Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI) — PubMed Research Citations for October, November, December 2021

Prepared by Staff of the RACGWVI.

RACGWVI: Gulf War Illness — PubMed Citations for Oct, Nov, Dec 2021

The following is a list of published research projects that focus on Gulf War Illness (GWI) for the months of October, November, December 2021.

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Delayed treatment with the immunotherapeutic LNFPIII ameliorates multiple neurological deficits in a pesticide-nerve agent prophylactic mouse model of Gulf War Illness

Neurotoxicol Teratol. Sep-Oct 2021; 87:107012. doi: 10.1016/j.ntt.2021.107012. Epub 2021 Jul 10.

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Abstract

Residual effects of the 1990-1991 Gulf War (GW) still plague veterans 30 years later as Gulf War Illness (GWI). Thought to stem mostly from deployment-related chemical overexposures, GWI is a disease with multiple neurological symptoms with likely immunological underpinnings. Currently, GWI remains untreatable, and the long-term neurological disease manifestation is not characterized fully. The present study sought to expand and evaluate the long-term implications of prior GW chemicals exposure on neurological function 6-8 months post GWI-like symptomatology induction. Additionally, the beneficial effects of delayed treatment with the glycan immunotherapeutic lacto-N-fucopentaose III (LNFPIII) were evaluated. Male C57BL/6J mice underwent a 10-day combinational exposure (i.p.) to GW chemicals, the nerve agent prophylactic pyridostigmine bromide (PB) and the insecticide permethrin (PM; 0.7 and 200 mg/kg, respectively). Beginning 4 months after PB/PM exposure, a subset of the mice were treated twice a week until study completion with LNFPIII. Evaluation of cognition/memory, motor function, and mood was performed beginning 1 month after LNFPIII treatment initiation. Prior exposure to PB/PM produced multiple locomotor, neuromuscular, and sensorimotor deficits across several motor tests. Subtle anxiety-like behavior was also present in PB/PM mice in mood tests. Further, PB/PM-exposed mice learned at a slower rate, mostly during early phases of the learning and memory tests employed. LNFPIII treatment restored or improved many of these behaviors, particularly in motor and cognition/memory domains. Electrophysiology data collected from hippocampal slices 8 months post PB/PM exposure revealed modest aberrations in basal synaptic transmission and long-term potentiation in the dorsal or ventral hippocampus that were improved by LNFPIII treatment. Immunohistochemical analysis of tyrosine hydroxylase (TH), a dopaminergic marker, did not detect major PB/PM effects along the nigrostriatal pathway, but LNFPIII increased striatal TH. Additionally, neuroinflammatory cells were increased in PB/PM mice, an effect reduced by LNFPIII. Collectively, long-term neurobehavioral and neurobiological dysfunction associated with prior PB/PM exposure was characterized; delayed LNFPIII treatment provided multiple behavioral and biological beneficial effects in the context of GWI, highlighting its potential as a GWI therapeutic.

Experiential avoidance is associated with medical and mental health diagnoses in a national sample of deployed Gulf War veterans

J Psychiatr Res. 2021 Oct; 142:17-24. doi: 10.1016/j.jpsychires.2021.07.033. Epub 2021 Jul 22.

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Abstract

A substantial minority of deployed Gulf War veterans developed posttraumatic stress disorder (PTSD), depression, and several chronic illnesses. Although military combat and exposure to certain nuclear, biological, and chemical agents (NBCs) increase risk for post-deployment health problems, they do not fully explain many Gulf War veteran health diagnoses and are not viable treatment targets. Experiential avoidance (EA; one's unwillingness to remain in contact with unpleasant internal experiences) is a modifiable psychosocial risk factor associated with PTSD and depression in veterans as well as pain and gastrointestinal diseases in the general population. In this study, we recruited a national sample of deployed Gulf War veterans (N = 454) to test the hypothesis that greater EA would be significantly associated with higher lifetime odds of PTSD, depression, "Gulf War Illness" (GWI/CMI), and other chronic illnesses common in this veteran

cohort. Participants completed a self-report battery assessing demographic, military-related, and health-related information. Multivariate analyses showed that after adjusting for age, sex, race, combat exposure, and NBC exposure, worse EA was associated with higher lifetime odds of PTSD, depression GWI/CMI, gastrointestinal problems, irritable bowel syndrome, arthritis, fibromyalgia, and chronic fatigue syndrome (ORs ranged 1.25 to 2.89; effect sizes ranged small to large), but not asthma or chronic obstructive pulmonary disease. Our findings suggest medical and mental health providers alike should assess for EA and potentially target EA as part of a comprehensive, biopsychosocial approach to improving Gulf War veterans' health and wellbeing. Study limitations and future research directions are also discussed.

Neuroimmune mechanisms of cognitive impairment in a mouse model of Gulf War illness

Brain Behav Immun. 2021 Oct; 97:204-218. doi: 10.1016/j.bbi.2021.07.015. Epub 2021 Jul 29.

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Abstract

Gulf War Illness (GWI) is a chronic, multi-symptom disorder affecting approximately 30 percent of the nearly 700,000 Veterans of the 1991 Persian Gulf War. GWI-related chemical (GWIC) exposure promotes immune activation that correlates with cognitive impairment and other symptoms of GWI. However, the molecular mechanisms and signaling pathways linking GWIC to inflammation and neurological symptoms remain unclear. Here we show that acute exposure of murine macrophages to GWIC potentiates innate immune signaling and inflammatory cytokine production. Using an established mouse model of GWI, we report that neurobehavioral changes and neuroinflammation are attenuated in mice lacking the cyclic GMP-AMP synthase (cGAS)-Stimulator of Interferon Genes (STING) and NOD-, LRR- or pyrin domain-containing protein 3 (NLRP3) innate immune pathways. In addition, we report sex differences in response to GWIC, with female mice showing more pronounced cognitive impairment and hippocampal astrocyte hypertrophy. In contrast, male mice display a GWIC-dependent upregulation of proinflammatory cytokines in the plasma that is not present in female mice. Our results indicate that STING and NLRP3 are key mediators of the cognitive impairment and inflammation observed in GWI and provide important new information on sex differences in this model.

Moderate, intermittent voluntary exercise in a model of Gulf War Illness improves cognitive and mood function with alleviation of activated microglia and astrocytes, and enhanced neurogenesis in the hippocampus

Brain Behav Immun. 2021 Oct; 97:135-149. doi: 10.1016/j.bbi.2021.07.005. Epub 2021 Jul 8.

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Abstract

Persistent cognitive and mood impairments in Gulf War Illness (GWI) are associated with chronic neuroinflammation, typified by hypertrophied astrocytes, activated microglia, and increased proinflammatory mediators in the brain. Using a rat model, we investigated whether a simple lifestyle change such as moderate voluntary physical exercise would improve cognitive and mood function in GWI. Because veterans with GWI exhibit fatigue and post-exertional malaise, we employed an intermittent voluntary running exercise (RE) regimen, which prevented exercise-induced stress. The GWI rats were provided access to running wheels three days per week for 13 weeks, commencing ten weeks after the exposure to GWI-related chemicals and stress (GWI-RE group). Groups of age-matched sedentary GWI rats (GWI-SED group) and naïve rats were maintained parallelly. Interrogation of rats with behavioral tests after the 13-week RE regimen revealed improved hippocampus-dependent object location memory and pattern separation function and reduced anxiety-like behavior in the GWI-RE group compared to the GWI-SED group. Moreover, 13 weeks of RE in GWI rats significantly reversed activated microglia with short and less ramified processes into non-inflammatory/antiinflammatory microglia with highly ramified processes and reduced the hypertrophy of astrocytes. Moreover, the production of new neurons in the hippocampus was enhanced when examined eight weeks after the commencement of RE. Notably, increased neurogenesis continued even after the cessation of RE. Collectively, the results suggest that even a moderate, intermittent physical exercise has the promise to improve brain function in veterans with GWI in association with suppression of neuroinflammation and enhancement of hippocampal neurogenesis.

Research tool for classifying Gulf War illness using survey responses: Lessons for writing replicable algorithms for symptom-based conditions

Life Sci. 2021 Oct 1; 282: 119808. doi: 10.1016/j.lfs.2021.119808. Epub 2021 Jul 6.

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Abstract

Aims: Gulf War illness (GWI), a chronic symptom-based disorder, affects up to 30% of Veterans who served in the 1990-1991 Gulf War1. Because no diagnostic test or code for GWI exists, researchers typically determine case status using self-reported symptoms and conditions according to Kansas2 and CDC3 criteria. No validated algorithm has been published and case definitions have varied slightly by study. This paper aims to standardize the application of the original CDC and Kansas case definitions by defining a framework for writing reliable code for complex case definitions, implementing this framework on a sample of 1343 Gulf War Veterans (GWVs), and validating the framework by applying the code to a sample of 41,077 GWVs.

Main methods: Methods were drawn from software engineering: write pseudocode, write test cases, and write code; then test code. Code was examined for accuracy, flexibility, replicability, and reusability.

