Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI) — PubMed Research Citations for April, May, June 2023

Prepared by Staff of the RACGWVI.

RACGWVI: Gulf War Illness — PubMed Citations for April, May, June 2023

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

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

Randomized Controlled Trial J Psychosom Res. 2023 Apr;167:111193. doi: 10.1016/j.jpsychores.2023.111193. Epub 2023 Feb 14.

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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.

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

J Cell Mol Med. 2023 Apr;27(7):891-905. doi: 10.1111/jcmm.17631. Epub 2023 Jan 30.

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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.

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

Psychopharmacology (Berl). 2023 Apr;240(4):673-697. doi: 10.1007/s00213-023-06319-5. Epub 2023 Feb 15.

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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.

Associations between risky alcohol use, disability, and problem-solving impairment among Veterans with Gulf War Illness: Secondary data analysis of a randomized clinical trial

J Psychosom Res. 2023 Apr 11;170:111336. doi: 10.1016/j.jpsychores.2023.111336. Online ahead of print.

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Abstract

Objective: Gulf War Illness (GWI) and alcohol use are both major sources of disability among Gulf War Veterans. The goal of this secondary data analysis was to examine associations between risky alcohol use, problem-solving impairment, and disability among Veterans in a randomized clinical trial of problem-solving treatment (PST) for GWI. We examined cross-sectional associations and conducted longitudinal analyses to test if alcohol use moderated treatment outcome of PST.

Methods: Participants were 268 United States military Veterans with GWI randomized to PST or a control intervention. Participants were assessed at four timepoints. Measures included the World Health Organization Disability Assessment Schedule 2.0 (WHO-DAS 2.0), Problem Solving Inventory (PSI), and Alcohol Use Disorders Identification Test-Concise (AUDIT-C). We conducted multivariate regression (cross-sectional) and mixed model analyses (longitudinal) with separate models for WHO-DAS 2.0 and PSI. All models included AUDIT-C and household income. This analysis was pre-registered on the Open Science Framework.

Results: Cross-sectional analyses revealed a significant negative association with small effect size between AUDIT-C and WHO-DAS 2.0 ($p = 0.006$; $f2 = 0.05$); worse disability was associated with less risky alcohol use. There was no evidence that risky alcohol use moderated effects of PST on disability or PSI.

Conclusion: If replicated, the cross-sectional findings suggest high levels of disability may deter heavy drinking among Veterans with GWI. We did not find evidence that risky alcohol use moderated treatment outcome of PST for GWI. More research is needed to identify moderators of GWI interventions and to understand risky drinking among Veterans with complex health problems.

Experiential Avoidance, Posttraumatic Stress Disorder, and Self-Injurious Thoughts and Behaviors: A Moderation Analysis in a National Veteran Sample

Int J Cogn Ther. 2023 Apr 14;1:10.1007/s41811-023-00164-2. doi: 10.1007/s41811-023-00164-2.

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Abstract

Experiential avoidance (EA) is associated with posttraumatic stress disorder (PTSD) and self-injurious thoughts and behaviors (SITBs) across different populations, and extant literature has demonstrated a strong relationship between PTSD and SITBs. However, no study has explored the potential moderating role EA plays in the association of PTSD with nonsuicidal self-injury (NSSI), suicidal ideation, and suicide attempts. The objective of the present study was to determine if EA would moderate the association with PTSD and SITBs such that the association between PTSD and individuals SITBs would be stronger among individuals with higher EA. In a large national sample of Gulf War Era veterans (N = 1,138), EA was associated with PTSD, lifetime and past-year NSSI, current suicidal ideation, and lifetime suicide attempts in bivariate analyses. Multivariate analyses detected a significant EA by PTSD interaction on lifetime NSSI (AOR = 0.96), past-year NSSI (AOR = 1.03), and suicide attempts (AOR =1.03). Probing of the interactions revealed that the respective associations between PTSD, lifetime and past-year NSSI, and suicide attempts were stronger at lower levels of EA (i.e., better), counter to our hypotheses. These preliminary findings contextualize the relationship between these variables in a Gulf War veterans sample and signal the need to further investigate these relationships. Further, these findings highlight the need for advancement in assessment and intervention of EA and SITBs.

