jpsychores.2023.111193. Online ahead of print.

Darren M Winograd 1, Justeen K Hyde 2, Katharine Bloeser 3, Susan L Santos 4, Nicole Anastasides 4, Beth Ann Petrakis 5, Wilfred R Pigeon 6, David R Litke 7, Drew A Helmer 8, Lisa M McAndrew 9

Affiliations

1Veterans Affairs New Jersey Healthcare System, 385 Tremont Ave. East Orange, NJ 07018, USA; University at Albany, State University of New York, Albany, NY, USA.

2Center for Healthcare Organization and Implementation Research (CHOIR), VA Bedford Healthcare System, Bedford, MA, USA; Department of Medicine, Section of General Internal Medicine, Boston University School of Medicine, Boston, MA, USA.

3Veterans Affairs New Jersey Healthcare System, 385 Tremont Ave. East Orange, NJ 07018, USA; Silberman School of Social Work at Hunter College, The City University of New York, New York, NY, USA.

4Veterans Affairs New Jersey Healthcare System, 385 Tremont Ave. East Orange, NJ 07018, USA.

5Center for Healthcare Organization and Implementation Research (CHOIR), VA Bedford Healthcare System, Bedford, MA, USA.

6VISN 2 Center of Excellence for Suicide Prevention, Veterans Affairs Finger Lakes Healthcare System, Canandaigua, NY, USA; Department of Psychiatry, University of Rochester Medical Center, Rochester, NY, USA.

7Veterans Affairs New Jersey Healthcare System, 385 Tremont Ave. East Orange, NJ 07018, USA; Department of Rehabilitation Medicine, New York University Grossman School of Medicine, New York, NY, USA.

8Center for Innovations in Quality, Effectiveness, and Safety (IQuESt), Michael E. DeBakey VA Medical Center, Houston, TX 77030, USA; Baylor College of Medicine, Houston, TX 77030, USA.

9Veterans Affairs New Jersey Healthcare System, 385 Tremont Ave. East Orange, NJ 07018, USA. Electronic address: lisa.mcandrew@va.gov.

Abstract

Objective: This study evaluated the factors that led to enrollment in, and satisfaction with, behavioral interventions for Veterans living with Gulf War Illness (GWI).

Methods: One-on-one interviews were conducted pre- and post-intervention with participants randomized to receive either telephone delivered problem-solving treatment (n = 51) or health education (N = 49). A total of 99 Veterans were interviewed pre-intervention and 60 post-intervention. Qualitative data were thematically coded and similarities in themes across the two interventions were examined.

Results: Before the study began, participants reported desiring to learn new information about their GWI, learn symptom-management strategies, and support improvements to care for other patients with GWI. After the intervention, Veterans felt positively about both interventions because they built strong therapeutic relationships with providers, their experiences were validated by providers, and they were provided GWI information and symptom-management strategies. Results also suggested that interventions do not have to be designed to meet all of the needs held by patients to be acceptable. A minority of participants described that they did not benefit from the interventions.

Conclusion: The results suggest that satisfaction with behavioral interventions for GWI is driven by a strong therapeutic relationship, validating patient's experiences with GWI, and the intervention meeting some of the patient's needs, particularly increasing knowledge of GWI and improving symptom management.

Understanding veteran barriers to specialty outpatient PTSD clinical care

J Anxiety Disord. 2023 Feb 14;95:102675. doi: 10.1016/j.janxdis.2023.102675. Online ahead of print.

David C Rozek 1, Victoria L Steigerwald 2, Shelby N Baker 2, Georgina Gross 3, Kelly P Maieritsch 4, Rani Hoff 5, Ilan Harpaz-Rotem 6, Noelle B Smith 5

Affiliations

1UCF RESTORES and Department of Psychology, University of Central Florida, USA. Electronic address: david.rozek@ucf.edu.

2UCF RESTORES and Department of Psychology, University of Central Florida, USA.

3VA Northeast Program Evaluation Center, USA; Yale University School of Medicine, USA; VA Connecticut Healthcare System, USA.

4VA National Center for PTSD, USA.

5VA Northeast Program Evaluation Center, USA; Yale University School of Medicine, USA.