Key findings: The pseudocode promoted understanding of the planned algorithm, encouraging discussion and leading to agreement on the case definition algorithms among all team members. The completed SAS code was written for and tested in the Gulf War Era Cohort and Biorepository (GWECB)4. This code was adapted and tested in the Million Veteran Program (MVP)5. The code was documented for reproducibility and reusability.

Significance: Ease of reuse suggests that this method could be used to standardize the application of other case definitions, reducing time and resources spent by each study team. Documentation, code, and test cases are available through the Department of Veterans Affairs (VA) Phenomics catalog6.

Vagal nerve stimulation as a possible non-invasive treatment for chronic widespread pain in Gulf Veterans with Gulf War Illness

Randomized Controlled Trial Life Sci. 2021 Oct 1; 282:119805. doi: 10.1016/j.lfs.2021.119805. Epub 2021 Jul 5.

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Abstract

Aims: Widespread pain and headache are common in Gulf War Illness with suboptimal treatments available. We tested the efficacy of non-invasive, transcutaneous vagal nerve stimulation (nVNS) for relief of widespread pain and migraine in Gulf War Veterans with GWI.

Main methods: A 10-week double-blind, randomized controlled trial of nVNS used the gammaCore (ElectroCore, Inc.) compared to sham stimulation with the same device followed by a 10-week open-label follow up with active nVNS. The primary outcome was a numerical pain rating at the end of the blinded period. Secondary outcomes included physical function, migraine frequency and severity, and impression of change during the blinded and open-label periods. Two-factor MANOVA models tested for significant differences between groups from baseline to end of the blinded period and during the open-label period.

Key findings: Among 27 participants enrolled and issued a nVNS device, there was a slight improvement in pain ratings from baseline to the end of the blinded phase [6.18 (±0.82) vs. 5.05 (±2.3); p = 0.040] which did not differ between active and sham nVNS. Physical function was also slightly improved overall without group differences. There were no significant changes in migraine frequency or severity during the blinded period. Twenty participants started in the open-label phase; no statistically significant changes in pain, physical function, migraine measures, or impression of change were noted during this phase.

Significance: Veterans with GWI actively treated with nVNS reported no improvement in either widespread pain or migraine frequency or severity relative to Veterans with GWI who received sham nVNS.

The association of pre-war medical conditions to Gulf War Illness

Life Sci. 2021 Oct 1; 282:119795. doi: 10.1016/j.lfs.2021.119795. Epub 2021 Jul 4.

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Abstract

Aims: Gulf War Illness (GWI) remains a significant health concern for many veterans. The relation of pre-war health conditions and symptoms to GWI could aid in developing a more accurate case definition of GWI. The objective of this study was to investigate pre-war predictors of GWI in a population-based sample of Gulf War veterans using two definitions of GWI.

Main methods: Data come from the 1995-1997 National Health Survey of Persian Gulf War Era Veterans, a survey of a representative sample of deployed and non-deployed US veterans. Using two definitions of GWI (CDC/Kansas and a newly developed 3-domain definition), we conducted a series of multivariable logistic regression analyses to assess the associations of demographic, lifestyle factors, and pre-war medical conditions and symptoms to subsequent GWI.

Key findings: All pre-war symptom predictor domains were significantly and positively associated with GWI using a new 3-domain definition with aORs for individual domains ranging from 2.17 (95% CI = 1.99-2.38) for dermatologic conditions to 3.06 (95% CI = 2.78-3.37) for neurological conditions. All symptom predictor domains were associated with significantly increased likelihood of GWI using the CDC/Kansas definition, with aORs ranging from 2.54 (95% CI = 2.31-2.81) for inflammatory conditions to 3.22 (95% CI = 2.94-3.55) for neurological conditions. These estimates were attenuated but remained significant after inclusion of all significant symptom predictor domains.

Significance: Results from this study suggest that demographic/lifestyle factors and pre-war medical conditions are strong predictors of GWI. Additional research is needed to confirm these findings, and to clarify the unique characteristics of this common, but still poorly understood illness.

Subcortical brain segment volumes in Gulf War Illness and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Clinical Trial Life Sci. 2021 Oct 1; 282:119749. doi: 10.1016/j.lfs.2021.119749. Epub 2021 Jun 29.

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Abstract

Aims: There is controversy about brain volumes in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (CFS) and Gulf War Illness (GWI). Subcortical regions were assessed because of significant differences in blood oxygenation level dependent signals in the midbrain between these diseases.

Materials and method: Magnetization-prepared rapid acquisition with gradient echo (MPRAGE) images from 3 Tesla structural magnetic resonance imaging scans from sedentary control (n = 34), CFS (n = 38) and GWI (n = 90) subjects were segmented in FreeSurfer. Segmented subcortical volumes were regressed against intracranial volume and age, then iteratively analyzed by multivariate general linear modeling with disease status, gender and demographics as independent co-variates.

Key findings: The optimal model for all subjects used disease status and gender as fixed factors with independent variables eliminated after iteration. Volumes of anterior and midanterior corpus callosum were significantly larger in GWI than CFS. Gender was a significant variable for many segment volumes, and so female and male subjects were analyzed separately. CFS females had smaller left putamen, right caudate and left cerebellum white matter than control women. CFS males had larger left hippocampus than GWI males. Orthostatic status and posttraumatic distress syndrome were not significant covariates.

Significance: CFS and GWI were appropriate "illness controls" for each other. The different patterns of adjusted segment volumes suggested that sexual dimorphisms contributed to pathological changes. Previous volumetric studies may need to be reevaluated to account for gender differences. The findings are framed by comparison to the spectrum of magnetic resonance imaging outcomes in the literature.

Diagnosis of Gulf War Illness Using Laser-Induced Spectra Acquired from Blood Samples

Appl Spectrosc. 2021 Oct 1; 37028211042049. doi: 10.1177/00037028211042049. Online ahead of print.

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Abstract

Gulf War illness (GWI) is a chronic illness with no known validated biomarkers that affects the lives of hundreds of thousands of people. As a result, there is an urgent need for the development of an untargeted and unbiased method to distinguish GWI patients from non-GWI patients. We report on the application of laser-induced breakdown spectroscopy (LIBS) to distinguish blood plasma samples from a group of subjects with GWI and from subjects with chronic low back pain as controls. We initially obtained LIBS data from blood plasma samples of four GWI patients and four non-GWI patients. We used an analytical method based on taking the difference between a mean LIBS spectrum obtained with those of GWI patients from the mean LIBS spectrum of those of the control group, to generate a "difference" spectrum for our classification model. This model was cross-validated using different numbers of differential LIBS emission peaks. A subset of 17 of the 82 atomic and ionic transitions that provided 70% of correct diagnosis was selected test in a blinded fashion using 10 additional samples and was found to yield 90% classification accuracy, 100% sensitivity, and 83.3% specificity. Of the 17 atomic and ionic transitions, eight could be assigned unambiguously to species of Na, K, and Fe.

Safety and efficacy of short-term structured resistance exercise in Gulf War Veterans with chronic unexplained muscle pain: A randomized controlled trial

Clinical Trial Life Sci. 2021 Oct 1; 282:119810. doi: 10.1016/j.lfs.2021.119810. Epub 2021 Jul 10.

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Abstract

Aims: Chronic widespread musculoskeletal pain (CMP) is a primary condition of Veterans suffering from Gulf War illness. This study evaluated the influence of resistance exercise training (RET) on symptoms, mood, perception of improvement, fitness, and total physical activity in Gulf War Veterans (GWV) with CMP.

Main methods: Fifty-four GWV with CMP were randomly assigned to 16 weeks of RET (n = 28) or wait-list control (n = 26). Supervised exercise was performed twice weekly starting at a low intensity. Outcomes, assessed at baseline, 6, 11 and 17 weeks and 6- and 12-months post-intervention, were: pain, fatigue, mood, sleep quality, perception of improvement, and physical activity via self-report and accelerometry. Muscular strength was assessed at baseline, 8 and 16 weeks. Accelerometer data yielded estimates of time spent in sedentary, light, and moderate-to-vigorous physical activities. Analyses used separate linear mixed models with group and time point as fixed effects. All models, except for perceived improvement, included baseline values as a covariate.

Key findings: Participants assigned to RET completed 87% of training sessions and exhibited strength increases between 16 and 34% for eight lifts tested (Hedges' g range: 0.47-0.78). The treatment by time interaction for perceived improvement ($F_{1,163} = 16.94$, $p < 0.001$) was characterized by greater perceived improvement since baseline for RET at each time point, until the 12-month follow-up. Effects were not significant for other outcomes ($p > 0.05$). RET caused no adverse events.

Significance: After 16 weeks of RET, GWV with CMP reported improvements in their condition and exhibited increases in muscular strength, without symptom exacerbation or reductions in total physical activity.

A randomized phase II remote study to assess Bacopa for Gulf War Illness associated cognitive dysfunction: Design and methods of a national study

Clinical Trial Life Sci. 2021 Oct 1; 282: 119819. doi: 10.1016/j.lfs.2021.119819. Epub 2021 Jul 10.

