

[Gulf War Illness: Mechanisms Underlying Brain Dysfunction and Promising Therapeutic Strategies.](#)

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Abstract

Gulf War Illness (GWI), a chronic multisymptom health problem, afflicts ~30% of veterans served in the first GW. Impaired brain function is among the most significant symptoms of GWI, which is typified by persistent cognitive and mood impairments, concentration problems, headaches, chronic fatigue, and musculoskeletal pain. This review aims to discuss findings from animal prototypes and veterans with GWI on mechanisms underlying its pathophysiology and emerging therapeutic strategies for alleviating brain dysfunction in GWI. Animal model studies have linked brain impairments to incessantly elevated oxidative stress, chronic inflammation, inhibitory interneuron loss, altered lipid metabolism and peroxisomes, mitochondrial dysfunction, modified expression of genes relevant to cognitive function, and waned hippocampal neurogenesis. Furthermore, the involvement of systemic alterations such as the increased intensity of reactive oxygen species and proinflammatory cytokines in the blood, transformed gut microbiome, and activation of the adaptive immune response have received consideration. Investigations in veterans have suggested that brain dysfunction in GWI is linked to chronic activation of the executive control network, impaired functional connectivity, altered blood flow, persistent inflammation, and changes in miRNA levels. Lack of protective alleles from Class II HLA genes, the altered concentration of phospholipid species and proinflammatory factors in the circulating blood have also been suggested as other aiding factors. While some drugs or combination therapies have shown promise for alleviating symptoms in clinical trials, larger double-blind, placebo-controlled trials are needed to validate such findings. Based on improvements seen in animal models of GWI, several antioxidants and anti-inflammatory compounds are currently being tested in clinical trials. However, reliable blood biomarkers that facilitate an appropriate screening of veterans for brain pathology need to be discovered. A liquid biopsy approach involving analysis of brain-derived extracellular vesicles in the blood appears efficient for discerning the extent of neuropathology both before and during clinical trials.

[Respiratory illness among Gulf War and Gulf War era veterans who use the Department of Veterans Affairs for healthcare.](#)

Am J Ind Med. 2020 Nov;63(11):980-987. doi: 10.1002/ajim.23172. Epub 2020 Aug 26. PMID: 32851693.

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Abstract

Background: Veterans of the 1990-1991 Gulf War were exposed to a variety of toxic substances during their service that included several airborne hazards, but only a few small studies have assessed respiratory outcomes in Gulf War veterans. This paper presents population prevalence estimates and prevalence ratios of respiratory disease among Gulf War and Gulf War Era veterans who use VA healthcare.

Methods: A total of 360,909 Gulf War deployed veterans and 323,638 Gulf War Era non-deployed veterans were included in the analysis. Ten-year period prevalence rates (PRs) for fifteen respiratory diseases were calculated for Gulf War and Gulf War Era veterans and period prevalence ratios comparing Gulf War veterans to Gulf War Era veterans were calculated.

Results: The five respiratory conditions with the highest prevalence per 100,000 veterans across both Gulf War deployed and Gulf War Era non-deployed veterans (respectively) were: allergic rhinitis (8,400 and 8,041), chronic obstructive pulmonary disease (4,763 and 4,795), asthma (4,685 and 4,477), chronic airway obstruction (3,983 and 4,059), and chronic sinusitis (2,863 and 2,672). The adjusted PRs showed a small, but significantly increased, elevation in Gulf War-deployed compared to Gulf War Era non-deployed veterans for chronic bronchitis (PR 1.19; 95% CI 1.10, 1.28), emphysema (PR 1.11; 95% CI 1.01, 1.21), chronic airway obstruction (PR 1.09; 95% CI 1.07, 1.12), and chronic obstructive pulmonary disease (PR 1.09; 1.07, 1.11).

Discussion: Gulf War veterans should continue to be monitored in the future to better evaluate the potential long-term consequences on respiratory health.