6VA Northeast Program Evaluation Center, USA; Yale University School of Medicine, USA; VA National Center for PTSD, USA.

Abstract

Objective: Veterans seeking treatment for posttraumatic stress disorder (PTSD) commonly report general and veteran-specific barriers to treatment such as stigma and challenges with navigating the Veterans Health Affairs (VHA) system. This study aimed to characterize barriers endorsed by a national sample of veterans seeking care in VHA PTSD specialty outpatient clinics, as well as to examine the impact of demographics on endorsed barriers.

Methods: This study included 17,069 veterans referred to PTSD specialty outpatient clinics in the VHA during Fiscal Year 2019. Barriers to care, demographics, clinical concerns, and PTSD symptom severity (PCL-5) were assessed at intake.

Results: Veterans (mean age=47.6 years, 83.3% male) endorsed an average of 2.39 barriers. The most commonly endorsed barriers included difficulty interacting with others (37.9%), difficulty being in public (33.8%), work (30.3%), concern for finances (20%), and difficulty getting out of bed (19.5%). A significant minority of veterans (22%) endorsed no barriers. Male sex (23.1%) and White race (23.6%) were associated with a greater likelihood of reporting no barriers.

Conclusions: These findings indicate the need for a comprehensive approach to addressing multi-faceted barriers for veterans seeking treatment in PTSD specialty clinics. Findings also highlight the potential importance of tailoring strategies to reduce barriers based on demographic and clinical characteristics such as race, sex, and degree of avoidance. Future research should seek to longitudinally examine the impact of barriers on treatment engagement.

Pathophysiological basis and promise of experimental therapies for Gulf War Illness, a chronic neuropsychiatric syndrome in veterans

Psychopharmacology (Berl). 2023 Feb 15. doi: 10.1007/s00213-023-06319-5. Online ahead of print.

Maheedhar Kodali 1, Tanvi Jankay 2, Ashok K Shetty 1 3, Doodipala Samba Reddy 4 5

Affiliations

1Institute for Regenerative Medicine, Department of Molecular and Cellular Medicine, Texas A&M University School of Medicine, College Station, TX, USA.

2Department of Neuroscience and Experimental Therapeutics, Texas A&M University School of Medicine, Bryan, TX, USA.

3Texas A&M Health Institute of Pharmacology and Neurotherapeutics, Texas A&M University Health Science Center, 8447 Riverside Pkwy, Bryan, TX, 77807, USA.

4Department of Neuroscience and Experimental Therapeutics, Texas A&M University School of Medicine, Bryan, TX, USA. sambareddy@tamu.edu.

5Texas A&M Health Institute of Pharmacology and Neurotherapeutics, Texas A&M University Health Science Center, 8447 Riverside Pkwy, Bryan, TX, 77807, USA. sambareddy@tamu.edu.

Abstract

This article describes the pathophysiology and potential treatments for Gulf War Illness (GWI), which is a chronic neuropsychiatric illness linked to a combination of chemical exposures experienced by service personnel during the first Gulf War in 1991. However, there is currently no effective treatment for veterans with GWI. The article focuses on the current status and efficacy of existing therapeutic interventions in preclinical models of GWI, as well as potential perspectives of promising therapies. GWI stems from changes in brain and peripheral systems in veterans, leading to neurocognitive deficits, as well as physiological and psychological effects resulting from multifaceted changes such as neuroinflammation, oxidative stress, and neuronal damage. Aging not only renders veterans more susceptible to GWI symptoms, but also attenuates their immune capabilities and response to therapies. A variety of experimental models are being used to investigate the pathophysiology and develop therapies that have the ability to alleviate devastating symptoms. Over two dozen therapeutic interventions targeting neuroinflammation, mitochondrial dysfunction, neuronal injury, and neurogenesis are being tested, including agents such as curcumin, curcumin nanoparticles, monosodium luminol, melatonin, resveratrol, fluoxetine, rolipram, oleoylethanolamide, ketamine, levetiracetam, nicotinamide riboside, minocycline, pyridazine derivatives, and neurosteroids. Preclinical outcomes show that some agents have promise, including curcumin, resveratrol, and ketamine, which are being tested in clinical trials in GWI veterans. Neuroprotectants and other compounds such as monosodium luminol, melatonin, levetiracetam, oleoylethanolamide, and nicotinamide riboside appear promising for future clinical trials. Neurosteroids have been shown to have neuroprotective and disease-modifying properties, which makes them a promising medicine for GWI. Therefore, accelerated clinical studies are urgently needed to evaluate and launch an effective therapy for veterans displaying GWI.