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Abstract

Aims: Gulf War Illness (GWI) is a chronic, debilitating, multi-symptom condition affecting as many as one-third of the nearly 700,000 U.S. troops deployed to the Middle East during the 1990-1991 Gulf War (GW). The treatment of GWI relies on symptom management. A common challenge in studying the efficacy of interventions for symptom management is participant recruitment related to factors such as the burden of travelling to study sites and the widespread dispersion of Veterans with GWI. The goal of this study is to assess the efficacy of a novel low-risk therapeutic agent, Bacopa monnieri, for cognitive function in Veterans with GWI and to evaluate the utility of a remote patient-centric study design developed to promote recruitment and minimize participant burden.

Main methods: To promote effective participant recruitment, we developed a remote patient-centric study design. Participants will be recruited online through social media and through a web-based research volunteer list of GW Veterans. An online assessment platform will be used, and laboratory blood draws will be performed at clinical laboratory sites that are local to participants. Furthermore, the assigned intervention will be mailed to each participant.

Significance: These study design adaptations will open participation to Veterans nearly nationwide and reduce administrative costs while maintaining methodologic rigor and participant safety in a randomized, placebo-controlled phase II clinical trial.

Experimental respiratory exposure to putative Gulf War toxins promotes persistent alveolar macrophage recruitment and pulmonary inflammation

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Abstract

Aims: Respiratory disorders are a prominent component of Gulf War Illness. Although much of the underlying mechanisms of Gulf War Illness remain undefined, chronic immune dysfunction is a consistent feature of this multi-symptomatic, multi-organ disorder. Alveolar macrophages represent the predominant mononuclear phagocytes of the pulmonary mucosa, orchestrating the host response to pathogens and environmental stimuli. Herein, we sought to characterize the innate immune response of the pulmonary mucosa, with a focus on macrophages, to experimental respiratory exposure to two putative Gulf War Toxins (GWTs).

Materials and methods: Utilizing commercially available instrumentation, we evaluated the effect of aerosolized exposure to the pesticide malathion and diesel exhaust particulate (DEP) on the immune composition and inflammatory response of the lung in FVB/N mice using multiparametric spectral cytometry, cytokine analysis, and histology.

Key findings: Aerosolized GWTs induced gross pulmonary pathology with transient recruitment of neutrophils and sustained accumulation of alveolar macrophages to the lung for up to two weeks after exposure cessation. High-dimensional cytometry and unbiased computational analysis identified novel myeloid subsets recruited to the lung post-exposure driven by an influx of peripheral monocyte-derived progenitors. DEP and malathion, either alone or in combination, induced soluble mediators in bronchoalveolar lavage indicative of oxidative stress (PGF2α), inflammation (LTB4, TNFα, IL-12), and immunosuppression (IL-10), that were sustained or increased two weeks after exposures concluded.

Significance: These findings indicate that macrophage accumulation and pulmonary inflammation induced by GWTs continue in the absence of toxin exposure and may contribute to the immunopathology of respiratory Gulf War Illness.

The Health of Gulf War and Gulf Era Veterans Over Time: U.S. Department of Veterans Affairs' Gulf War Longitudinal Study

J Occup Environ Med. 2021 Oct 1; 63(10):889-894. doi: 10.1097/JOM.0000000000002331.

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Abstract

Objective: The aim of this study was to describe the self-reported physical and mental health over the course over 19 years of follow up of a population-based cohort of Gulf War and Gulf Era veterans.

Methods: A multi-modal health survey of 6338 Gulf War and Gulf Era veterans who participated in all three waves of the longitudinal study.

Results: Gulf War and Gulf War Era veterans experienced an increase in prevalence of chronic disease over time. The adjusted odds ratios suggest that Gulf War veterans not only had significantly higher odds of reporting medical conditions, but also began to report them earlier.

Conclusions: The findings from this analysis suggest that Gulf War veterans are not only more likely than their non-deployed counterparts to report chronic disease, they were more likely to report it earlier.

Physical health, behavioral and emotional functioning in children of gulf war veterans

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Abstract

Objective: We examined whether the prevalence of medical and behavioral conditions is higher in children of deployed veterans (DVs) versus non-deployed veterans (NDVs) after the 1991 Gulf War.

Methods: We examined 1387 children of 737 veterans. Children ages 2-18 had physical exams and parental reports of physical history and behavior.

Results: Physical health was analyzed using GEE models. Behavioral health [total, internalizing, and externalizing behavior problems (TBP, IBP, EBP)] was analyzed with mixed-effects regression models. Analyses were conducted by age group (2-3, 4-11, 12-18), and gender (ages 4-11, 12-18). Children of DVs ages 2-3 had significantly worse dentition (13.9% vs. 4.8%, P = 0.03) and more EBP {least square means (lsmeans) 54.31 vs. 47.59, P = 0.02}. Children of DVs ages 4-11 had significantly more obesity (18.8% vs. 12.7%, P = 0.02). Among children 4-11, male children of DVs had significantly more TBP (lsmeans 70.68 vs. 57.34, P = 0.003), IBP (lsmeans 63.59 vs. 56.16, P = 0.002) and EBP (lsmeans 61.60 vs. 52.93, P = 0.03), but female children did not. For children ages 12-18, male children of DVs had more EBP (lsmeans 63.73 vs. 43.51, P = 0.008), while female children of DVs had fewer EBP (lsmeans 45.50 vs. 50.48, P = 0.02). Veteran military characteristics and mental health, and children's social status and health, including obesity, predicted children's TBP for one or more age groups.

Conclusions: Children of DVs experienced worse dentition, greater obesity, and more behavioral problems compared to NDV children, suggesting adverse health effects associated with parental deployment in need of further exploration.

The insecticide deltamethrin enhances sodium channel slow inactivation of human Nav1.9, Nav1.8 and Nav1.7

Toxicol Appl Pharmacol. 2021 Oct 1; 428:115676. doi: 10.1016/j.taap.2021.115676. Epub 2021 Aug 10.

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Abstract

The insecticide deltamethrin of the pyrethroid class mainly targets voltage-gated sodium channels (Navs). Deltamethrin prolongs the opening of Navs by slowing down fast inactivation and deactivation. Pyrethroids are supposedly safe for humans, however, they have also been linked to the gulf-war syndrome, a neuropathic pain condition that can develop following exposure to certain chemicals. Inherited neuropathic pain conditions have been linked to mutations in the Nav subtypes Nav1.7, Nav1.8, and Nav1.9. Here, we examined the effect of deltamethrin on the human isoforms Nav1.7, Nav1.8, and Nav1.9_C4 (chimera containing the C-terminus of rat Nav1.4) heterologously expressed in HEK293T and ND7/23 cells using whole-cell patch-clamp electrophysiology. For all three Nav subtypes, we observed increased persistent and tail currents that are typical for Nav channels modified by deltamethrin. The most surprising finding was an enhanced slow inactivation induced by deltamethrin in all three Nav subtypes. An enhanced slow inactivation is contrary to the prolonged opening caused by pyrethroids and has not been described for deltamethrin or any other pyrethroid before. Furthermore, we found that the fraction of deltamethrin-modified channels increased use-dependently. However, for Nav1.8, the use-dependent potentiation occurred only when the holding potential was increased to -90 mV, a potential at which the tail currents decay more slowly. This indicates that use-dependent modification is due to an accumulation of tail currents. In summary, our findings support a novel mechanism whereby deltamethrin enhances slow inactivation of voltage-gated sodium channels, which may, depending on the cellular resting membrane potential, reduce neuronal excitability and counteract the well-described pyrethroid effects of prolonging channel opening.

Association of the tissue microstructural diffusivity and translocator protein PET in Gulf War Illness

Brain Behav Immun Health. 2021 Oct 6; 18:100364. doi: 10.1016/j.bbih.2021.100364. eCollection 2021 Dec.

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Abstract

About a third of all United States veterans who served in the 1991 Gulf War (GW) report a range of chronic health symptoms including fatigue, neurocognitive symptoms, and musculoskeletal pain. There is growing evidence supporting the detrimental effects of maladaptive neuroimmune reactions in this multi-symptom illness. Indeed, recent studies using positron emission tomography (PET) using the radioligand [11C]PBR28, which binds the neuroinflammation marker 18 kDa translocator protein (TSPO), and diffusion magnetic resonance imaging (dMRI) have independently identified the anterior cingulate (ACC) and midcingulate cortices (MCC) as key regions for differentiating GWI veterans from healthy controls (HC). Here, we used integrated (i.e., simultaneous) PET/MRI imaging techniques, paired with dMRI processing methods (neurite density imaging, NDI, and free-water diffusion tensor model to single-shell high-order dMRI), to directly evaluate the relationship between ACC and MCC microstructural tissue parameters, TSPO signal and clinical parameters in the same cohorts of 10 GWI veterans and 19 HCs. Within the regions evaluated, TSPO signal elevations were associated with restricted diffusivity in the extracellular compartment, while clinical measures were best explained by neurite density and cellular structure complexity measures. Our study is the first to provide evidence of a relationship between PET and dMRI modalities in GWI and suggests that microstructural changes in the ACC and MCC are correlated to mood symptoms and cognitive performances in GWI veterans.

The Department of Veterans Affairs Gulf War Veterans' Illnesses Biorepository: Supporting Research on Gulf War Veterans' Illnesses

Brain Sci. 2021 Oct 14; 11(10):1349. doi: 10.3390/brainsci11101349.

