

**Research Advisory Committee on
Gulf War Veterans' Illnesses (RACGWVI)
— PubMed Research Citations
for January, February, March 2022**

Prepared by Staff of the RACGWVI.

RACGWVI: Gulf War Illness — PubMed Citations for Jan, Feb, March 2022

The following is a list of published research projects that focus on Gulf War Illness (GWI) for the months of January, February and March 2022.

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

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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

Life Sci. 2022 Jan 1; 288:120153. doi: [10.1016/j.lfs.2021.120153](https://doi.org/10.1016/j.lfs.2021.120153). Epub 2021 Nov 18.

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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.

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

Toxicol Appl Pharmacol. 2022 Jan 1; 434:115821. doi: 10.1016/j.taap.2021.115821. Epub 2021 Dec 9.

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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; V_h = -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 μM) 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.

A perspective on persistent toxicants in veterans and amyotrophic lateral sclerosis: identifying exposures determining higher ALS risk

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Abstract

Multiple studies indicate that United States veterans have an increased risk of developing amyotrophic lateral sclerosis (ALS) compared to civilians. However, the responsible etiological factors are unknown. In the general population, specific occupational (e.g. truck drivers, airline pilots) and environmental exposures (e.g. metals, pesticides) are associated with an increased ALS risk. As such, the increased prevalence of ALS in veterans strongly suggests that there are exposures experienced by military personnel that are disproportionate to civilians. During service, veterans may encounter numerous neurotoxic exposures (e.g. burn pits, engine exhaust, firing ranges). So far, however, there is a paucity of studies investigating environmental factors contributing to ALS in veterans and even fewer assessing their exposure using biomarkers. Herein, we discuss ALS pathogenesis in relation to a series of persistent neurotoxicants (often emitted as mixtures) including: chemical elements, nanoparticles and lipophilic toxicants such as dioxins, polycyclic aromatic hydrocarbons and polychlorinated biphenyls. We propose these toxicants should be directly measured in veteran central nervous system tissue, where they may have accumulated for decades. Specific toxicants (or mixtures thereof) may accelerate ALS development following a multistep hypothesis or act synergistically with other service-linked exposures (e.g. head trauma/concussions). Such possibilities could explain the lower age of onset observed in veterans compared to civilians. Identifying high-risk exposures within vulnerable populations is key to understanding ALS etiopathogenesis and is urgently needed to act upon modifiable risk factors for military personnel who deserve enhanced protection during their years of service, not only for their short-term, but also long-term health.

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)

Brain Sci. 2022 Jan 5;12(1):78. doi: 10.3390/brainsci12010078.

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Abstract

Background: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Gulf War Illness (GWI) and control subjects underwent 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 a 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 subjects showed greater activation during cognition than ME/CFS in the left pedunculotegmental nucleus. Post exercise, ME/CFS subjects showed greater activation than GWI ones 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. The controls had no changes.

Conclusions: Exercise caused the 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.

Health symptom trajectories and neurotoxicant exposures in Gulf War veterans: the Ft. Devens cohort

Environ Health. 2022 Jan 8;21(1):7. doi: [10.1186/s12940-021-00812-0](https://doi.org/10.1186/s12940-021-00812-0).

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Abstract

Background: Thirty years ago, Gulf War (GW) veterans returned home with numerous health symptoms that have been associated with neurotoxicant exposures experienced during deployment. The health effects from these exposures have been termed toxic wounds. Most GW exposure-outcome studies utilize group analyses and thus individual fluctuations in symptoms may have been masked. This study investigates health symptom trajectories in the same veterans over 25 years.

Methods: Veterans were categorized into 5 a priori trajectory groups for each health symptom and Chronic Multisymptom Illness (CMI) clinical case status. Multinomial logistic regression models were used to investigate associations between these trajectories and neurotoxicant exposures.