Dynamic Interpersonal Therapy for U.S. Veterans in a Primary Care Setting

Am J Psychother. 2023 Feb 16;appipsychotherapy20220007. doi: 10.1176/appi.psychotherapy.20220007. Online ahead of print.

Cassondra L Feldman 1, Christopher D Schadt 1, Binhuan Wang 1, Aliza J Polkes 1, Bella Ratner 1, Cory K Chen 1

Affiliation

1College of Psychology, Nova Southeastern University, Fort Lauderdale, Florida (Feldman); Santa Monica Therapy, Santa Monica, California (Schadt); Division of Biostatistics, School of Medicine, New York University, New York City (Wang); U.S. Department of Veterans Affairs (VA) New York Harbor Healthcare System, New York City (Polkes, Ratner, Chen); Department of Clinical Psychology, Long Island University, New York City (Chen).

Abstract

Objective: Brief dynamic interpersonal therapy (DIT) is an evidence-based psychodynamic intervention for depression offered by the U.K. National Health Service and previously studied in the context of a U.S. Department of Veterans Affairs medical center. This study assessed the clinical value of DIT in primary care for veterans with general medical conditions.

Methods: The authors examined outcome data of veterans (N=30; all but one had ≥1 comorbid general medical conditions) referred to DIT from primary care.

Results: Veterans who began treatment with clinically elevated depression or anxiety experienced a 42% reduction in symptom severity, as measured by the nine-item Patient Health Questionnaire or by the seven-item Generalized Anxiety Disorder questionnaire, respectively, representing large effect sizes.

Conclusions: Significant decreases in depression and anxiety symptoms suggest the utility of DIT for veterans with comorbid general medical conditions. DIT's dynamically informed framework may improve patients' help seeking, which is relevant for patients experiencing comorbid medical conditions.

Acute Exposure to Pyridostigmine Bromide Disrupts Cholinergic Myenteric Neuroimmune Function in Mice

Adv Biol (Weinh). 2023 Feb 19;e2200254. doi: 10.1002/adbi.202200254. Online ahead of print.

Claudia A Collier 1, Steven Foncerrada 1, Abigail J Clevenger 1, Ashok Shetty 2, Shreya A Raghavan 1

Affiliations

1Department of Biomedical Engineering, College of Engineering, Texas A&M University, 3120 TAMU, College Station, TX, 77843, USA.

2Department of Cell Biology and Genetics, School of Medicine, Texas A&M University, 8447 Riverside Pkwy, Bryan, College Station, TX, 77807, USA.

Abstract

Gulf War Illness (GWI) results from chemical exposure during the Gulf War, with notable impacts on gastrointestinal motility. Due to the limited demographic impacted by this ailment, an in-depth investigation of the GWI has yielded little regarding the underlying pathophysiological mechanisms. Here, the hypothesis that exposure to pyridostigmine bromide (PB) results in severe enteric neuro-inflammation, that cascades to disruptions in colonic motility, is tested. The analyses are performed on male C57BL/6 mice that are treated with physiologically similar doses of PB given to GW veterans. When colonic motility is assessed, GWI colons have significantly reduced forces in response to acetylcholine or electrical field stimulation. GWI is also accompanied by high levels of pro-inflammatory cytokines and chemokines, associated with increased numbers of CD40+ pro-inflammatory macrophages within the myenteric plexus. Enteric neurons responsible for mediating colonic motility reside within the myenteric plexus, and PB exposure reduced their numbers. Significant smooth muscle hypertrophy is also observed due to increased inflammation. Together, the results show that PB exposure caused functional and anatomical dysfunction, promoting impaired motility within the colon. Achieving a greater understanding of the mechanisms of GWI will allow more refinement in therapeutic options that improve veterans' quality of life.