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Abstract

Aims: To introduce a resource supporting research on Gulf War illness (GWI) and related disorders, the Gulf War Veterans' Illnesses Biorepository (GWVIB).

Methods: Gulf War era veterans (GWVs) are recruited nationally and enrolled via telephone and email/postal mail. Enrolled veterans receive annual telephone and mail follow-up to collect health data until their passing. A postmortem neuropathological examination is performed, and fixed and frozen brain and spinal cord samples are banked to support research. Investigators studying GWI and related disorders may request tissue and data from the GWVIB.

Results: As of September 2021, 127 GWVs from 39 states were enrolled; 60 met the criteria for GWI, and 14 met the criteria for chronic multisymptom illness (CMI). Enrollees have been followed up to six years. Postmortem tissue recoveries were performed on 14 GWVs. The most commonly found neuropathologies included amyotrophic lateral sclerosis, chronic traumatic encephalopathy, and Lewy body disease. Tissue was of good quality with an average RNA integrity number of 5.8 (SD = 1.0) and ≥4.8 in all of the cases.

Discussion: The availability of health data and high-quality CNS tissue from this well-characterized GWV cohort will support research on GWI and related disorders affecting GWVs. Enrollment is ongoing.

Exposure to Gulf War Illness-related agents leads to the development of chronic pain and fatigue

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Abstract

Aims: A substantial contingent of veterans from the first Gulf War continues to suffer from a number of Gulf War-related illnesses (GWI) affecting the neurological and musculoskeletal systems; the most common symptoms include chronic pain and fatigue. Although animal models have recapitulated several aspects of cognitive impairments in GWI, the pain and fatigue symptoms have not been well documented to allow examination of potential pathogenic mechanisms.

Main methods: We used a mouse model of GWI by exposing mice repeatedly to a combination of Gulf War chemicals (pyridostigmine bromide, permethrin, DEET, and chlorpyrifos) and mild immobilization stress, followed by investigating their pain susceptibilities and fatigue symptoms. To assess whether enhanced antioxidant capacity can counter the effects of GW agents, transgenic mice overexpressing extracellular superoxide dismutase (SOD3OE) were also examined.

Key findings: The mouse model recapitulated several aspects of the human illness, including hyperalgesia, impaired descending inhibition of pain, and increased tonic pain. There is a close association between chronic pain and fatigue in GWI patients. Consistent with this observation, the mouse model showed a significant reduction in physical endurance on the treadmill. Examination of skeletal muscles suggested reduction in mitochondrial functions may have contributed to the fatigue symptoms. Furthermore, the negative impacts of GW agents in pain susceptibilities were largely diminished in SOD3OE mice, suggesting that increased oxidative stress was associated with the emergence of these Gulf War symptoms.

Significance: the mouse model will be suitable for delineating specific defects in the pain pathways and mechanisms of fatigue in GWI.

IL-17 and IL-17C Signaling Protects the Intestinal Epithelium against Diisopropyl Fluorophosphate Exposure in an Acute Model of Gulf War Veterans' Illnesses

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Abstract

Gulf War Veterans' Illnesses (GWI) encompasses a broad range of unexplained symptomology specific to Veterans of the Persian Gulf War. Gastrointestinal (GI) distress is prominent in veterans with GWI and often presents as irritable bowel syndrome (IBS). Neurotoxins, including organophosphorus pesticides and sarin gas, are believed to have contributed to the development of GWI, at least in a subset of Veterans. However, the effects of such agents have not been extensively studied for their potential impact to GI disorders and immunological stability. Here we utilized an established murine model of GWI to investigate deleterious effects of diisopropyl fluorophosphate (DFP) exposure on the mucosal epithelium in vivo and in vitro. In vivo, acute DFP exposure negatively impacts the mucosal epithelium by reducing tight junction proteins and antimicrobial peptides as well as altering intestinal microbiome composition. Furthermore, DFP treatment reduced the expression of IL-17 in the colonic epithelium. Conversely, both IL-17 and IL-17C treatment could combat the negative effects of DFP and other cholinesterase inhibitors in murine intestinal organoid cells. Our findings demonstrate that acute exposure to DFP can result in rapid deterioration of mechanisms protecting the GI tract from disease. These results are relevant to suspected GWI exposures and could help explain the propensity for GI disorders in GWI Veterans.

Persistent exercise fatigue and associative learning deficits in combination with transient glucose dyshomeostasis in a GWI mouse model

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Abstract

Aims: To characterize exercise fatigue, metabolic phenotype and cognitive and mood deficits correlated with brain neuroinflammatory and gut microbiome changes in a chronic GWI mouse model.

Main methods: Adult male C57Bl/6N mice were exposed for 28 days (5 days/week) to pyridostigmine bromide: 6.5 mg/kg/day, b.i.d., P.O. (GW1) or 8.7 mg/kg/day, q.d., P.O. (GW2); topical permethrin (1.3 mg/kg in 100% DMSO) and N,N-diethyl-meta-toluamid (DEET 33% in 70% EtOH) and restraint stress (5 min/day). Exercise, metabolic and behavioral endpoints were compared to sham stress control (CON/S).

Key findings: Relative to CON/S, GW2 presented persistent exercise intolerance (through post-treatment (PT) day 161), deficient associative learning, and transient insulin insensitivity. In contrast to GW2, GW1 showed deficient long-term object recognition memory and behavioral despair.

Significance: Our findings demonstrate that GW chemicals dose-dependently determine the severity of exercise fatigue and cognitive/mood-deficient phenotypes that show persistence. Our comprehensive mouse model of GWI recapitulates the major multiple symptoms/pathology characterizing GWI, including fatigue and cognitive impairment that can be used to more efficiently develop diagnostic tests and curative treatments for ill GWVs.

Associations of Immune Genetic Variability with Gulf War Illness in 1990-1991 Gulf War Veterans from the Gulf War Illness Consortium (GWIC) Multisite Case-Control Study

Veterans.Brain Sci. 2021 Oct 26; 11(11):1410. doi: 10.3390/brainsci11111410.

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Abstract

Gulf War illness (GWI) encompasses a constellation of persistent debilitating symptoms associated with significant changes in central nervous system (CNS) and immune functioning. Currently, there is no validated biomarker for GWI risk susceptibility. Given the impact of immune responses linked to GWI symptomology, genetic variability that causes persistent inflammatory/immune alterations may be key. This Boston University-based Gulf War Illness Consortium (GWIC) study investigated the impact of single nucleotide polymorphisms (SNPs) in variants of immune and pain genetic markers IL1B, IL2, IL6, IL6R, IL10, TNF, TGF, TLR2, TLR4, MD2, MYD88, BDNF, CRP, ICE, COMT and OPRM1 on GWI occurrence in a Caucasian subset of Gulf War (GW) veterans with (cases, n = 170) and without (controls, n = 34) GWI. Logistic regression modeling created a prediction model of GWI risk that associated genetic variability in TGF (rs1800469, p = 0.009), IL6R (rs8192284, p = 0.004) and TLR4 (rs4986791, p = 0.013) with GWI occurrence. This prediction model was specific and sensitive, with a receiver operator characteristic area under the curve of 71.4%. This is the first report of immune genetic variability being predictive of GWI and warrants validation in larger independent cohorts. Future reports will present interactions of these genetic risk factors with other characteristics of GW service.

Gulf War Era Veterans' perspectives on research: a qualitative study

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Abstract

Aims: Many veterans of the 1990-1991 Gulf War Era (GWE) have experienced poorly understood health issues. In response to challenges recruiting this population for research, we conducted focus groups and semi-structured phone interviews with GWE veterans and subject matter experts (SMEs) to explore GWE veterans' perceptions about research.

Main methods: Transcribed discussions were content-analyzed. Participants discussed research-related motivators and barriers identified among other populations, and nuances that may be specific to GWE veterans.

Key findings: Examples of motivating factors included: seeking answers about causes of and treatment for health issues; helping oneself; and helping other veterans. Examples of barriers included: distrust and dissatisfaction with federal entities; lack of research follow-through; and concerns about privacy and confidentiality.

Significance: Researchers can use this information to better address GWE veterans' concerns and motivate them to participate in research. Inclusion of GWE veterans in research will allow researchers and clinicians to better understand and address health issues affecting this population.

A cellular approach to understanding and treating Gulf War Illness

Cell Mol Life Sci. 2021 Nov; 78(21-22):6941-6961. doi: 10.1007/s00018-021-03942-3. Epub 2021 Sep 27.

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Abstract

Gulf War Illness (GWI), a disorder suffered by approximately 200,000 veterans of the first Gulf War, was caused by exposure to low-level organophosphate pesticides and nerve agents in combination with battlefield stress. To elucidate the mechanistic basis of the brain-related symptoms of GWI, human-induced pluripotent stem cells (hiPSCs) derived from veterans with or without GWI were differentiated into forebrain glutamatergic neurons and then exposed to a Gulf War (GW) relevant toxicant regimen consisting of a sarin analog and cortisol, a human stress hormone. Elevated levels of total and phosphorylated tau, reduced microtubule acetylation, altered mitochondrial dynamics/transport, and decreased neuronal activity were observed in neurons exposed to the toxicant regimen. Some of the data are consistent with the possibility that some veterans may have been predisposed to acquire GWI. Wistar rats exposed to a similar toxicant regimen showed a mild learning and memory deficit, as well as cell loss and tau pathology selectively in the CA3 region of the hippocampus. These cellular responses offer a mechanistic explanation for the memory loss suffered by veterans with GWI and provide a cell-based model for screening drugs and developing personalized therapies for these veterans.