VA, NIH Launch Major Study of Veterans With Gulf War Illness

JAMA. 2023 Apr 26. doi: 10.1001/jama.2023.6625. Online ahead of print.

Emily Harris

A new study sponsored by the US Department of Veterans Affairs (VA) and the National Institutes of Health (NIH) will enroll people who served in the 1990-1991 era Gulf War to better understand Gulf War illness, according to a statement. The 5-year study, called the VA-NIH Investigative Deep Phenotyping of Gulf War Veterans Health, will investigate participants' immune, metabolic, and autonomic nervous systems.

Gulf War illness affects between 175 000 and 250 000 veterans—about a third of those deployed during operations Desert Shield and Desert Storm—and includes symptoms such as forgetfulness and loss of concentration, muscle and joint pain, and gastrointestinal distress, the project website notes.

Study visits at the NIH will involve a 14-day inpatient stay that includes an exercise stress test and thinking and memory assessments. Additional details, including how to volunteer for the study, are available online. (https://research.ninds.nih.gov/patients/va-nih-project-depth)

Genetic association between the APOE ε4 allele, toxicant exposures and Gulf War Illness diagnosis

Preprint from Research Square, 26 Apr 2023, DOI: 10.21203/rs.3.rs-2810223/v1 PPR: PPR651305

Abdullah L , Nkiliza A , Niedospial D , Aldrich G , Bartenfelder G , Keegan A , Hoffmann M , Mullan M , Klimas N , Baraniuk J , Crawford F , Krengel M , Chao L , Sullivan K

Abstract

Introduction: Exposure to nerve agents, pyridostigmine bromide (PB), pesticides, and oil-well fires during the 1991 Gulf War (GW) are major contributors to the etiology of Gulf War Illness (GWI). Since the apolipoprotein E (APOE) ε4 allele is associated with the risk of cognitive decline with age, particularly in the presence of environmental exposures, and cognitive impairment is one of the most common symptoms experienced by veterans with GWI, we examined whether the ε4 allele was associated with GWI.

Methods: Using a case-control design, we obtained data on APOE genotypes, demographics, and self-reported GW exposures and symptoms that were deposited in the Boston Biorepository and Integrative Network (BBRAIN) for veterans diagnosed with GWI (n = 220) and healthy GW control veterans (n = 131). Diagnosis of GWI was performed using the Kansas and/or Center for Disease Control (CDC) criteria.

Results: Age- and sex-adjusted analyses showed a significantly higher odds ratio for meeting the GWI case criteria in the presence of the ε4 allele (Odds ratio [OR] = 1.84, 95% confidence interval [CI = 1.07 – 3.15], p ≤ 0.05) and with two copies of the ε4 allele (OR = 1.99, 95% CI [1.23 - 3.21], p ≤ 0.01). Combined exposure to pesticides and PB pills (OR = 4.10 [2.12-7.91], p ≤ 0.05) as well as chemical alarms and PB pills (OR = 3.30 [1.56-6.97] p ≤ 0.05) during the war were also associated with a higher odds ratio for meeting GWI case criteria. There was also an interaction between the ε4 allele and exposure to oil well fires (OR = 2.46, 95% CI [1.07-5.62], p ≤ 0.05) among those who met the GWI case criteria.

Conclusion: These findings suggest that the presence of the ε4 allele was associated with meeting the GWI case criteria. Gulf War veterans who reported exposure to oil well fires and have an ε4 allele were more likely to meet GWI case criteria. Long-term surveillance of veterans with GWI, particularly those with oil well fire exposure, is required to better assess the future risk of cognitive decline among this vulnerable population.

Mycoplasma fermentans infection induces human necrotic neuronal cell death via IFITM3-mediated amyloid-β (1-42) deposition

Sci Rep. 2023 Apr 26;13(1):6864. doi: 10.1038/s41598-023-34105-y.