Microbiome Dysbiosis Shows Strong Association of Gut-Derived Altered Metabolomic Profile in Gulf War Chronic Multisymptom Illness Symptom Persistence Following Western Diet Feeding and Development of Obesity

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Dipro Bose 1, Vitalli Stebliankin 2, Trevor Cickovski 2, Punnag Saha 1, Ayushi Trivedi 1, Subhajit Roy 1, Madhura More 1, Ashok Tuteja 3, Kalai Mathee 4 5, Giri Narasimhan 2 5, Saurabh Chatterjee 1 6 7

Affiliations

1Environmental Health and Disease Laboratory, Department of Environmental and Occupational Health, Program in Public Health, Susan and Henry Samueli College of Health Sciences, University of California, Irvine, CA 92697, USA.

2Knight Foundation School of Computing and Information Sciences, College of Engineering and Computing, Florida International University, Miami, FL 33199, USA.

3Division of Internal Medicine, University of Utah School of Medicine, Salt Lake City VAMC, Salt Lake City, UT 84132, USA.

4Department of Human and Molecular Genetics, Herbert Wertheim College of Medicine, Florida International University, Miami, FL 33199, USA.

5Biomolecular Sciences Institute, Florida International University, Miami, FL 33199, USA.

6Department of Medicine, Infectious Disease, UCI School of Medicine, Irvine, CA 92697, USA.

7VA Research and Development, VA Long Beach Health Care System, Long Beach, CA 90822, USA.

Abstract

The pathophysiology of Gulf War Illness (GWI) remains elusive even after three decades. The persistence of multiple complex symptoms along with metabolic disorders such as obesity worsens the health of present Gulf War (GW) Veterans often by the interactions of the host gut microbiome and inflammatory mediators. In this study, we hypothesized that the administration of a Western diet might alter the host metabolomic profile, which is likely associated with the altered bacterial species. Using a five-month symptom persistence GWI model in mice and whole-genome sequencing, we characterized the species-level dysbiosis and global metabolomics, along with heterogenous co-occurrence network analysis, to study the bacteriome-metabolomic association. Microbial analysis at the species level showed a significant alteration of beneficial bacterial species. The beta diversity of the global metabolomic profile showed distinct clustering due to the Western diet, along with the alteration of metabolites associated with lipid, amino acid, nucleotide, vitamin, and xenobiotic metabolism pathways. Network analysis showed novel associations of gut bacterial species with metabolites and biochemical pathways that could be used as biomarkers or therapeutic targets to ameliorate symptom persistence in GW Veterans.

Experimental Models of Gulf War Illness, a Chronic Neuropsychiatric Disorder in Veterans

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Doodipala Samba Reddy 1 2 3 4 5, Xin Wu 1 2, Tanveer Singh 1 2, Michael Neff 1 2

Affiliations

1Department of Neuroscience and Experimental Therapeutics, School of Medicine, Texas A&M University Health Science Center, Bryan, Texas.

2Institute of Pharmacology and Neurotherapeutics, School of Medicine, Texas A&M University Health Science Center, Bryan, Texas.

3School of Engineering Medicine (EnMed), Texas A&M University, Houston, Texas.

4Department of Biomedical Engineering, College of Engineering, Texas A&M University, College Station, Texas.

5Department of Veterinary Integrative Biosciences, College of Veterinary Medicine & Biomedical Sciences, Texas A&M University, College Station, Texas.