Results: Results indicate that more than 21 Pyridostigmine Bromide (PB) pill exposure was associated with consistent reporting of fatigue, pain, and cognitive/mood symptoms as well as the development of six additional symptoms over time. Chemical weapons exposure was associated with both consistent reporting and development of neurological symptoms over time. Reported exposure to tent heater exhaust was associated with later development of gastrointestinal and pulmonary symptoms. Veterans reporting exposure to more than 21 PB pills were more than 8 times as likely to consistently meet the criteria for CMI over time.

Conclusion: This study highlights the importance of the continued documentation of the health impacts experienced by GW veterans', their resulting chronic health symptoms, and the importance of exposure-outcome relationships in these veterans now 30 years post-deployment.

Persistent exercise fatigue and associative learning deficits in combination with transient glucose dyshomeostasis in a mouse model of Gulf War Illness

Life Sci. 2022 Jan 15; 289:120094. doi: 10.1016/j.lfs.2021.120094. Epub 2021 Oct 26.

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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 Gulf War Illness (GWI) mouse model. The latter have been described in an accompanying paper [1].

Main methods: Adult male C57Bl/6N mice were exposed for 28 days (5 days/week) to pyridostigmine bromide: 6.5 mg/kg, b.i.d., P.O. (GW1) or 8.7 mg/kg, q.d., P.O. (GW2); topical permethrin (1.3 mg/kg in 100% DMSO) and N,N-diethyl-meta-toluamide (DEET 33% in 70% EtOH) and restraint stress (5 min). 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/memory, and transient insulin insensitivity. In contrast to GW2, GW1 showed deficient long-term object recognition memory, milder associative learning/memory deficit, and behavioral despair.

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

Review of the Midbrain Ascending Arousal Network Nuclei and Implications for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Gulf War Illness (GWI) and Postexertional Malaise (PEM)

Brain Sci. 2022 Jan 19;12(2):132. doi: [10.3390/brainsci12020132](https://doi.org/10.3390/brainsci12020132).

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Abstract

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Gulf War Illness (GWI) share features of post-exertional malaise (PEM), exertional exhaustion, or postexertional symptom exacerbation. In a two-day model of PEM, submaximal exercise induced significant changes in activation of the dorsal midbrain during a high cognitive load working memory task (Washington 2020) (Baraniuk this issue). Controls had no net change. However, ME/CFS had increased activity after exercise, while GWI had significantly reduced activity indicating differential responses to exercise and pathological mechanisms. These data plus findings of the midbrain and brainstem atrophy in GWI inspired a review of the anatomy and physiology of the dorsal midbrain and isthmus nuclei in order to infer dysfunctional mechanisms that may contribute to disease pathogenesis and postexertional malaise. The nuclei of the ascending arousal network were addressed. Midbrain and isthmus nuclei participate in threat assessment, awareness, attention, mood, cognition, pain, tenderness, sleep, thermoregulation, light and sound sensitivity, orthostatic symptoms, and autonomic dysfunction and are likely to contribute to the symptoms of postexertional malaise in ME/CFS and GWI.

A common language for Gulf War Illness (GWI) research studies: GWI common data elements

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Abstract

Aims: The Gulf War Illness programs (GWI) of the United States Department of Veteran Affairs and the Department of Defense Congressionally Directed Medical Research Program collaborated with experts to develop Common Data Elements (CDEs) to standardize and systematically collect, analyze, and share data across the (GWI) research community.

Main methods: A collective working group of GWI advocates, Veterans, clinicians, and researchers convened to provide consensus on instruments, case report forms, and guidelines for GWI research. A similar initiative, supported by the National Institute of Neurologic Disorders and Stroke (NINDS) was completed for a comparative illness, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), and provided the foundation for this undertaking. The GWI working group divided into two sub-groups (symptoms and systems assessment). Both groups reviewed the applicability of instruments and forms recommended by the NINDS ME/CFS CDE to GWI research within specific domains and selected assessments of deployment exposures. The GWI CDE recommendations were finalized in March 2018 after soliciting public comments.