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Abstract

Mycoplasma fermentans is a proposed risk factor of several neurological diseases that has been detected in necrotic brain lesions of acquired immunodeficiency syndrome patients, implying brain invasiveness. However, the pathogenic roles of M. fermentans in neuronal cells have not been investigated. In this study, we found that M. fermentans can infect and replicate in human neuronal cells, inducing necrotic cell death. Necrotic neuronal cell death was accompanied by intracellular amyloid-β (1-42) deposition, and targeted depletion of amyloid precursor protein by a short hairpin RNA (shRNA) abolished necrotic neuronal cell death. Differential gene expression analysis by RNA sequencing (RNA-seq) showed that interferon-induced transmembrane protein 3 (IFITM3) was dramatically upregulated by M. fermentans infection, and knockdown of IFITM3 abolished both amyloid-β (1-42) deposition and necrotic cell death. A toll-like receptor 4 antagonist inhibited M. fermentans infection-mediated IFITM3 upregulation. M. fermentans infection also induced necrotic neuronal cell death in the brain organoid. Thus, neuronal cell infection by M. fermentans directly induces necrotic cell death through IFITM3-mediated amyloid-β deposition. Our results suggest that M. fermentans is involved in neurological disease development and progression through necrotic neuronal cell death.

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

Neurogastroenterol Motil. 2023 May;35(5):e14548. doi: 10.1111/nmo.14548. Epub 2023 Mar 21.

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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.

PTSD symptom severity mediates the impact of war zone stress exposure on postdeployment physical health: The Fort Devens Gulf War veterans cohort

Psychol Trauma. 2023 May;15(4):681-689. doi: 10.1037/tra0001286. Epub 2022 Jul 18.

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Abstract

Objective: Exposure to traumatic events is associated with increased risk for negative physical health outcomes, but more work is needed to advance understanding of the mechanisms underlying this relationship. As military deployments frequently involve trauma exposure, this issue has clear implications for veteran populations. This longitudinal study examined the role of mental health symptomatology (i.e., PTSD, depression, and anxiety) in the association between war zone stress and postdeployment physical health in Gulf War veterans.

Method: Data were collected in three waves over 7 years from a sample of 2,929 (92% male) Army personnel who were deployed to the 1990-1991 Gulf War. Structural equation modeling (SEM) was used to examine the associations linking war zone stress exposure reported at deployment return with subsequent physical health 6 to 7 years later, including the postdeployment onset of health symptoms and conditions and health functioning. The roles of PTSD, depression, and anxiety symptom severity as potential risk mechanisms linking stress exposure with later health outcomes were examined.

Results: Self-reported higher stress exposure was linked with greater severity of PTSD, depression, and anxiety symptoms. SEM analyses revealed that PTSD symptom severity was the only significant mediator of stress exposure on subsequent physical health.

Conclusion: Findings support the unique and significant role of PTSD in the development of physical health problems in the wake of war zone stress for Gulf War veterans. These results suggest that targeted PTSD interventions could reduce or prevent future physical health problems that can result from trauma exposure and mental health sequelae linked to military service. (PsycInfo Database Record (c) 2023 APA, all rights reserved).

0321 Manually scoring actigraphy in the absence of a sleep diary: Reliability analysis in Gulf War veterans

Sleep, 46(Supplement_1), a143-a143 - May 2023,
https://academic.oup.com/sleep/article/46/Supplement_1/A143/7181620