Abstract

Gulf War illness (GWI) is a chronic multifaceted condition with debilitating pain and fatigue, as well as sleep, behavioral, and cognitive impairments in war veterans. Currently, there is no effective treatment or cure for GWI; therefore, there is a critical need to develop experimental models to help better understand its mechanisms and interventions related to GWI-associated neuropsychiatric disorders. Chemical neurotoxicity appears to be one cause of GWI, and its symptoms manifest as disruptions in neuronal function. However, the mechanisms underlying such incapacitating neurologic and psychiatric symptoms are poorly understood. The etiology of GWI is complex, and many factors including chemical exposure, psychological trauma, and environmental stressors have been associated with its development. Attempts have been made to create GWI-like symptomatic models, including through chronic induction in mice and rats. Here, we present a brief protocol of GWI in rats and mice, which exhibit robust neuropsychiatric signs and neuropathologic changes reminiscent of GWI. This article provides a guide to working protocols, application of therapeutic drugs, outcomes, troubleshooting, and data analysis. Our broad profiling of GWI-like symptoms in rodents reveals features of progressive morphologic and long-lasting neuropsychiatric features. Together, the GWI model in rodents shows striking consistency in recapitulating major hallmark features of GWI in veterans. These models help identify mechanisms and interventions for GWI. © 2023 Wiley Periodicals LLC. Basic Protocol 1: Experimental induction of Gulf War illness in rats Support Protocol 1: Monitoring of Gulf War illness signs and neuroimaging analysis in rats Basic Protocol 2: Experimental induction of Gulf War illness in mice Support Protocol 2: Monitoring of Gulf War illness signs and neuropathology analysis in mice.

Ocular and inflammatory markers associated with Gulf War illness symptoms

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Karthik Kalahasty 1, Yonghoon Lee 1, Elyana Locatelli 1 2, Mak Djulbegovic 1, Kimberly Cabrera 2, Parastou Pakravan 1, Courtney Goodman 1, Andrew Jensen 2, Kristina Aenlle 3 4, Nancy Klimas 3 4, Raquel Goldhardt 2 5, Anat Galor 6 7

Affiliations

1University of Miami Miller School of Medicine, Miami, FL, USA.

2Ophthalmology, Miami Veterans Affairs Medical Center, 1201 NW 16th St, Miami, FL, 33125, USA.

3Nova Southeastern University, Ft Lauderdale, FL, USA.

4Research Services, Miami Veterans Affairs Medical Center, Miami, FL, USA.

5Bascom Palmer Eye Institute, University of Miami, Miami, FL, USA.

6Ophthalmology, Miami Veterans Affairs Medical Center, 1201 NW 16th St, Miami, FL, 33125, USA. agalor@med.miami.edu.

7Bascom Palmer Eye Institute, University of Miami, Miami, FL, USA. agalor@med.miami.edu.

Abstract

To examine the utility of ocular coherence tomography (OCT) metrics, in conjunction with systemic markers of inflammation, in identifying individuals with Gulf War Illness (GWI) symptoms. Prospective case-control study of 108 Gulf War Era veterans, split into 2 groups based on the presence of GWI symptoms, defined by the Kansas criteria. Information on demographics, deployment history, and co-morbidities were captured. 101 individuals underwent OCT imaging and 105 individuals provided a blood sample which was analyzed for inflammatory cytokines using an enzyme-linked immunosorbent assay-based chemiluminescent assay. The main outcome measure was predictors of GWI symptoms, examined with multivariable forward stepwise logistic regression analysis followed by receiver operating characteristic (ROC) analysis. The mean age of the population was 55 ± 4, 90.7% self-identified as male, 53.3% as White, and 54.3% as Hispanic. A multivariable model that considered demographics and co-morbidities found that a lower inferior temporal ganglion cell layer-inner plexiform layer (GCL–IPL) thickness, higher temporal nerve fiber layer (NFL) thickness, lower interleukin (IL)-1β levels, higher IL-1α levels, and lower tumor necrosis factor-receptor I levels correlated with GWI symptoms. ROC analysis demonstrated an area under the curve of 0.78 with the best cut-off value for the prediction model having a sensitivity of 83% and specificity of 58%. RNFL and GCL–IPL measures, namely increased temporal thickness and decreased inferior temporal thickness, respectively, in conjunction with a number of inflammatory cytokines, had a reasonable sensitivity for the diagnosis of GWI symptoms in our population.

Chemical exposures and suspected impact on Gulf War Veterans

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Rami Elhaj 1, Joseph M Reynolds 2

Affiliations

1Center for Cancer Biology, Immunology and Infection, Chicago Medical School, Rosalind Franklin University of Medicine and Science, North Chicago, IL, 60064, USA.

2Center for Cancer Biology, Immunology and Infection, Chicago Medical School, Rosalind Franklin University of Medicine and Science, North Chicago, IL, 60064, USA. joseph.reynolds@rosalindfranklin.edu.