[Grappling with Gulf War Illness: Perspectives of Gulf War Providers.](#)

Int J Environ Res Public Health. 2020 Nov 19;17(22):8574. doi: 10.3390/ijerph17228574. PMID: 33227919

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Abstract

Background: Although the Gulf War occurred almost 30 years ago, the chronic symptoms of Gulf War illness (GWI), which include respiratory, gastrointestinal, and skin problems, as well as fatigue, pain, and mood alterations, currently affect over 200,000 veterans. Meanwhile, healthcare providers lack clear guidelines about how to best treat this illness. The objective in this study was to learn about the perceptions and experiences of healthcare providers of GWI veterans in terms of medical symptoms, resources for treatment, and quality of care. *Methods:* We interviewed 10 healthcare providers across the United States and subsequently conducted a qualitative grounded theory study which entailed both systematic data analysis and generating a grounded theory framework. *Results:* Our findings indicated multiple challenges for providers of veterans with GWI, including gaps in knowledge about GWI, lack of treatment options, absence of consistent communication within the Department of Veterans Affairs (VA) system, and personalized care that was limited to validation. *Conclusion:* While this study had several limitations, it supported the notion that healthcare providers have inadequate knowledge and awareness about GWI, which leads to continued uncertainty about how to best care for GWI veterans. This could be remedied by the creation of a comprehensive curriculum for a Massive Open Online Course (MOOC) to serve as an educational tool for those attending to this largely overlooked veteran population.

[Yoga is effective in treating symptoms of Gulf War illness: A randomized clinical trial.](#)

J Psychiatr Res. 2020 Nov 11;S0022-3956(20)31083-9. doi: 10.1016/j.jpsychires.2020.11.024. Online ahead of print. PMID: 33218747

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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](https://clinicaltrials.gov/ct2/show/study/NCT02378025) Registration Number [NCT02378025](https://clinicaltrials.gov/ct2/show/study/NCT02378025).

[Bruxism and Stress Among Veterans With Gulf War Illness](#)

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Abstract

Introduction: This study explores perceived stress and experience with bruxism among veterans with Gulf War Illness (GWI). Stress may manifest physically as bruxism, a parafunctional oral activity that consists of teeth grinding and/or clenching.

Materials and methods: An online survey of GWI veterans (n = 28, 27.7% response rate) assessed perceived general stress and self-reported behaviors, symptoms, and outcomes associated with bruxism. Survey questions also collected basic demographic data and past military experience. The appropriate Institutional Review Board approved this study (IRB-300001376). Statistical analyses utilized both analysis of variance and linear regression techniques in addition to descriptive statistics.

Results: This sample of GWI veterans reported higher levels of perceived stress (M = 20.2, SD = 7.0) than general population males (M = 12.1, SD = 5.9). A majority of GWI veterans reported both grinding (77.8%) and clenching (85.2%) teeth on a weekly or daily basis. Grinding frequency did not predict perceived stress scale values (F = 2.38, P = .11). Clenching frequency did significantly predict perceived stress scale values (F = 4.07, P = .03). Those who reported daily clenching had significantly higher perceived stress scores (M = 22.17, SD = 5.87) than did those who reported never clenching (M = 12.00, SD = 5.35). Length of military service did not significantly predict perceived stress or bruxism experience.

Conclusions: GWI veterans reported higher levels of perceived stress in comparison with that of general population males. Both the high frequency of teeth grinding and clenching in these patients is a potential physical manifestation of the high perceived stress levels reported. It is imperative that both military and civilian dentists and physicians are aware of the potential for increased stress and consequently bruxism in this patient population as it can have negative impacts on oral and mental health. Treatment of these patients can include but is not limited to behavior modification, stress reduction training, and the fabrication of mouth guards. The dental and medical implications of bruxism and stress in veterans with GWI should be further investigated.