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Abstract

Abstract Introduction Sleep disturbance and chronic health conditions are common in military and veteran populations. These individuals may have difficulty accurately and consistently completing sleep diaries, which traditionally have been used as a prominent data input in scoring actigraphy. While actigraphy is considered an objective sleep measure, the process of manually scoring actigraphy data can be subjective, particularly in military/veteran and clinical populations. Few studies utilize and report clear actigraphy scoring guidelines. To promote internal consistency and replicability in actigraphy scoring procedures, this study developed a detailed actigraphy scoring protocol for cases without sleep diary data and performed an inter-rater reliability analysis using a sample of veterans with Gulf War Illness (GWI). Methods One hundred fifty-nine nights of actigraphy (Phillips Respironics) data from a random subsample of 25 veterans with GWI were independently, manually scored using the protocol. Mean values for the start and end of rest intervals and derived sleep parameters—time in bed (TIB), total sleep time (TST), and sleep efficiency (SE)—and mean differences were calculated. Inter-rater reliability was evaluated using intra-class correlation (ICC). Results No significant differences were observed between manual scorers for mean values for the end of manually scored rest intervals and derived sleep parameters (TIB, TST, and SE). There were significant differences in the start of a rest interval, though the magnitude of the difference (0:06 ± 28) was less than the clinically important 15-minute difference noted in the literature. ICC demonstrated excellent agreement between manual scorers for rest interval start (0.98) and end times (0.99), TIB (0.94), TST (0.98), and SE (0.97). Conclusion This protocol may serve as a reproducible set of guidelines for researchers manually scoring actigraphy and enhance internal consistency for studies using this actigraphy scoring software, especially for those working with military populations and clinical populations with significant sleep disturbance and related difficulties yielding quality sleep diary data. Support (if any) Veterans Affairs, Office of Research and Development, Clinical Science Research and Development under Merit Review Grant #SPLD-013-13S.

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

Adv Biol (Weinh). 2023 May;7(5):e2200254. doi: 10.1002/adbi.202200254. Epub 2023 Feb 19.

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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.

Fingolimod mitigates memory loss in a mouse model of Gulf War Illness amid decreasing the activation of microglia, protein kinase R, and NFκB

Neurotoxicology. 2023 May;96:197-206. doi: 10.1016/j.neuro.2023.05.006. Epub 2023 May 7.

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Abstract

Gulf War Illness (GWI) is an unrelenting multi-symptom illness with chronic central nervous system and peripheral pathology affecting veterans from the 1991 Gulf War and for which effective treatment is lacking. An increasing number of studies indicate that persistent neuroinflammation is likely the underlying cause of cognitive and mood dysfunction that affects veterans with GWI. We have previously reported that fingolimod, a drug approved for the treatment of relapsing-remitting multiple sclerosis, decreases neuroinflammation and improves cognition in a mouse model of Alzheimer's disease. In this study, we investigated the effect of fingolimod treatment on cognition and neuroinflammation in a mouse model of GWI. We exposed C57BL/6 J male mice to GWI-related chemicals pyridostigmine bromide, DEET, and permethrin, and to mild restraint stress for 28 days (GWI mice). Control mice were exposed to the chemicals' vehicle only. Starting 3 months post-exposure, half of the GWI mice and control mice were orally treated with fingolimod (1 mg/kg/day) for 1 month, and the other half were left untreated. Decreased memory on the Morris water maze test was detected in GWI mice compared to control mice and was reversed by fingolimod treatment. Immunohistochemical analysis of brain sections with antibodies to Iba1 and GFAP revealed that GWI mice had increased microglia activation in the hippocampal dentate gyrus, but no difference in reactive astrocytes was detected. The increased activation of microglia in GWI mice was decreased to the level in control mice by treatment with fingolimod. No effect of fingolimod treatment on gliosis in control mice was detected. To explore the signaling pathways by which decreased memory and increased neuroinflammation in GWI may be protected by fingolimod, we investigated the involvement of the inflammatory signaling pathways of protein kinase R (PKR) in the cerebral cortex of these mice. We found increased phosphorylation of PKR in the brain of GWI mice compared to controls, as well as increased phosphorylation of its most recognized downstream effectors: the α subunit of eukaryotic initiation factor 2 (eIF2α), IκB kinase (IKK), and the p65 subunit of nuclear factor-κB (NFκB-p65). Furthermore, we found that the increased phosphorylation level of these three proteins were suppressed in GWI mice treated with fingolimod. These results suggest that activation of PKR and NFκB signaling may be important for the regulation of cognition and neuroinflammation in the GWI condition and that fingolimod, a drug already approved for human use, may be a potential candidate for the treatment of GWI.

Gulf War Illness: A Randomized Controlled Trial Combining Mindfulness Meditation and Auricular Acupuncture

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Abstract

Background: Many Gulf War (GW) Veterans report chronic symptoms including pain, fatigue, and cognitive impairment, commonly defined as Gulf War Illness (GWI). Complementary and integrative health (CIH) therapies may potentially improve multiple symptoms of GWI.