Yoga is effective in treating symptoms of Gulf War illness: A randomized clinical trial

Randomized Controlled Trial J Psychiatr Res. 2021 Nov; 143:563-571. doi: 10.1016/j.jpsychires.2020.11.024. Epub 2020 Nov 11.

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Abstract

Many Veterans of the 1990-1991 Gulf War report symptoms of Gulf War Illness, a condition involving numerous chronic symptoms including pain, fatigue, and mood/cognition symptoms. Little is known about this condition's etiology and treatment. This study reports outcomes from a randomized controlled single-blind trial comparing yoga to cognitive behavioral therapy for chronic pain and other symptoms of Gulf War Illness. Participants were Veterans with symptoms of GWI: chronic pain, fatigue and cognition-mood symptoms. Seventy-five Veterans were randomized to treatment via selection of envelopes from a bag (39 yoga, 36 cognitive behavioral therapy), which consisted of ten weekly group sessions. The primary outcomes of pain severity and interference (Brief Pain Inventory- Short Form) improved in the yoga condition (Cohen's d = .35, p = 0.002 and d = 0.69, p < 0.001, respectively) but not in the CBT condition (d = 0.10, p = 0.59 and d = 0.25 p = 0.23). However, the differences between groups were not statistically significant (d = 0.25, p = 0.25; d = 0.43, p = 0.076), though the difference in an a-priori-defined experimental outcome variable which combines these two variables into a total pain variable (d = 0.47, p = 0.047) was significant. Fatigue, as indicated by a measure of functional exercise capacity (6-min walk test) was reduced significantly more in the yoga group than in the CBT group (between-group d = .27, p = 0.044). Other secondary outcomes of depression, wellbeing, and self-reported autonomic nervous system symptoms did not differ between groups. No adverse events due to treatment were reported. Yoga may be an effective treatment for core Gulf War Illness symptoms of pain and fatigue, making it one of few treatments with empirical support for GWI. Results support further evaluation of yoga for treating veterans with Gulf War Illness. CLINICAL TRIAL REGISTRY: clinicaltrials.gov Registration

Neuropathological profile of long-duration amyotrophic lateral sclerosis in military Veterans

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Abstract

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder affecting both the upper and lower motor neurons. Although ALS typically leads to death within 3 to 5 years after initial symptom onset, approximately 10% of patients with ALS live more than 10 years after symptom onset. We set out to determine similarities and differences in clinical presentation and neuropathology in persons with ALS with long vs. those with standard duration. Participants were United States military Veterans with a pathologically confirmed diagnosis of ALS (n = 179), dichotomized into standard duration (<10 years) and long-duration (≥10 years). The ALS Functional Rating Scale-Revised (ALSFRS-R) was administered at study entry and semi-annually thereafter until death. Microglial density was determined in a subset of participants. long-duration ALS occurred in 76 participants (42%) with a mean disease duration of 16.3 years (min/max = 10.1/42.2). Participants with long-duration ALS were younger at disease onset (P = 0.002), had a slower initial ALS symptom progression on the ALSFRS-R (P < 0.001) and took longer to diagnose (P < 0.002) than standard duration ALS. Pathologically, long-duration ALS was associated with less frequent TDP-43 pathology (P < 0.001). Upper motor neuron degeneration was similar; however, long-duration ALS participants had less severe lower motor neuron degeneration at death (P < 0.001). In addition, the density of microglia was decreased in the corticospinal tract (P = 0.017) and spinal cord anterior horn (P = 0.009) in long-duration ALS. Notably, many neuropathological markers of ALS were similar between the standard and long-duration groups and there was no difference in the frequency of known ALS genetic mutations. These findings suggest that the lower motor neuron system is relatively spared in long-duration ALS and that pathological progression is likely slowed by as yet unknown genetic and environmental modifiers.

Boston biorepository, recruitment and integrative network (BBRAIN): A resource for the Gulf War Illness scientific community

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Abstract

Aims: Gulf War Illness (GWI), a chronic debilitating disorder characterized by fatigue, joint pain, cognitive, gastrointestinal, respiratory, and skin problems, is currently diagnosed by self-reported symptoms. The Boston Biorepository, Recruitment, and Integrative Network (BBRAIN) is the collaborative effort of expert Gulf War Illness (GWI) researchers who are creating objective diagnostic and pathobiological markers and recommend common data elements for GWI research.

Main methods: BBRAIN is recruiting 300 GWI cases and 200 GW veteran controls for the prospective study. Key data and biological samples from prior GWI studies are being merged and combined into retrospective datasets. They will be made available for data mining by the BBRAIN network and the GWI research community. Prospective questionnaire data include general health and chronic symptoms, demographics, measures of pain, fatigue, medical conditions, deployment and exposure histories. Available repository biospecimens include blood, plasma, serum, saliva, stool, urine, human induced pluripotent stem cells and cerebrospinal fluid.

Key findings: To date, multiple datasets have been merged and combined from 15 participating study sites. These data and samples have been collated and an online request form for repository requests as well as recommended common data elements have been created. Data and biospecimen sample requests are reviewed by the BBRAIN steering committee members for approval as they are received.

Significance: The BBRAIN repository network serves as a much needed resource for GWI researchers to utilize for identification and validation of objective diagnostic and pathobiological markers of the illness.

Collage-based graphic elicitation method for capturing the lived experiences of veterans with Gulf War illness

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Abstract

Aims: Graphic elicitation is an emergent data gathering approach in qualitative research. An overview of the development and application of a collage based graphic elicitation method in gaining greater understanding about the experience of Gulf War Illness (GWI) is presented in this paper. The unique contributions of this method are also discussed.

Main methods: Fourteen veterans with GWI were interviewed and then invited to represent their experiences in a visual format through a collage graphic elicitation task. Interviews and collage artworks were coded and compared to both verbal and art responses during the graphic elicitation process.

Key findings: Comparison of the content in the interview responses and collage artwork indicates that the graphic elicitation process resulted in three distinct responses: (1) Synthesis and confirmation of content articulated in the interviews, (2) focus on salient aspects of living with GWI, and (3) revealing previously unarticulated experiences.

Significance: This work demonstrates the unique contributions of collage graphic elicitation, including allowing for spontaneity, metaphorical thinking, enriching verbal explication, and uncovering lived experiences and new affective responses. The sample size was too small to make any generalizations, and more research is needed to further validate these initial findings.

A cohort study of neuropsychological functioning in spouses of U.S. Gulf War veterans

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Abstract

Aims: Veterans of the 1991 Gulf War reported symptoms in their spouses that mirrored veterans' symptoms following their return from the war, including problems with attention and memory. Neuropsychological functioning in these spouses has not been examined with objective tests. This study sought to determine if these spouses exhibited deficits in neuropsychological functioning.

Main methods: Spouses of a national cohort of 1991 Gulf War deployed (n = 470) and non-deployed veterans (n = 524) were examined with neuropsychological tests in 1999-2001.

Key findings: Neuropsychological tests were factor analyzed yielding five factors: verbal memory, visual memory, attention/working memory, visual organization, and motor speed. Spouses of deployed and nondeployed veterans did not differ on mean factor scores, percentage of impaired factors, or individual test scores. Spouse attention/working memory was related to their having diagnoses of PTSD or anxiety disorders, or self-reported symptoms of current anxiety. Spouse visual memory was related to a diagnosis of current depression. Spouse motor speed was related to their own status of having chronic multisymptom illness (CMI).

Significance: Spouses of Gulf War deployed and nondeployed veterans demonstrated similar neuropsychological functioning, although spouses with psychiatric diagnoses and symptoms, or CMI demonstrated neuropsychological impairments characteristic of those conditions, suggesting that monitoring spouses for these conditions and impairments may be warranted. This pattern of relative weaknesses mirrors some of the previously reported findings for Gulf War veterans, although the veterans displayed neuropsychological impairments beyond what was accounted for by these conditions.

Acute gene expression changes in the mouse hippocampus following a combined Gulf War toxicant exposure

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Abstract

Aims: Approximately 30% of the nearly 700,000 Veterans who were deployed to the Gulf War from 1990 to 1991 have reported experiencing a variety of symptoms including difficulties with learning and memory, depression and anxiety, and increased incidence of neurodegenerative diseases. Combined toxicant exposure to acetylcholinesterase (AChE) inhibitors has been studied extensively as a likely risk factor. In this study, we modeled Gulf War exposure in male C57Bl/6J mice with simultaneous administration of three chemicals implicated as exposure hazards for Gulf War Veterans: pyridostigmine bromide, the anti-sarin prophylactic; chlorpyrifos, an organophosphate insecticide; and the repellant N,N-diethyl-m-toluamide (DEET).