[Neuroimaging Markers for Studying Gulf-War Illness: Single-Subject Level Analytical Method Based on Machine Learning.](#)

Brain Sci. 2020 Nov 20;10(11):884. doi: 10.3390/brainsci10110884. PMID: 33233672

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Abstract

Gulf War illness (GWI) refers to the multitude of chronic health symptoms, spanning from fatigue, musculoskeletal pain, and neurological complaints to respiratory, gastrointestinal, and dermatologic symptoms experienced by about 250,000 GW veterans who served in the 1991 Gulf War (GW). Longitudinal studies showed that the severity of these symptoms often remain unchanged even years after the GW, and these veterans with GWI continue to have poorer general health and increased chronic medical conditions than their non-deployed counterparts. For better management and treatment of this condition, there is an urgent need for developing objective biomarkers that can help with simple and accurate diagnosis of GWI. In this study, we applied multiple neuroimaging techniques, including T1-weighted magnetic resonance imaging (T1W-MRI), diffusion tensor imaging (DTI), and novel neurite density imaging (NDI) to perform both a group-level statistical comparison and a single-subject level machine learning (ML) analysis to identify diagnostic imaging features of GWI. Our results supported NDI as the most sensitive in defining GWI characteristics. In particular, our classifier trained with white matter NDI features achieved an accuracy of 90% and F-score of 0.941 for classifying GWI cases from controls after the cross-validation. These results are consistent with our previous study which suggests that NDI measures are sensitive to the microstructural and macrostructural changes in the brain of veterans with GWI, which can be valuable for designing better diagnosis method and treatment efficacy studies.

[Diminished corticomotor excitability in Gulf War Illness related chronic pain symptoms; evidence from TMS study.](#)

Sci Rep. 2020 Oct 28;10(1):18520. doi: 10.1038/s41598-020-75006-8. PMID: 33116195. PMCID: PMC7595115. DOI: 10.1038/s41598-020-75006-8

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Abstract

Chronic diffuse body pain is unequivocally highly prevalent in Veterans who served in the 1990-91 Persian Gulf War and diagnosed with Gulf War Illness (GWI). Diminished motor cortical excitability, as a measurement of increased resting motor threshold (RMT) with transcranial magnetic stimulation (TMS), is known to be associated with chronic pain conditions. This study compared RMT in Veterans with GWI related diffuse body pain including headache, muscle and joint pain with their military counterparts without GWI related diffuse body pain. Single pulse TMS was administered over the left motor cortex, using anatomical scans of each subject to guide the TMS coil, starting at 25% of maximum stimulator output (MSO) and increasing in steps of 2% until a motor response with a 50 μ V peak to peak amplitude, defined as the RMT, was evoked at the contralateral flexor pollicis brevis muscle. RMT was then analyzed using Repeated Measures Analysis of Variance (RM-ANOVA). Veterans with GWI related chronic headaches and body pain (N = 20, all males) had a significantly (P < 0.001) higher average RMT (% \pm SD) of 77.2% \pm 16.7% compared to age and gender matched military controls (N = 20, all males), whose average was 55.6% \pm 8.8%. Veterans with GWI related diffuse body pain demonstrated a state of diminished corticomotor excitability, suggesting a maladaptive supraspinal pain modulatory state. The impact of this observed supraspinal functional impairment on other GWI related symptoms and the potential use of TMS in rectifying this abnormality and providing relief for pain and co-morbid symptoms requires further investigation. Trial registration: This study was registered on January 25, 2017, on ClinicalTrials.gov with the identifier: [NCT03030794](#). Retrospectively registered. <https://clinicaltrials.gov/ct2/show/NCT03030794>.

[Genome-wide transcriptome architecture in a mouse model of Gulf War Illness.](#)

Brain Behav Immun. 2020 Oct;89:209-223. doi: 10.1016/j.bbi.2020.06.018. Epub 2020 Jun 20. PMID: 32574576