Objective: To examine the effectiveness of combining 2 commonly available CIH therapies, mindfulness meditation and auricular acupuncture, in improving health-related functioning and multiple symptom domains of GWI (e.g., pain, fatigue).

Methods: This study was a randomized controlled trial in which Veterans with GWI were randomly assigned to either the intervention group (n = 75), wherein they received 2 distinct CIH therapies - mindfulness meditation and auricular acupuncture, or the active control group, wherein they received a GW Health Education (GWHE) program (n = 74), each lasting 8 weeks. Self-report health measures were assessed at baseline, endpoint, and 3 month follow-up.

Results: In the intention-to-treat analyses, there were significant between-group differences for mental-health related functioning, fatigue, depression symptoms, and Kansas total severity scores for symptoms in which the CIH group had improved scores for these outcomes at endpoint compared to the GWHE group (all $P \leq .05$). The CIH group also had significant reductions in pain interference at endpoint and follow-up compared to baseline (estimated marginal mean difference: -2.52 and -2.22, respectively; all $P = .01$), whereas no significant changes were observed in the GWHE group. For pain characteristics, the GWHE group had a worsening of pain at endpoint compared to baseline (estimated marginal mean difference: +2.83; $P = .01$), while no change was observed in the CIH group.

Conclusion: Findings suggest a possible beneficial effect of combining 2 CIH therapies, mindfulness meditation and auricular acupuncture, in reducing overall symptom severity and individual symptom domains of fatigue, musculoskeletal, and mood/cognition in Veterans with GWI.

The Department of Veterans' Affairs Depleted Uranium Cohort in the Time of COVID-19: Translating a Traditional Surveillance Protocol to a Telehealth Platform

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Abstract

Objective: In 2021, 37 members of a cohort of depleted uranium-exposed Gulf War I veterans were evaluated using a protocol tailored to accommodate COVID-19 safety practices on a telehealth platform.

Methods: Individual elements of the legacy protocol were reviewed for urgency and feasibility of inclusion in a modified, telehealth platform.

Results: The redesigned protocol included a participant readiness for telehealth assessment, nurse and physician telehealth visits, collection of usual health questionnaires and urine collections for exposure monitoring for uranium and other fragment-related metal measures.

Conclusions: Despite some limitations in scope, the telehealth platform permitted a visual 'visit' with surveillance participants who expressed a high comfort level with the format. The telehealth platform has apparent utility for occupational surveillance and should be explored as a standard approach for surveillance outside of public health emergencies.

Institutional Courage in Healthcare: An Improvement Project Exploring the Perspectives of Veterans Exposed to Airborne Hazards

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Abstract

Background: Military environmental exposures and care for subsequent health concerns have been associated with institutional betrayal, or a perception on the part of veterans that the US government has failed to adequately prevent, acknowledge, and treat these conditions and in doing so has betrayed its promise to veterans. Institutional courage is a term developed to describe organizations that proactively protect and care for their members. While institutional courage may be useful in mitigating institutional betrayal, there is a lack of definitions of institutional courage in healthcare from the patient perspective.

Methods: Using qualitative methods, we sought to explore the notions of institutional betrayal and institutional courage among veterans exposed to airborne hazards (i.e., airborne particulate matter such as open burn pits; N = 13) to inform and improve clinical practice. We performed initial interviews and follow-up interviews with veterans.

Results: Veterans' depictions of courageous institutions contained key themes of being accountable, proactive, and mindful of unique experiences, supporting advocacy, addressing stigma related to public benefits, and offering safety. Veterans described institutional courage as including both individual-level traits and systems or organizational-level characteristics.

Conclusions: Several existing VA initiatives already address many themes identified in describing courageous institutions (e.g., accountability and advocacy). Other themes, especially views of public benefits and being proactive, hold particular value for building trauma-informed healthcare.