Main methods: Following two weeks of daily exposure, we examined changes in gene expression by whole transcriptome sequencing (RNA-Seq) with hippocampal isolates. Hippocampal-associated spatial memory was assessed with a Y-maze task. We hypothesized that genes important for neuronal health become dysregulated by toxicant-induced damage and that these detrimental inflammatory gene expression profiles could lead to chronic neurodegeneration.

Key findings: We found dysregulation of genes indicating a pro-inflammatory response and downregulation of genes associated with neuronal health and several important immediate early genes (IEGs), including Arc and Egr1, which were both reduced approximately 1.5-fold. Mice exposed to PB + CPF + DEET displayed a 1.6-fold reduction in preference for the novel arm, indicating impaired spatial memory.

Significance: Differentially expressed genes observed at an acute timepoint may provide insight into the pathophysiology of Gulf War Illness and further explanations for chronic neurodegeneration after toxicant exposure.

Healthcare providers' perceived learning needs and barriers to providing care for chronic multisymptom illness and environmental exposure concerns

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Abstract

Objective: Patient provider encounters for chronic multisympom illness (CMI) and/or environmental exposures are difficult often resulting in Veterans and providers having high levels of dissatisfaction. Patients attribute these difficulties to providers lacking knowledge about these health concerns. It is not known whether providers perceive themselves as lacking expertise in CMI and environmental exposure concerns.

Methods: This needs assessment used a descriptive online survey design. A total of 3632 VA healthcare providers across disciplines were surveyed.

Results: Healthcare providers reported speaking with Veterans about CMI and environmental exposures despite feeling they have minimal to no knowledge of these topics. At the same time, only half of the providers had taken an available training on CMI or environmental exposure within the last year.

Conclusion: Healthcare providers recognize a knowledge gap regarding CMI and environmental exposures, despite this, there is low uptake of provider education on these topics.

Practice implications: A better understanding of barriers to uptake of training on CMI and environmental exposures is needed to increase engagement with these important trainings.

Keywords: Exposures; Functional somatic disorder; Functional somatic syndrome; Gulf war illness; Medical education; Medically unexplained symptoms; Needs assessment; Online survey; Persistent physical symptoms; Physician training; Provider training; Toxic exposure; Veterans.

The Gulf War Era Cohort and Biorepository: A Longitudinal Research Resource of Veterans of the 1990-1991 Gulf War Era

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Abstract

The US Department of Veterans Affairs (VA) Gulf War Era Cohort and Biorepository (GWECB) is a nationally representative longitudinal cohort of US veterans who served during the 1990-1991 Gulf War era. The GWECB combines survey data, such as demographic, health behavior, and environmental exposure data; medical records; and a linked biorepository of blood specimens that can support a broad range of future research regarding health concerns unique to veterans of this era. To build this resource, the VA Cooperative Studies Program initiated a pilot study (2014-2016) to establish the GWECB and evaluate the processes required to build and maintain the resource. Participants (n = 1,275) consented to future sharing of their data and biospecimens for research purposes. Here we describe the pilot study, including recruitment and enrollment procedures, data collection and management, quality control, and challenges experienced. The GWECB data available to investigators under approved sharing mechanisms and the procedures for accessing them are extensively detailed. The study's consenting documents and a website link for the research survey are provided. Our hope is that new research drawing on the GWECB data and biospecimens will result in effective treatments and improved approaches to address the health concerns of Gulf War-era veterans.

Restorative potential of (-)-epicatechin in a rat model of Gulf War illness muscle atrophy and fatigue

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Abstract

We examined in a rat model of Gulf War illness (GWI), the potential of (-)-epicatechin (Epi) to reverse skeletal muscle (SkM) atrophy and dysfunction, decrease mediators of inflammation and normalize metabolic perturbations. Male Wistar rats (n = 15) were provided orally with pyridostigmine bromide (PB) 1.3 mg/kg/day, permethrin (PM) 0.13 mg/kg/day (skin), DEET 40 mg/kg/day (skin) and were physically restrained for 5 min/day for 3 weeks. A one-week period ensued to fully develop the GWI-like profile followed by 2 weeks of either Epi treatment at 1 mg/kg/day by gavage (n = 8) or water (n = 7) for controls. A normal, control group (n = 15) was given vehicle and not restrained. At 6 weeks, animals were subjected to treadmill and limb strength testing followed by euthanasia. SkM and blood sampling was used for histological, biochemical and plasma pro-inflammatory cytokine and metabolomics assessments. GWI animals developed an intoxication profile characterized SkM atrophy and loss of function accompanied by increases in modulators of muscle atrophy, degradation markers and plasma pro-inflammatory cytokine levels. Treatment of GWI animals with Epi yielded either a significant partial or full normalization of the above stated indicators relative to normal controls. Plasma metabolomics revealed that metabolites linked to inflammation and SkM waste pathways were dysregulated in the GWI group whereas Epi, attenuated such changes. In conclusion, in a rat model of GWI, Epi partially reverses detrimental changes in SkM structure including modulators of atrophy, inflammation and select plasma metabolites yielding improved function.

Dry eye symptoms and signs in US veterans with Gulf War Illness

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Abstract

Purpose: To examine dry eye (DE) symptoms and signs in individuals with versus without Gulf War Illness (GWI).

Design: Prospective cross-sectional study.

Methods: We performed a prospective, cross-sectional study of South Florida veterans who were active duty during the Gulf War Era (GWE; 1990-91) and seen at an eye clinic between October 1, 2020, and March 13, 2021. Veterans were split into two groups: those who met Kansas criteria for GWI (cases, N=30) and those who did not (controls, N=41). DE symptoms were assessed via standardized questionnaires while DE signs were assessed using a series of ocular surface parameters. Differences between groups were assessed via Mann-Whitney U test. Linear regressions analyses were used to examine which GWI symptoms most closely aligned with DE symptoms.

Results: Veterans with GWI had higher DE symptoms scores compared to controls (Ocular Surface Disease Index (OSDI) scores: mean 41.20±22.92 vs 27.99±24.03, p=0.01). In addition, veterans with GWI had higher eye pain scores compared to controls (average eye pain over past week: 2.63±2.72 vs 1.22±1.50, p=0.03), including on neuropathic ocular pain questionnaires (Neuropathic Pain Symptom Inventory- modified for the Eye (NPSI-E): 17.33±17.20 vs 9.63±12.64, p=0.03). DE signs were mostly similar between the groups. GWI symptoms "nausea or upset stomach" (β=14.58. SE=3.02, p<0.001) and "headache" (β=7.90, SE=2.91, p=0.011) correlated with higher OSDI scores.

Conclusion: Individuals with GWI have more severe DE symptoms and ocular pain scores but similar tear and ocular surface parameters compared to controls without GWI. This finding suggests that mechanisms beyond tear dysfunction drive eye symptoms in GWI.

The β-adrenergic receptor blocker and anti-inflammatory drug propranolol mitigates brain cytokine expression in a long-term model of Gulf War Illness

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Abstract

Aims: Growing evidence suggests that Gulf War Illness (GWI) is the result of underlying neuroimmune dysfunction. For example, previously we found that several GWI-relevant organophosphate acetylcholinesterase inhibitors produce heightened neuroinflammatory responses following subchronic exposure to stress hormone as a mimic of high physiological stress. The goal of the current study was to evaluate the potential for the β-adrenergic receptor inhibitor and anti-inflammatory drug, propranolol, to treat neuroinflammation in a novel long-term mouse model of GWI.

Main methods: Adult male C57BL/6J mice received a subchronic exposure to corticosterone (CORT) at levels mimicking high physiological stress followed by exposure to the sarin surrogate, diisopropyl fluorophosphate (DFP). These mice were then re-exposed to CORT every other week for a total of five weeks, followed by a systemic immune challenge with lipopolysaccharide (LPS). Animals receiving the propranolol treatment were given a single dose (20 mg/kg, i.p.) either four or 11 days prior to the LPS challenge. The potential anti-neuroinflammatory effects of propranolol were interrogated by analysis of cytokine mRNA expression.

Key findings: We found that our long-term GWI model produces a primed neuroinflammatory response to subsequent immune challenge that is dependent upon GWI-relevant organophosphate exposure. Propranolol treatment abrogated the elaboration of inflammatory cytokine mRNA expression in the brain instigated in our model, having no treatment effects in non-DFP exposed groups.

Significance: Our results indicate that propranolol may be a promising therapy for GWI with the potential to treat the underlying neuroinflammation associated with the illness.

Long-term changes in neuroimaging markers, cognitive function and psychiatric symptoms in an experimental model of Gulf War Illness

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Abstract

Aims: Gulf War Illness (GWI) is a multi-symptom disease with debilitating cognitive and emotional impairments in veterans. GWI, like epilepsy, is caused by chemical neurotoxicity and manifests from disturbances in neuronal excitability. However, the mechanisms underlying such devastating neurological and psychiatric symptoms remain unclear. Here we investigated the long-term changes in neural behavior and brain structural abnormalities in a rat model of GWI. GWI is linked to exposure to GWI-related organophosphate chemicals (pyridostigmine bromide or PB and insecticide DEET, permethrin) during the stressful Gulf war.