Abstract

Gulf War Illness (GWI) encompass a spectrum of maladies specific to troops deployed during the Persian Gulf War (1990-1991). There are several hypothesized factors believed to contribute to GWI, including (but not limited to) exposures to chemical agents and a foreign environment (e.g., dust, pollens, insects, and microbes). Moreover, the inherent stress associated with deployment and combat has been associated with GWI. While the etiology of GWI remains uncertain, several studies have provided strong evidence that chemical exposures, especially neurotoxicants, may be underlying factors for the development of GWI. This mini style perspective article will focus on some of the major evidence linking chemical exposures to GWI development and persistence decades after exposure.

Exercise-induced changes in gene expression do not mediate post exertional malaise in Gulf War illness

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Alexander E Boruch 1 2, Jacob B Lindheimer 1 2 3, Jacob V Ninneman 1 2 3, Glenn R Wylie 4 5 6, Thomas Alexander 4, Jacquelyn C Klein-Adams 4, Aaron J Stegner 1 2, Nicholas P Gretzon 1 2, Bishoy Samy 4, Michael J Falvo 4 6, Dane B Cook 1 2

Affiliations

1William S. Middleton Memorial Veterans Hospital, Madison, WI, USA.

2Department of Kinesiology, University of Wisconsin-Madison, Madison, WI, USA.

3Department of Medicine, University of Wisconsin-Madison, Madison, WI, USA.

4War Related Illness and Injury Study Center, Department of Veterans Affairs New Jersey Health Care System, East Orange, NJ, USA.

5Kessler Foundation, West Orange, NJ, USA.

6New Jersey Medical School, Rutgers Biomedical and Health Sciences, Newark, NJ, USA.

Abstract

Background: Post-exertional malaise (PEM) is considered a characteristic feature of chronic multi-symptom illnesses (CMI) like Gulf War illness (GWI); however, its pathophysiology remains understudied. Previous investigations in other CMI populations (i.e., Myalgic Encephalomyelitis/Chronic Fatigue Syndrome) have reported associations between PEM and expression of genes coding for adrenergic, metabolic, and immune function.

Objectives: To investigate whether PEM is meditated by gene expression in Veterans with GWI.

Methods: Veterans with GWI (n = 37) and healthy control Gulf War Veterans (n = 25) provided blood samples before and after 30-min of cycling at 70% of age-predicted heart rate reserve. Relative quantification of gene expression, symptom measurements, and select cardiopulmonary parameters were compared between groups at pre-, 30 minpost-, and 24 hpost-exercise using a doubly multivariate repeated measures analysis of variance (RM-MANOVA). Mediation analyses were used to test indirect effects of changes in gene expression on symptom responses (i.e., PEM) to the standardized exercise challenge.

Results: Veterans with GWI experienced large symptom exacerbations following exercise compared to controls (Cohen's d: 1.65; $p < 0.05$). Expression of β -actin (ACTB), catechol-O-methyltransferase (COMT), and toll-like receptor 4 (TLR4) decreased in Veterans with GWI at 30 min ($p < 0.05$) and 24 h post-exercise ($p < 0.05$). Changes in gene expression did not mediate post-exercise symptom exacerbation in GWI (Indirect Effect Slope Coefficient: 0.06 - 0.02; 95% CI: 0.19, 0.12).

Conclusion: An acute bout of moderate intensity cycling reduced the expression of select structural, adrenergic, and immune genes in Veterans with GWI, but the pathophysiological relevance to PEM is unclear.

Pyridostigmine Bromide Pills and Pesticides Exposure as Risk Factors for Eye Disease in Gulf War Veterans

J Clin Med. 2023 Mar 21;12(6):2407. doi: 10.3390/jcm12062407.

Lauren E Truax 1, Jaxon J Huang 2 3, Katherine Jensen 2, Elyana V T Locatelli 2 3, Kimberly Cabrera 2, Haley O Peterson 1, Noah K Cohen 1 3, Simran Mangwani-Mordani 2, Andrew Jensen 2, Raquel Goldhardt 2 3, Anat Galor 2 3

Affiliations

1Ophthalmology, University of Miami Miller School of Medicine, Miami, FL 33136, USA.