Probiotic Treatment Ameliorates Exercise Intolerance, Deficits in Fear Learning and Systemic and Neuro-inflammation in a Mouse Model of Gulf War Illness

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Abstract

Veterans of the Persian Gulf War (GW) continue to suffer from Gulf War Illness (GWI) characterized by cognitive deficit and fatigue. Our group and others have suggested possible involvement of the microbiota-gut-brain axis in GWI pathology (Kozlova et a., 2021a; 2021b). The current study tested the hypothesis that probiotic treatment (P) prevents GWI symptoms, and systemic and neuro-inflammation. Adult male C57Bl/6N mice were separated into 4 groups (n=16/group): GW group was exposed to 8.7 mg/kg/d pyridostigmine bromide (PB) in saline (150uL/30g bw, oral gavage), 1.3 mg/kg PER in 100% DMSO (dermal), and 33% DEET in 70% EtOH (dermal) for 28 days (5 days/week). CON/S group was sham-treated. CON/S+P and GW+P groups were treated with a probiotic (P) cocktail of L. reuteri, L. rhamnosus, L. casei, B. longum (108 CFU/mL, oral gavage) 3 times/week for 2 weeks prior to and during sham/GW agent treatment and until sacrifice (post-treatment (PT) 150). All groups were subjected to restraint stress (5 min/d for 28 d). RT-qPCR on fecal pellets showed bacteria colonization of all strains except L. rhamnosus and B. longum after administration of 6-7 doses. At PT1, all strains showed increased colonization relative to baseline, which persisted to PT150, except B. longum. Body weight, fat, lean mass at PT150 showed no changes among groups. An exercise endurance (EE) test was performed to measure differences in fatigue. GW mice tired faster relative to CON/S at PT56 which persisted at PT150. Probiotic normalized exercise endurance to CON/S levels at PT56. On the passive avoidance test all groups behaved normally at PT50 but GW showed deficits on day 1 acquisition trial of fear learning when tested again 14 weeks later at PT150. GW+P behaved similarly to CON/S. Strength and depression-like behavior was examined before and after exercise stress to simulate post-exertional malaise. Mean percent time spent mobile on tail suspension test (TST) were significantly lower for GW but not GW+P at PT50. All groups were normal at PT150. There was no effect of GW agents or probiotics on the hanging wire test. Systemic and neuroinflammatory markers: C-reactive protein (CRP), high mobility group box 1 (HMGB1), and interleukin-6 (IL-6) were examined using ELISA. Liver and plasma CRP was increased in GW group but not GW+P in liver (p=0.06 in plasma). Plasma HMGB1 was reduced and brain IL-6 was elevated in GW mice but not GW+P. Immunofluorescence analysis in fixed hippocampal sections showed more Iba-1 positive cells in CA1 and DG in GW vs CON/S, while GW+P showed no significant changes vs CON/S. These results show that GW mice can be used to model long-lasting fatigue and other GWI symptoms as well as systemic and neuro-inflammation concurrently. After exercise stress GW agents produced depression. Importantly, probiotic treatment improved exercise endurance, depression, systemic and neuro-inflammation in GW mice, indicating its potential therapeutic use in GWI.

The Gulf War Illness and the Iraqi Population's Forgotten Pain and Suffering

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Abstract

Exposure to chemical warfare agents results in long-term biopsychosocial complaints. A recent study has revealed an association between exposure to a low dose of Sarin and Gulf War illness in American veterans from the Gulf War. The prevalence of Gulf War illness has not been studied in the Iraqi population. In light of recent research results, Iraqi chemical warfare agent survivors' multiple physical and mental illnesses should be highlighted. For this reason, establishing both legislation and medical commissions is most needed.

Misclassification Bias in the Assessment of Gene-By-Environment Interactions

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Abstract

Background: Misclassification bias is a common concern in epidemiologic studies. Despite strong bias on main effects, gene-environment interactions have been shown to be biased towards the null under gene-environment independence. In the context of a recent paper examining the interaction between nerve agent exposure and paraoxonase-1 gene on Gulf War Illness, we aimed to assess the impact of recall bias-a common misclassification bias-on the identification of gene-environment interactions when the independence assumption is violated.