Methods: To mimic GWI, we generated an experimental GWI prototype in rats by daily exposure to GWI-related chemicals with restraint stress (GWIR-CS) for 4 weeks. Changes in MRI scan and cognitive function were assessed at 5- and 10- months post-exposure.

Key findings: In MRI scans, rats displayed significant increases in lateral ventricle T2 relaxation times at both 5- and 10-months after GWIR-CS, indicating alterations in the cerebrospinal fluid (CSF) density. Furthermore, at 10 months, there were significant decreases in the volumes of the hippocampus and thalamus and an increase in the lateral ventricle volume. At both time points, they exhibited impairments in multiple neurobehavioral tests, confirming substantial deficits in memory and mood function. GWI-CS rats also displayed aggressive behavior and a marked decrease in social interaction and forced swimming, indicating depression.

Conclusions: These results confirm that chronic GWIR-CS exposure led to cognitive and psychiatric symptoms with concurrent neuroimaging abnormalities in CSF, with morphological neural lesions, demonstrating the role of divergent etiological mechanisms in GWI and its comorbidities.

Induction of distinct neuroinflammatory markers and gut dysbiosis by differential pyridostigmine bromide dosing in a chronic mouse model of GWI showing persistent exercise fatigue and cognitive impairment

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Abstract

Aims: To characterize neuroinflammatory and gut dysbiosis signatures that accompany exaggerated exercise fatigue and cognitive/mood deficits in a mouse model of Gulf War Illness (GWI).

Methods: Adult male C57Bl/6N mice were exposed for 28 d (5 d/wk) to pyridostigmine bromide (P.O.) at 6.5 mg/kg/d, b.i.d. (GW1) or 8.7 mg/kg/d, q.d. (GW2); topical permethrin (1.3 mg/kg), topical N,N-diethyl-meta-toluamide (33%) and restraint stress (5 min). Animals were phenotypically evaluated as described in an accompanying article [124] and sacrificed at 6.6 months post-treatment (PT) to allow measurement of brain neuroinflammation/neuropathic pain gene expression, hippocampal glial fibrillary acidic protein, brain Interleukin-6, gut dysbiosis and serum endotoxin.

Key findings: Compared to GW1, GW2 showed a more intense neuroinflammatory transcriptional signature relative to sham stress controls. Interleukin-6 was elevated in GW2 and astrogliosis in hippocampal CA1 was seen in both GW groups. Beta-diversity PCoA using weighted Unifrac revealed that gut microbial communities changed after exposure to GW2 at PT188. Both GW1 and GW2 displayed systemic endotoxemia, suggesting a gut-brain mechanism underlies the neuropathological signatures. Using germ-free mice, probiotic supplementation with Lactobacillus reuteri produced less gut permeability than microbiota transplantation using GW2 feces.

Significance: Our findings demonstrate that GW agents dose-dependently induce differential neuropathology and gut dysbiosis associated with cognitive, exercise fatigue and mood GWI phenotypes. Establishment of a comprehensive animal model that recapitulates multiple GWI symptom domains and neuroinflammation has significant implications for uncovering pathophysiology, improving diagnosis and treatment for GWI.

Differential Effects of Exercise on fMRI of the Midbrain Ascending Arousal Network Nuclei in Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS) and Gulf War Illness (GWI) in a Model of Postexertional Malaise (PEM)

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Abstract:

Background: Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS), Gulf War Illness (GWI) and control subjects had fMRI during difficult cognitive tests performed before and after submaximal exercise provocation (Washington 2020). Exercise caused increased activation in ME/CFS but decreased activation for GWI in the dorsal midbrain, left Rolandic operculum and right middle insula. Midbrain and isthmus nuclei participate in threat assessment, attention, cognition, mood, pain, sleep, and autonomic dysfunction. Methods: Activated midbrain nuclei were inferred by re-analysis of data from 31 control, 36 ME/CFS and 78 GWI subjects using a seed region approach and the Harvard Ascending Arousal Network. Results: Before exercise, control and GWI had greater activation during cognition than ME/CFS in left pedunculotegmental nucleus. Postexercise ME/CFS had greater activation than GWI for midline periaqueductal gray, dorsal and median raphe, and right midbrain reticular formation, parabrachial complex and locus coeruleus. The change between days (delta) was positive for ME/CFS but negative for GWI indicating reciprocal patterns of activation. Controls had no changes. Conclusions: Exercise caused opposite effects with increased activation in ME/CFS but decreased activation in GWI indicating different pathophysiological responses to exertion and mechanisms of disease. Midbrain and isthmus nuclei contribute to postexertional malaise in ME/CFS and GWI.

Microglial ERK-NRBP1-CREB-BDNF signaling in sustained antidepressant actions of (R)-ketamine

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Correction: Microglial ERK-NRBP1-CREB-BDNF signaling in sustained antidepressant actions of (R)-ketamine.

Mol Psychiatry. 2021 Dec 8. doi: 10.1038/s41380-021-01417-2. Online ahead of print.

Yao W, Cao Q, Luo S, He L, Yang C, Chen J, Qi Q, Hashimoto K, Zhang JC.

Abstract

(R,S)-ketamine elicits rapid-acting and sustained antidepressant actions in treatment-resistant patients with depression. (R)-ketamine produces longer-lasting antidepressant effects than (S)-ketamine in rodents; however, the precise molecular mechanisms underlying antidepressant actions of (R)-ketamine remain unknown. Using isobaric Tag for Relative and Absolute Quantification, we identified nuclear receptor-binding protein 1 (NRBP1) that could contribute to different antidepressant-like effects of the two enantiomers in chronic social defeat stress (CSDS) model. NRBP1 was localized in the microglia and neuron, not astrocyte, of mouse medial prefrontal cortex (mPFC). (R)-ketamine increased the expression of NRBP1, brain-derived neurotrophic factor (BDNF), and phosphorylated cAMP response element binding protein (p-CREB)/CREB ratio in primary microglia cultures thorough the extracellular signal-regulated kinase (ERK) activation. Furthermore, (R)-ketamine could activate BDNF transcription through activation of CREB as well as MeCP2 (methyl-CpG binding protein 2) suppression in microglia. Single intracerebroventricular (i.c.v.) injection of CREB-DNA/RNA heteroduplex oligonucleotides (CREB-HDO) or BDNF exon IV-HDO blocked the antidepressant-like effects of (R)-ketamine in CSDS susceptible mice. Moreover, microglial depletion by colony-stimulating factor 1 receptor (CSF1R) inhibitor PLX3397 blocked the antidepressant-like effects of (R)-ketamine in CSDS susceptible mice. In addition, inhibition of microglia by single i.c.v. injection of mannosylated clodronate liposomes (MCLs) significantly blocked the antidepressant-like effects of (R)-ketamine in CSDS susceptible mice. Finally, single i.c.v. injection of CREB-HDO, BDNF exon IV-HDO or MCLs blocked the beneficial effects of (R)-ketamine on the reduced dendritic spine density in the mPFC of CSDS susceptible mice. These data suggest a novel ERK-NRBP1-CREB-BDNF pathways in microglia underlying antidepressant-like effects of (R)-ketamine.

Gene–Toxicant Interactions in Gulf War Illness: Differential Effects of the PON1 Genotype

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Abstract

About 25–35% of United States veterans who fought in the 1990–1991 Gulf War report several moderate or severe chronic systemic symptoms, defined as Gulf War illness (GWI). Thirty years later, there is little consensus on the causes or biological underpinnings of GWI. The Gulf War Era Cohort and Biorepository (GWECB) was designed to investigate genetic and environmental associations with GWI and consists of 1343 veterans. We investigate candidate gene–toxicant interactions that may be associated with GWI based on prior associations found in human and animal model studies, focusing on SNPs in or near ACHE, BCHE, and PON1 genes to replicate results from prior studies. SOD1 was also considered as a candidate gene. CDC Severe GWI, the primary outcome, was observed in 26% of the 810 deployed veterans included in this study. The interaction between the candidate SNP rs662 and pyridostigmine bromide (PB) pills was found to be associated with CDC Severe GWI. Interactions between PB pill exposure and rs3917545, rs3917550, and rs2299255, all in high linkage disequilibrium in PON1, were also associated with respiratory symptoms. These SNPs could point toward biological pathways through which GWI may develop, which could lead to biomarkers to detect GWI or to better treatment options for veterans with GWI.

Under-recognition of medically unexplained symptom conditions among US Veterans with Gulf War Illness

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Abstract

Objective: Conditions defined by persistent "medically unexplained" physical symptoms and syndromes (MUS) are common and disabling. Veterans from the Gulf War (deployed 1990-1991) have notably high prevalence and disability from MUS conditions. Individuals with MUS report that providers do not recognize their MUS conditions. Our goal was to determine if Veterans with MUS receive an ICD-10 diagnosis for a MUS condition or receive disability benefits available to them for these conditions.

Methods: A chart review was conducted with US Veterans who met case criteria for Gulf War Illness, a complex MUS condition (N = 204, M = 53 years-old, SD = 7). Three coders independently reviewed Veteran's medical records for MUS condition diagnosis or service-connection along with comorbid mental and physical health conditions. Service-connection refers to US Veterans Affairs disability benefits eligibility for conditions or injuries experienced during or exacerbated by military service.