2Surgical Services, Miami Veterans Affairs Medical Center, Miami, FL 33125, USA.

3Bascom Palmer Eye Institute, University of Miami, Miami, FL 33136, USA.

Abstract

To examine associations between the pyridostigmine bromide (PB) pill and/or pesticide exposure during the 1990-1991 Gulf War (GW) and eye findings years after deployment. A cross-sectional study of South Florida veterans who were deployed on active duty during the GW Era (GWE). Information on GW exposures and ocular surface symptoms were collected via standardized questionnaires and an ocular surface examination was performed. Participants underwent spectral domain-ocular coherence tomography (SD-OCT) imaging that included retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), and macular maps. We examined for differences in eye findings between individuals exposed versus not exposed to PB pills or pesticides during service. A total of 40.7% (n = 44) of individuals reported exposure to PB pills and 41.7% (n = 45) to pesticides; additionally, 24 reported exposure to both in the GW arena. Demographics were comparable across groups. Individuals exposed to PB pills reported higher dry eye (DE) symptoms scores (the 5-Item Dry Eye Questionnaire, DEQ-5: 9.3 ± 5.3 vs. 7.3 ± 4.7, p = 0.04) and more intense ocular pain (average over the last week: 2.4 ± 2.6 vs. 1.5 ± 1.8, p = 0.03; Neuropathic Pain Symptom Inventory modified for the Eye (NPSI-E): 18.2 ± 20.0 vs. 10.8 ± 13.8, p = 0.03) compared to their non-exposed counterparts. DE signs were comparable between the groups. Individuals exposed to PB pills also had thicker OCT measurements, with the largest difference in the outer temporal segment of the macula (268.5 ± 22.2 µm vs. 260.6 ± 14.5 µm, p = 0.03) compared to non-exposed individuals. These differences remained significant when examined in multivariable models that included demographics and deployment history. Individuals exposed to pesticides had higher neuropathic ocular pain scores (NPSI-E: 17.1 ± 21.1 vs. 11.6 ± 12.9, p = 0.049), but this difference did not remain significant in a multivariable model. Individuals exposed to PB pills during the GWE reported more severe ocular surface symptoms and had thicker OCT measures years after deployment compared to their non-exposed counterparts.

Self-reported gastrointestinal disorders among veterans with gulf war illness with and without posttraumatic stress disorder

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D Malhotra 1 2, S H Boyle 2, E J Gifford 2 3, B A Sullivan 1 2, T H Nguyen Wenker 4 5, Nono-Djotsa Abs 4 5 6, S T Ahmed 4 5, J Upchurch 2, J Vahey 2 7, C Stafford 2, J T Efird 8 9, S C Hunt 10 11, A Bradford 4, K J Sims 2, E R Hauser 2 12, D A Helmer 4 5, C D Williams 2

Affiliations

1Duke University School of Medicine, Durham, North Carolina, USA.

2Cooperative Studies Program Epidemiology Center, Durham VA Medical Center, Durham VA Health Care System, Durham, North Carolina, USA.

3Center for Child and Family Policy, Duke Margolis Center for Health Policy, Duke University Sanford School of Public Policy, Durham, North Carolina, USA.

4Department of Medicine, Baylor College of Medicine, Houston, Texas, USA.

5VA HSR&D Center for Innovations in Quality, Effectiveness and Safety (IQuEST), Michael E. DeBakey VA Medical Center, Houston, Texas, USA.

6Big Data Scientist Training Enhancement Program (BD-STEP), VA Office of Research and Development, Washington, DC, Washington, USA.

7Computational Biology and Bioinformatics Program, Duke University School of Medicine, Durham, North Carolina, USA.

8VA Cooperative Studies Program Coordinating Center, Boston, Massachusetts, USA.

9Department of Radiation Oncology, School of Medicine, Case Western Reserve University, Cleveland, Ohio, USA.

10VA Puget Sound Health Care System, Seattle, Washington, USA.

11Department of Medicine, University of Washington, Seattle, Washington, USA.

12Department of Biostatistics and Bioinformatics, Duke University Medical Center, Duke Molecular Physiology Institute, Durham, North Carolina, USA.