Methods: We derive equations to quantify the bias of the interaction, and numerically illustrate these results through simulating a case-control study of 1,000 cases and 1,000 controls. Simulation input parameters included exposure prevalence, strength of gene-environment dependence, strength of main effect, exposure specificity among cases, and strength of the gene-environment interaction.

Results: We show that, even if gene-environment independence is violated, we can bound possible gene-environment interactions by knowing the strength and direction of the gene-environment dependence (ORGE) and the observed gene-environment interaction (ORINT-O)-thus often still allowing for identification of such interactions. Depending on whether ORINT-O is larger or smaller than the inverse of ORGE, ORINT-O is a lower (if ORINT-O>1/ORGE) or upper (if ORINT-O<1/ORGE) bound for the true interaction. In addition, the bias magnitude is somewhat predictable by examining other characteristics like exposure prevalence, strength of the exposure main effect, and directions of the recall bias and gene-environment dependence.

Conclusions: Even if gene-environment dependence exists, we may still be able to identify gene-environment interactions even when misclassification bias is present.

Nontraditional Occupational Exposures to Crude Oil Combustion Disasters and Respiratory Disease Risk: A Narrative Review of Literature

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Abstract

Purpose of review: Burning of petroleum products has been consistently associated with adverse respiratory health effects. Combustion of crude oil, specifically, produces toxic byproducts, but there have been relatively few studies of health effects. Burning of crude oil is increasingly employed as a means of mitigating environmental disasters despite the potential health risks to workers involved in clean-up efforts. Here, we review epidemiological studies of respiratory effects following unique crude oil burning events to (1) characterize respiratory health effects from this nontraditional occupational exposure and (2) identify approaches used to characterize exposures that could be applied to future disaster-related studies.

Recent findings: We searched PubMed and EMBASE for references from inception to January 30, 2023. We also manually screened references cited in eligible articles. We identified 14 eligible publications. Our review suggests that exposure to crude oil combustion has adverse respiratory effects, including reduced lung function and increased occurrence of respiratory symptoms and disease. However, the evidence is inconsistent, and quality of data varied across studies. While some studies used quantitative, modeled exposure estimates, most used self-reported proxies of exposure. Although disasters involving crude oil combustion are relatively rare, limited evidence suggests that some worker populations may be at risk for respiratory effects from burning exposures in disaster settings. Future studies that use improved exposure assessment methods (e.g., personal monitors, remote sensing data) may help further quantify the respiratory risk from crude oil burning exposures.

The association of military sexual assault and nonsuicidal self-injury in U.S. Gulf War-I era veterans

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Abstract

Military sexual assault (MSA) is a prevalent issue among military personnel that has been linked to adverse mental and physical health outcomes, including posttraumatic stress disorder (PTSD) and suicidal thoughts and behaviors. The present study sought to investigate the relationship between MSA and nonsuicidal self-injury (NSSI) in a national sample of Gulf War-I Era U.S. veterans. The study analyzed data from 1,153 Gulf War-I veterans collected through a cross-sectional survey that assessed demographic information, clinical outcomes, military background, and history of MSA and NSSI. MSA was found to be significantly associated with NSSI at the bivariate level (OR = 2.19, $p < .001$). Further, MSA remained significantly associated with NSSI (AOR = 2.50, $p = .002$) after controlling for relevant demographics and clinical outcomes. Veterans with a history of MSA were approximately two and half times more likely to engage in NSSI than veterans who had not experienced MSA. The present findings provide preliminary evidence linking MSA and NSSI. Further, the findings highlight the importance of assessing MSA and NSSI in veteran populations, particularly among those seeking treatment for PTSD.