Key findings: GWI CDE recommendations are organized in 12 domains that include instruments, case report forms, and guidelines. Recommendations were categorized as core (essential), supplemental-highly recommended (essential for specified conditions, study types, or designs), supplemental (commonly collected, but not required), and exploratory (reasonable to use, but require further validation). Recommendations will continually be updated as GWI research progresses.

Significance: The GWI CDEs reflect the consensus recommendations of GWI research community stakeholders and will allow studies to standardize data collection, enhance data quality, and facilitate data sharing.

Slow Burns: A Qualitative Study of Burn Pit and Toxic Exposures Among Military Veterans Serving in Afghanistan, Iraq and Throughout the Middle East

Ann Psychiatry Clin Neurosci. 2021;4(1):1042. Epub 2021 Dec 27. Author manuscript; available in PMC 2022 Feb 4. PMID: [PMC8816568](https://pubmed.ncbi.nlm.nih.gov/348816568/)

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Abstract

During deployment to the Persian Gulf War and Southwest Asia theatre of operations, Veterans often experienced various hazards, foremost being open-air burn pits and oil well fires. While over 23 presumptive conditions (ranging from brain cancer, interstitial lung disease, and lymphomas to sleep/mood disorders, depression, and cognitive impairment) have been studied in connection with their military-related exposures, there is a paucity of qualitative research on this topic. This is especially true in the context of explanatory models and health belief systems, vis-à-vis underlying social and cultural factors. The current paper provides a balanced conceptual framework (summarizing causal virtues and shortcomings) about the challenges that Veterans encounter when seeking medical care, screening assessments and subsequent treatments.

Sex-specific differences in plasma lipid profiles are associated with Gulf War Illness

J Transl Med. 2022 Feb 5;20(1):73. doi: [10.1186/s12967-022-03272-3](https://doi.org/10.1186/s12967-022-03272-3).

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Abstract

Background: Nearly 250,000 veterans from the 1990-1991 Gulf War have Gulf War Illness (GWI), a condition with heterogeneous pathobiology that remains difficult to diagnose. As such, availability of blood biomarkers that reflect the underlying biology of GWI would help clinicians provide appropriate care to ill veterans. In this study, we measured blood lipids to examine the influence of sex on the association between blood lipids and GWI diagnosis.

Methods: Plasma lipid extracts from GWI (n = 100) and control (n = 45) participants were subjected to reversed-phase nano-flow liquid chromatography-mass spectrometry analysis.

Results: An influence of sex and GWI case status on plasma neutral lipid and phospholipid species was observed. Among male participants, triglycerides, diglycerides, and phosphatidylcholines were increased while cholesterol esters were decreased in GWI cases compared to controls. In female participants, ceramides were increased in GWI cases compared to controls. Among male participants, unsaturated triglycerides, phosphatidylcholine and diglycerides were increased while unsaturated cholesterol esters were lower in GWI cases compared to controls. The ratio of arachidonic acid- to docosahexaenoic acid-containing triglyceride species was increased in female and male GWI cases as compared to their sex-matched controls.

Conclusion: Differential modulation of neutral lipids and ratios of arachidonic acid to docosahexaenoic acid in male veterans with GWI suggest metabolic dysfunction and inflammation. Increases in ceramides among female veterans with GWI also suggest activation of inflammatory pathways. Future research should characterize how these lipids and their associated pathways relate to GWI pathology to identify biomarkers of the disorder.

The impact of neurotoxicant exposures on posttraumatic stress disorder trajectories: The Ft. Devens Gulf War Veterans Cohort