Abstract

Background: Gulf War Illness (GWI) is a chronic, multi-symptom disorder affecting 25%-32% of Gulf War veterans. Veterans with GWI disproportionately suffer from gastrointestinal (GI) disorders. Given the increasing evidence supporting a gut-brain axis, we explore the relationship between post-traumatic stress disorder (PTSD), GWI, and self-reported GI disorders among GW veterans.

Methods: Veterans from the Gulf War Era Cohort and Biorepository responded to a mail-based survey (N = 1058). They were stratified by GWI (Centers for Disease Control definition) and PTSD status. This yielded three groups: GWI-, GWI+/PTSD-, and GWI+/PTSD+. Multivariable logistic regression adjusting for demographic and military characteristics examined associations between GWI/PTSD groups and GI disorders. Results were expressed as adjusted odds ratios (aOR) with 95% confidence intervals (95% CI).

Key results: The most frequently reported GI disorders were irritable bowel syndrome (IBS), gastroesophageal reflux disease (GERD), and colon polyps (CP). The GWI+/PTSD+ group had a higher odds of these disorders than the GWI+/PTSD- group (aORIBS = 3.12, 95% CI: 1.93-5.05; aORGERD = 2.04, 95% CI: 1.44-2.90; aORCP = 1.85, 95% CI: 1.23-2.80), which had a higher odds of these disorders than the GWI- group (aORIBS = 4.38, 95% CI: 1.55-12.36; aORGERD = 2.51 95% CI: 1.63-3.87; aORCP = 2.57, 95% CI: 1.53-4.32).

Conclusions & inferences: GW veterans with GWI and PTSD have significantly higher odds of specific self-reported GI disorders than the other groups. Given the known bidirectional influences of the gut and brain, these veterans may benefit from a holistic healthcare approach that considers biopsychosocial contributors to the assessment and management of disease.

Veteran Beliefs About the Causes of Gulf War Illness and Expectations for Improvement

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Naomi S Kane 1 2 3, Raghad Hassabelnaby 4 5, Nicole L Sullivan 4, Fiona Graff 4, David R Litke 4 6, Karen S Quigley 7 8, Wilfred R Pigeon 9 10, Joseph F Rath 6, Drew A Helmer 11 12, Lisa M McAndrew 4

Affiliations

1Department of Veterans Affairs, War Related Illness and Injury Study Center, VA New Jersey Health Care System, East Orange, NJ, USA. naomi.kane@va.gov.

2VA Ann Arbor Healthcare System, Ann Arbor, USA. naomi.kane@va.gov.

3Department of Psychiatry, Michigan Medicine, 2215 Fuller Road (116C), Ann Arbor, MI, 48105-2103, USA. naomi.kane@va.gov.

4Department of Veterans Affairs, War Related Illness and Injury Study Center, VA New Jersey Health Care System, East Orange, NJ, USA.

5William Paterson University, Wayne, NJ, USA.

6Department of Rehabilitation Medicine, NYU Grossman School of Medicine, New York, NY, USA.

7Department of Veteran Affairs, Bedford Memorial Hospital, Bedford, MA, USA.

8Northeastern University, Boston, MA, USA.

9Center of Excellence for Suicide Prevention, Canandaigua VA Medical Center, Canandaigua, NY, USA.

10Department of Psychiatry, University of Rochester, Rochester, NY, USA.

11Center for Innovations in Quality, Effectiveness, and Safety, Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, USA.

12Department of Medicine, Baylor College of Medicine, Houston, TX, USA.

Abstract

Background: Individuals' beliefs about the etiology of persistent physical symptoms (PPS) are linked to differences in coping style. However, it is unclear which attributions are related to greater expectations for improvement.

Method and results: A cross-sectional regression analysis (N = 262) indicated that Veterans with Gulf War Illness (GWI) who attributed their GWI to behavior, (e.g., diet and exercise), had greater expectations for improvement (p = .001) than those who attributed their GWI to deployment, physical, or psychological causes (p values > .05).

Conclusions: Findings support the possible clinical utility of exploring perceived contributing factors of PPS, which may increase perceptions that improvement of PPS is possible.