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Abstract

Gulf War Illness (GWI) is thought to be a chronic neuroimmune disorder caused by in-theater exposure during the 1990-1991 Gulf War. There is a consensus that the illness is caused by exposure to insecticides and nerve agent toxicants. However, the heterogeneity in both development of disease and clinical outcomes strongly suggests a genetic contribution. Here, we modeled GWI in 30 BXD recombinant inbred mouse strains with a combined treatment of corticosterone (CORT) and diisopropyl fluorophosphate (DFP). We quantified transcriptomes from 409 prefrontal cortex samples. Compared to the untreated and DFP treated controls, the combined treatment significantly activated pathways such as cytokine-cytokine receptor interaction and TNF signaling pathway. Protein-protein interaction analysis defined 6 subnetworks for CORT + DFP, with the key regulators being Cxcl1, Il6, Ccnb1, Tnf, Agt, and Itgam. We also identified 21 differentially expressed genes having significant QTLs related to CORT + DFP, but without evidence for untreated and DFP treated controls, suggesting regions of the genome specifically involved in the response to CORT + DFP. We identified Adamts9 as a potential contributor to response to CORT + DFP and found links to symptoms of GWI. Furthermore, we observed a significant effect of CORT + DFP treatment on the relative proportion of myelinating oligodendrocytes, with a QTL on Chromosome 5. We highlight three candidates, Magi2, Sema3c, and Gnai1, based on their high expression in the brain and oligodendrocyte. In summary, our results show significant genetic effects of the CORT + DFP treatment, which mirrors gene and protein expression changes seen in GWI sufferers, providing insight into the disease and a testbed for future interventions.

[Alterations in high-order diffusion imaging in veterans with Gulf War Illness is associated with chemical weapons exposure and mild traumatic brain injury.](#)

Brain Behav Immun. 2020 Oct;89:281-290. doi: 10.1016/j.bbi.2020.07.006. Epub 2020 Jul 31. PMID: 32745586

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Abstract

The complex etiology behind Gulf War Illness (GWI) has been attributed to the combined exposure to neurotoxicant chemicals, brain injuries, and some combat experiences. Chronic GWI symptoms have been shown to be associated with intensified neuroinflammatory responses in animal and human studies. To investigate the neuroinflammatory responses and potential causes in Gulf War (GW) veterans, we focused on the effects of chemical/biological weapons (CBW) exposure and mild traumatic brain injury (mTBI) during the war. We applied a novel MRI diffusion processing method, Neurite density imaging (NDI), on high-order diffusion imaging to estimate microstructural alterations of brain imaging in Gulf War veterans with and without GWI, and collected plasma proinflammatory cytokine samples as well as self-reported health symptom scores. Our study identified microstructural changes specific to GWI in the frontal and limbic regions due to CBW and mTBI, and further showed distinctive microstructural patterns such that widespread changes were associated with CBW and more focal changes on diffusion imaging were observed in GW veterans with an mTBI during the war. In addition, microstructural alterations on brain imaging correlated with upregulated blood proinflammatory cytokine markers TNFR1 and TNFR2 and with worse outcomes on self-reported symptom measures for fatigue and sleep functioning. Taken together, these results suggest TNF signaling mediated inflammation affects frontal and limbic regions of the brain, which may contribute to the fatigue and sleep symptoms of the disease and suggest a strong neuroinflammatory component to GWI. These results also suggest exposures to chemical weapons and mTBI during the war are associated with different patterns of peripheral and central inflammation and highlight the brain regions vulnerable to further subtle microscale morphological changes and chronic signaling to nearby glia.

[A role for neuroimmune signaling in a rat model of Gulf War Illness-related pain.](#)