Epigenetic analysis in a murine genetic model of Gulf War illness

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Abstract: Of the nearly 1 million military personnel who participated in the 1990–1991 Gulf War, between 25% and 35% became ill with what now is referred to as Gulf War Illness (GWI) by the Department of Defense. Symptoms varied from gastrointestinal distress to lethargy, memory loss, inability to concentrate, depression, respiratory, and reproductive problems. The symptoms have persisted for 30 years in those afflicted but the basis of the illness remains largely unknown. Nerve agents and other chemical exposures in the war zone have been implicated but the long-term effects of these acute exposures have left few if any identifiable signatures. The major aim of this study is to elucidate the possible genomic basis for the persistence of symptoms, especially of the neurological and behavioral effects. To address this, we performed a whole genome epigenetic analysis of the proposed cause of GWI, viz., exposure to organophosphate neurotoxicants combined with high circulating glucocorticoids in two inbred mouse strains, C57BL/6J and DBA/2J. The animals received corticosterone in their drinking water for 7 days followed by injection of diisopropylfluorophosphate, a nerve agent surrogate. Six weeks after DFP injection, the animals were euthanized and medial prefrontal cortex harvested for genome-wide DNA methylation analysis using high-throughput sequencing. We observed 67 differentially methylated genes, notably among them, Ttll7, Akr1c14, Slc44a4, and Rusc2, all related to different symptoms of GWI. Our results support proof of principle of genetic differences in the chronic effects of GWI-related exposures and may reveal why the disease has persisted in many of the now aging Gulf War veterans.

Gulf war illness inflammation reduction trial: A phase 2 randomized controlled trial of low-dose prednisone chronotherapy, effects on health-related quality of life

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Abstract

Background: Gulf War illness (GWI) is a deployment-related chronic multisymptom illness impacting the health-related quality of life (HRQOL) of many U.S. Military Veterans of the 1990-91 Gulf War. A proinflammatory blood biomarker fingerprint was discovered in our initial study of GWI. This led to the hypothesis that chronic inflammation is a component of GWI pathophysiology.

Objectives: The GWI inflammation hypothesis was tested in this Phase 2 randomized controlled trial (RCT) by measuring the effects of an anti-inflammatory drug and placebo on the HRQOL of Veterans with GWI. The trial is registered at ClinicalTrials.gov, Identifier: NCT02506192.

Rct design and methods: Gulf War Veterans meeting the Kansas case definition for GWI were randomized to receive either 10 mg modified-release prednisone or matching placebo. The Veterans RAND 36-Item Health Survey was used to assess HRQOL. The primary outcome was a change from baseline in the physical component summary (PCS) score, a measure of physical functioning and symptoms. A PCS increase indicates improved physical HRQOL.

Results: For subjects with a baseline PCS <40, there was a 15.2% increase in the mean PCS score from 32.9±6.0 at baseline to 37.9±9.0 after 8 weeks on modified-release prednisone. Paired t-test analysis determined the change was statistically significant ($p = 0.004$). Eight weeks after cessation of the treatment, the mean PCS score declined to 32.7±5.8.

Conclusions: The prednisone-associated improvement in physical HRQOL supports the GWI inflammation hypothesis. Determining the efficacy of prednisone as a treatment for GWI will require a Phase 3 RCT.

Is exposure to chemical pollutants associated with sleep outcomes? A systematic review

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Abstract

Environmental exposures may influence sleep; however, the contributions of environmental chemical pollutants to sleep health have not been systematically investigated. We conducted a systematic review to identify, evaluate, summarize, and synthesize the existing evidence between chemical pollutants (air pollution, exposures related to the Gulf War and other conflicts, endocrine disruptors, metals, pesticides, solvents) and dimensions of sleep health (architecture, duration, quality, timing) and disorders (sleeping pill use, insomnia, sleep-disordered breathing)). Of the 204 included studies, results were mixed; however, the synthesized evidence suggested associations between particulate matter, exposures related to the Gulf War, dioxin and dioxin-like compounds, and pesticide exposure with worse sleep quality; exposures related to the Gulf War, aluminum, and mercury with insomnia and impaired sleep maintenance; and associations between tobacco smoke exposure with insomnia and sleep-disordered breathing, particularly in pediatric populations. Possible mechanisms relate to cholinergic signaling, neurotransmission, and inflammation. Chemical pollutants are likely key determinants of sleep health and disorders. Future studies should aim to evaluate environmental exposures on sleep across the lifespan, with a particular focus on developmental windows and biological mechanisms, as well as in historically marginalized or excluded populations.