Results: Twenty-nine percent had a diagnosis of a MUS condition in their medical record, the most common were irritable colon/irritable bowel syndrome (16%) and fibromyalgia (11%). Slightly more Veterans were service-connected for a MUS condition (38%) as compared to diagnosed. There were high rates of diagnoses and service-connection for mental health (diagnoses 76% and service-connection 74%), musculoskeletal (diagnoses 86%, service-connection 79%), and illness-related conditions (diagnoses 98%, service-connection 49%).

Conclusion: Given that all participants were Gulf War Veterans who met criteria for a MUS condition, our results suggest that MUS conditions in Gulf War Veterans are under-recognized with regard to clinical diagnosis and service-connected disability. Veterans were more likely to be diagnosed and service-connected for musculoskeletal-related and mental health conditions than MUS conditions. Providers may need education and training to facilitate diagnosis of and service-connection for MUS conditions. We believe that greater acknowledgement and validation of MUS

conditions would increase patient engagement with healthcare as well as provider and patient satisfaction with care.

Development of KVO treatment strategies for chronic pain in a rat model of Gulf War Illness

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Abstract

We examined whether combinations of Kv7 channel openers could be effective modifiers of deep tissue nociceptor activity; and whether such combinations could then be optimized for use as safe analgesics for pain-like signs that developed in a rat model of GWI (Gulf War Illness) pain. Voltage clamp experiments were performed on subclassified nociceptors isolated from rat DRG (dorsal root ganglion). A stepped voltage protocol was applied (-55 to -40 mV; Vh = -60 mV; 1500 ms) and Kv7 evoked currents were subsequently isolated by linopirdine subtraction. Directly activated and voltage activated K+ currents were characterized in the presence and absence of Retigabine (5-100 μM) and/or Diclofenac (50-140 μM). Retigabine produced substantial voltage dependent effects and a maximal sustained current of 1.14 pA/pF ± 0.15 (ED50: 62.7 ± 3.18 μM). Diclofenac produced weak voltage dependent effects but a similar maximum sustained current of 1.01 ± 0.26 pA/pF (ED50: 93.2 ± 8.99 μM). Combinations of Retigabine and Diclofenac substantially amplified resting currents but had little effect on voltage dependence. Using a cholinergic challenge test (Oxotremorine, 10 μM) associated with our GWI rat model, combinations of Retigabine (5 uM) and Diclofenac (2.5, 20 and 50 μM) substantially reduced or totally abrogated action potential discharge to the cholinergic challenge. When combinations of Retigabine and Diclofenac were used to relieve pain-signs in our rat model of GWI, only those combinations associated with serious subacute side effects could relieve pain-like behaviors.

Gulf War Era Veterans' perspectives on research: a qualitative study

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Abstract

Aims: Many veterans of the 1990-1991 Gulf War Era (GWE) have experienced poorly understood health issues. In response to challenges recruiting this population for research, we conducted focus groups and semi-structured phone interviews with GWE veterans and subject matter experts (SMEs) to explore GWE veterans' perceptions about research.

Main methods: Transcribed discussions were content-analyzed. Participants discussed research-related motivators and barriers identified among other populations, and nuances that may be specific to GWE veterans.

Key findings: Examples of motivating factors included: seeking answers about causes of and treatment for health issues; helping oneself; and helping other veterans. Examples of barriers included: distrust and dissatisfaction with federal entities; lack of research follow-through; and concerns about privacy and confidentiality.

Significance: Researchers can use this information to better address GWE veterans' concerns and motivate them to participate in research. Inclusion of GWE veterans in research will allow researchers and clinicians to better understand and address health issues affecting this population.

Submaximal Exercise Provokes Increased Activation of the Anterior Default Mode Network During the Resting State as a Biomarker of Postexertional Malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Front Neurosci. 2021 Dec 15; 15:748426. doi: 10.3389/fnins.2021.748426. eCollection 2021.

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Abstract

Background: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is characterized by disabling fatigue and postexertional malaise. We developed a provocation paradigm with two submaximal bicycle exercise stress tests on consecutive days bracketed by magnetic resonance imaging, orthostatic intolerance, and symptom assessments before and after exercise in order to induce objective changes of exercise induced symptom exacerbation and cognitive dysfunction. Method: Blood oxygenation level dependent (BOLD) scans were performed while at rest on the preexercise and postexercise days in 34 ME/CFS and 24 control subjects. Seed regions from the FSL data library with significant BOLD signals were nodes that clustered into networks using independent component analysis. Differences in signal amplitudes between groups on pre- and post-exercise days were determined by general linear model and ANOVA. Results: The most striking exercise-induced effect in ME/CFS was the increased spontaneous activity in the medial prefrontal cortex that is the anterior node of the Default Mode Network (DMN). In contrast, this region had decreased activation for controls. Overall, controls had higher BOLD signals suggesting reduced global cerebral blood flow in ME/CFS. Conclusion: The dynamic increase in activation of the anterior DMN node after exercise may be a biomarker of postexertional malaise and symptom exacerbation in CFS. The specificity of this postexertional finding in ME/CFS can now be assessed by comparison to post-COVID fatigue, Gulf War Illness, fibromyalgia, chronic idiopathic fatigue, and fatigue in systemic medical and psychiatric diseases.

Evaluation of the Completeness of ALS Case Ascertainment in the U.S. National ALS Registry: Application of the Capture-Recapture Method

Neuroepidemiology. 2021 Dec 20. doi: 10.1159/000521591. Online ahead of print.

Lorene M Nelson, Barbara Topol, Wendy Kaye, Jaime Raymond, D Kevin Horton, Paul Mehta, Todd Wagner

Abstract

Introduction: The Centers for Disease Control and Prevention (CDC) National Amyotrophic Lateral Sclerosis (ALS) Registry is the first national registry for a chronic neurologic disease in the U.S. and uses a combination of case-finding methods including administrative healthcare data and patient self-registration.

Methods: We applied capture-recapture methodology to estimate the completeness of the Registry for ascertaining patients with ALS for the first full year and the fourth years of the Registry (2011, 2014). The Registry uses the combination of two national administrative claims databases (Medicare and Veterans Affairs) with a self-register option at the registry portal. We conducted descriptive analyses of the demographic and clinical characteristics of the ALS cases identified by each of the sources and estimated the completeness of case ascertainment for each of the three ALS Registry sources individually, pairwise, and in all combinations.

Results: Case-finding completeness was 54% in 2011 and improved to 56% in 2014. A smaller proportion of ALS patients under age 65 were ascertained than those 65 or older and ascertainment was also lower for non-White than White patients. The uncorrected ALS prevalence was 4.3/100,000 in 2011 (in 2014 5.0/100,000), but after correction for under-ascertainment, annual prevalence in 2011 was 7.9/100,000 (95% CI 7.6-8.2) (in 2014 was 8.9/100,000 (95% CI 8.7-9.2)).

Discussion/conclusion: Our findings indicate that administrative healthcare databases are a very efficient method for identifying the majority of ALS prevalent cases in the National ALS Registry and that the inclusion of a web registry portal for patients to self-register is important to ensure a more representative population for estimating ALS prevalence. Nonetheless, more than 40% of ALS cases were not ascertained by the Registry, with individuals younger than age 65 and people of color underrepresented. Recommendations are provided for additional methods that can be considered to improve the completeness of case ascertainment.

Self-Reported Autonomic Dysregulation in Gulf War Illness

Mil Med. 2021 Dec 30; usab546. doi: 10.1093/milmed/usab546. Online ahead of print.

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Abstract

Introduction: Autonomic nervous system dysregulation is commonly observed in Gulf War illness (GWI). Using a new sample, we sought to replicate and extend findings from a previous study that found autonomic symptoms predicted physical functioning in Veterans with GWI.

Materials and methods: A linear regression model was used to predict physical functioning (36-item Short Form Health Survey (SF-36); n = 73, 75% male). First, we examined the predictive value of independent variables individually in the model including: the 31-item Composite Autonomic Symptom Score (COMPASS-31) total score, body mass index (BMI), mental health burden (i.e., post-traumatic stress disorder [PTSD] and/or depression), and COMPASS-31 subscales: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor. Next, we estimated linear regression models containing the three variables (autonomic symptoms, BMI, and mental health burden) identified as predictors of physical functioning from the prior study.

Results: These linear regression models significantly predicted physical functioning and accounted for 15% of the variance with COMPASS-31, 36.6% of variance with COMPASS-31 and BMI, and 38.2% of variance with COMPASS-31, BMI, and mental health burden. Then, forward step-wise linear regressions were applied to explore new models including COMPASS-31 subscales. Two new models accounted for more of the variance in physical functioning: 39.3% with added gastrointestinal symptoms (β = -2.206, P = .001) and 43.4% of variance with both gastrointestinal (β = -1.592, P = .008) and secretomotor subscales (β = -1.533, P = .049). Unlike the previous study we intended to replicate, mental health burden was not a significant predictor in any of our models.

Conclusions: Treatments that address autonomic dysregulation should be prioritized for research and clinical recommendations for Veterans with GWI who experience chronic pain.