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Abstract

Gulf War veterans (GWVs) were exposed to neurotoxicants, including sarin nerve gas, anti-nerve agent pills, pesticides, oil well fires, and fumes from unvented tent heaters, all of which have been associated with subsequent adverse health. Posttraumatic stress disorder (PTSD) symptoms have also been associated with GW deployment; however, associations between exposures and PTSD symptoms have not been investigated. We assessed PTSD symptom trajectories and associations with neurotoxicant exposures in Ft. Devens Cohort (FDC) veterans (N = 259) who endorsed trauma exposure during deployment and completed the PTSD Checklist at three follow-ups (1992-1993, 1997-1998, 2013-2017). Results indicate that among veterans with more severe initial PTSD symptoms, symptoms remained significantly higher across follow-ups, $B_s = -1.489-1.028$, whereas among those with low initial PTSD symptoms, symptom severity increased significantly over time, $B_s = 1.043-10.304$. Additionally, neurotoxicant exposure was associated with a significant increase in PTSD symptoms, $B_s = -1.870-9.003$. Significant interactions between time and exposures were observed for PTSD symptom clusters, suggesting that among participants with high initial PTSD symptom, unexposed veterans experienced symptom alleviation, whereas exposed veterans' PTSD symptoms remained high. In GWVs with low initial PTSD symptoms, both unexposed and exposed veterans experienced PTSD symptom exacerbations over time; however, this occurred at a faster rate among exposed veterans. These findings suggest that in the years following deployment, GWVs who were exposed to both traumatic events and neurotoxicants may experience more severe and chronic PTSD symptoms than those without neurotoxicant exposures.

Posttraumatic Stress Disorder Does Not Compromise Behavioral Pain Treatment: Secondary Analysis of a Randomized Clinical Trial Among Veterans

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Abstract

Background: Individuals with posttraumatic stress disorder (PTSD) and chronic pain evince different presentations, coping strategies, and treatment utilization patterns than individuals with chronic pain alone. Theorists have suggested that comorbid PTSD may complicate chronic pain treatment, and that integrated pain and PTSD treatment may be preferable to pain treatment alone.

Objective: Assess whether comorbid PTSD moderates Veterans' response to yoga and/or cognitive behavioral therapy (CBT) for pain.

Methods: Veterans with Gulf War illness (n = 75) were assessed using the Brief Pain Inventory at baseline and posttreatment as part of a randomized clinical trial. PTSD status was abstracted from participants' medical records.

Results: PTSD+ participants (n = 41) reported more pain at baseline than PTSD- participants (n = 34; d = .66, p < .01). PTSD+ participants experienced more improvement in pain from baseline to posttreatment than PTSD- participants by a small to moderate, marginally statistically significant amount (d = .39, p = .07). The relationship between PTSD and treatment outcome was not moderated by treatment type (yoga vs CBT; p = .99). Observation of treatment responses across PTSD status (+ vs -) and treatment (yoga vs CBT) revealed that PTSD+ participants responded well to yoga.

Conclusion: PTSD is not associated with reduced effectiveness of behavioral chronic pain treatment among Veterans with Gulf War illness. Therefore behavioral pain treatment should be made readily available to Veterans with pain and PTSD. Yoga deserves further consideration as a treatment for pain among individuals with PTSD.

The impact of post-traumatic stress on quality of life and fatigue in women with Gulf War Illness

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Abstract

Background: Gulf War Illness (GWI) is a chronic, multi-symptomatic disorder characterized by fatigue, muscle pain, cognitive problems, insomnia, rashes, and gastrointestinal issues affecting an estimated 30% of the ~ 750,000 returning military Veterans of the 1990-1991 Persian Gulf War. Female Veterans deployed to combat in this war report medical symptoms, like cognition and respiratory troubles, at twice the rate compared to non-deployed female Veterans of the same era. The heterogeneity of GWI symptom presentation complicates diagnosis as well as the identification of effective treatments. This is exacerbated by the presence of co-morbidities. Defining subgroups of the illness may help alleviate these complications. One clear grouping is along the lines of gender. Our aim is to determine if women with GWI can be further subdivided into distinct subgroups based on post-traumatic stress disorder (PTSD) symptom presentation.

Methods: Veterans diagnosed with GWI (n = 35) and healthy sedentary controls (n = 35) were recruited through the Miami Veterans Affairs Medical Health Center. Symptoms were assessed via the RAND short form health survey, the multidimensional fatigue inventory, and the Davidson trauma scale. Hierarchical regression modeling was performed on measures of health and fatigue with PTSD symptoms as a covariate. This was followed by univariate analyses conducted with two separate GWI groups based on a cut-point of 70 for their total Davidson trauma scale value and performing heteroscedastic t-tests across all measures.

Results: Based on the distinct differences found in PTSD symptomology regarding all health and trauma symptoms, two subgroups were derived within female GWI Veterans. Hierarchical regression models displayed the comorbid effects of GWI and PTSD, as both conditions had measurable impacts on quality of life and fatigue ($\Delta R^2 = 0.08-0.672$), with notable differences in mental and emotional measures. Overall, a cut point analysis indicated poorer quality of life and greater fatigue within all measures for women with GWI and PTSD symptoms in comparison to those women with GWI without PTSD symptoms and healthy controls.

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Conclusions: Our current findings support the understanding that comorbid symptoms of GWI and PTSD subsequently result in poorer quality of life and fatigue, along with establishing the possibility of varying clinical presentations.

Association of Gulf War Illness-Related Symptoms with Military Exposures among 1990–1991 Gulf War Veterans Evaluated at the War-Related Illness and Injury Study Center (WRIISC)

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Abstract

Veterans with difficult-to-diagnose conditions who receive care in the Department of Veterans Affairs (VA) healthcare system can be referred for evaluation at one of three specialty VA War-Related Illness and Injury Study Centers (WRIISC). Veterans of the 1990–1991 Gulf War have long experienced excess rates of chronic symptoms associated with the condition known as Gulf War Illness (GWI), with hundreds evaluated at the WRIISC. Here we provide the first report from a cohort of 608 Gulf War Veterans seen at the WRIISC who completed questionnaires on chronic symptoms (>6 months) consistent with GWI as well as prominent exposures during Gulf War deployment. These included veterans' reports of hearing chemical alarms/donning Military-Ordered Protective Posture Level 4 (MOPP4) gear, pesticide use, and use of pyridostigmine bromide (PB) pills as prophylaxis against the effects of nerve agents. Overall, veterans in the cohort were highly symptomatic and reported a high degree of exposures. In multivariable models, these exposures were significantly associated with moderate-to-severe chronic symptoms in neurocognitive/mood, fatigue/sleep, and pain domains. Specifically, exposure to pesticides was associated with problems with concentration and memory, problems sleeping, unrefreshing sleep, and joint pain. Use of MOPP4 was associated with light sensitivity and unrefreshing sleep and use of PB was associated with depression. We also evaluated the association of exposures with symptom summary scores based on veterans' severity of symptoms in four domains and overall. In multivariable modeling, the

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pain symptom severity score was significantly associated with pesticide use (Odds ratio (OR): 4.13, 95% confidence intervals (CI): 1.78–9.57) and taking PB pills (OR: 2.28, 95% CI: 1.02–5.09), and overall symptom severity was significantly associated with use of PB pills (OR: 2.41, 95% CI: 1.01–5.75). Conclusion: Decades after deployment, Gulf War veterans referred to a VA tertiary evaluation center report a high burden of chronic symptoms, many of which were associated with reported neurotoxicant exposures during the war.

Changes in polyphenol serum levels and cognitive performance after dietary supplementation with Concord grape juice in veterans with Gulf War Illness

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Abstract

Aims: We investigated whether the consumption of Concord grape juice (CGJ) was associated with increased bioavailability of serum metabolites and their potential impact on cognitive performance in Veterans with Gulf War Illness (GWI).

Main methods: Twenty-six veterans were selected from a cohort of 36 enrolled in a 24-week randomized, double-blind, Phase I/IIA clinical trial exploring whether the consumption of Concord grape juice (CGJ) was tolerable and safe in Veterans with GWI and improved cognitive function and fatigue. These 26 veterans were selected based on their completion of the entire 24-week protocol and documented adherence to the study beverage $\geq 80\%$. Differences in serum metabolite levels between CGJ and placebo at midpoint and endpoint were evaluated using two-way repeated measures ANOVA with post hoc Sidak's multiple comparison test. Bivariate correlations to assess for possible relationships between change in serum metabolite levels and change in cognitive

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function as measured by the Halstead Category Test-Russell Revised Version (RCAT) were also conducted.

Key findings: Seventy-six metabolites were identified and quantified in this study, with three (cyanidin-glucuronide, me-cyanidin-glucuronide, and me-malvidin-glucuronide) found to be significantly higher ($p < 0.05$) in the CGJ group compared to placebo at 24 weeks. Significant associations between changes in cognitive function and changes in serum levels of epicatechin-sulphate ($r = 0.48$, $p = 0.01$) and petunidin-glucuronide ($r = 0.53$, $p < 0.01$) from baseline to 24 weeks were also observed.

Significance: Our data suggest that dietary supplementation with CGJ is associated with increased bioavailability of specific phenolic metabolites, some of which may be correlated with cognitive performance.

Protocol for a type 1 hybrid effectiveness/implementation clinical trial of collaborative specialty care for Veterans with Gulf War Illness

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Abstract

Aims: We describe a clinical trial which is seeking to determine the effectiveness and understand implementation outcomes for tele-collaborative specialty care for Veterans with Gulf War Illness (GWI).

Main methods: This study will be a hybrid type 1 randomized effectiveness-implementation trial comparing tele-collaborative specialty care to electronic consultation for Gulf War Veterans with GWI (N = 220). In tele-collaborative specialty care, the specialty provider team will deliver health coaching and problem-solving treatment to Veterans and recommend a plan for analgesic optimization. In electronic consultation, the specialty provider team will make a one-time recommendation to the primary care team for locally delivered health coaching, problem-solving treatment and analgesic optimization. The primary aim will be to determine the effectiveness of tele-collaborative specialty care as compared to electronic consultation to reduce disability related to GWI. Our secondary aim will be to understand implementation outcomes.

Significance: There is a need to improve care for Veterans with GWI. A potentially useful model to improve care is tele-collaborative specialty care, where the specialists work with the primary care provider to synergistically treat the patients.

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Discussion: This is the first clinical trial to prospectively compare different models of care for Veterans with GWI. This responds to multiple calls for research to improve treatment for Veterans with GWI, including from the National Academy of Medicine.

Gulf War Illness Inflammation Reduction Trial: Effects of Low-Dose Prednisone Chronotherapy on Health-Related Quality of Life

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23 Pages Posted: 14 Mar 2022

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Abstract

Aims: Gulf War illness (GWI) is a deployment-related chronic multisymptom illness impacting the health-related quality of life (HRQOL) of many Gulf War Veterans. A proinflammatory blood biomarker fingerprint was discovered in our initial study of GWI. This biomarker evidence led to the hypothesis that inflammation is an underlying cause of GWI. We tested the hypothesis in a clinic trial where inflammation was the therapeutic target. The study measured effects of an anti-inflammatory drug on HRQOL, specific symptoms, and GWI-associated blood biomarkers. The HRQOL data are the focus of this report.

Main Methods: Gulf War Veterans meeting the Kansas case definition for GWI were randomized to receive either prednisone or placebo. The 8-week intervention phase was followed by an 8-week washout. The Veterans RAND 36-Item Health Survey was used to assess HRQOL. Changes from baseline at 8 and 16 weeks were measured. The primary outcome was changes in the physical component summary score (PCS).

Key Findings: After 8 weeks on prednisone, the PCS increased by 6.5 points (18.7%) from baseline in the Veterans with low PCS <40 at baseline. This improvement was a statistically significant (N=19, P=0.038). No other significant changes were observed.

Significance: In this Phase 2 efficacy trial, prednisone induced a statistically significant PCS increase in Gulf War Veterans with low PCS <40 at baseline. The results of the GWIIRT support both the GWI inflammation hypothesis and the efficacy of prednisone as a treatment for GWI.