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Abstract

More than a quarter of veterans of the 1990-1991 Persian Gulf War suffer from Gulf War Illness (GWI), a chronic, multi-symptom illness that commonly includes musculoskeletal pain. Exposure to a range of toxic chemicals, including sarin nerve agent, are a suspected root cause of GWI. Moreover, such chemical exposures induce a neuroinflammatory response in rodents, which has been linked to several GWI symptoms in rodents and veterans with GWI. To date, a neuroinflammatory basis for pain associated with GWI has not been investigated. Here, we evaluated development of nociceptive hypersensitivity in a model of GWI. Male Sprague Dawley rats were treated with corticosterone in the drinking water for 7 days, to mimic high physiological stress, followed by a single injection of the sarin nerve agent surrogate, diisopropyl fluorophosphate. These exposures alone were insufficient to induce allodynia. However, an additional sub-threshold challenge (a single intramuscular injection of pH 4 saline) induced long-lasting, bilateral allodynia. Such allodynia was associated with elevation of markers for activated microglia/macrophages (CD11b) and astrocytes/satellite glia (GFAP) in the lumbar dorsal spinal cord and dorsal root ganglia (DRG). Additionally, Toll-like receptor 4 (TLR4) mRNA was elevated in the lumbar dorsal spinal cord, while IL-1 β and IL-6 were elevated in the lumbar dorsal spinal cord, DRG, and gastrocnemius muscle. Demonstrating a casual role for such neuroinflammatory signaling, allodynia was reversed by treatment with either minocycline, the TLR4 inhibitor (+)-naltrexone, or IL-10 plasmid DNA. Together, these results point to a role for neuroinflammation in male rats in the model of musculoskeletal pain related to GWI. Therapies that alleviate persistent immune dysregulation may be a strategy to treat pain and other symptoms of GWI.

[A Systematic Review of Therapeutic Interventions and Management Strategies for Gulf War Illness.](#)

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Abstract

Introduction: After the 1990 to 1991 conflict in the Persian Gulf, many Gulf War Veterans began reporting numerous unexplained symptoms including, but not limited to, systemic pain, fatigue, flu-like symptoms, and difficulty with memory/concentration. These symptom clusters are now referred to as Gulf War Illness (GWI). Although the etiology of GWI is still debated, as many as 250,000 former service members have been continually suffering from GWI since 1991, making the need for treatment urgent. A broad variety of treatments have been considered for GWI, but there has not been a broad and comprehensive assessment of what is known and not known about GWI treatment. We conducted a systematic review to catalogue the types of treatments that have been examined for GWI, to evaluate the effectiveness and harms of these interventions, and to identify promising and ongoing areas of future GWI treatment research.

Materials and methods: We searched electronic databases, trial registries, and reference lists through September 2019 for randomized controlled trial and nonrandomized controlled trial and cohort studies directly comparing interventions for Veterans with GWI to each other, placebo, or usual care. We abstracted data on study design, demographics, interventions, and outcomes. Two reviewers independently assessed studies for inclusion, quality, and strength of evidence (SOE) using prespecified criteria. We resolved discordant ratings by discussion and consensus.

Results: We identified 12 randomized controlled trials, each of which examined a different intervention for GWI. We found moderate SOE that cognitive behavioral therapy and exercise, separately and in combination, were associated with improvements in several GWI symptom domains. There was low SOE of benefit from two mindfulness-based interventions and continuous positive airway pressure (CPAP). Mindfulness-based stress reduction improved pain, cognitive functioning, fatigue, depression, and posttraumatic stress disorder (PTSD), whereas mind-body bridging improved fatigue, depression, posttraumatic stress disorder, and sleep, although pain and other outcomes did not improve. Continuous positive airway pressure improved overall physical health, pain, cognitive functioning, fatigue, mental health, and sleep quality in a small study of Veterans with sleep-disordered breathing and GWI. We found moderate SOE that doxycycline is ineffective for GWI in mycoplasma DNA-positive Veterans and increases the risk of adverse events compared with placebo. We also found 33 ongoing, single-arm pilot, or unpublished studies examining a variety of interventions.

Conclusion: Cognitive behavioral therapy (moderate SOE), exercise (moderate SOE), and mindfulness-based interventions (low SOE) may be effective in improving several symptom domains in patients with GWI. Doxycycline was ineffective and associated with harms (moderate SOE). Larger, more rigorous studies are needed to confirm the benefits found in completed trials. A wide array of treatments are being assessed in ongoing trials. A sufficient evidence base will need to be developed to guide clinicians about which treatments are most likely to be effective in clinical practice and which treatments should be avoided.

[Pyridostigmine bromide exposure creates chronic, underlying neuroimmune disruption in the gastrointestinal tract and brain that alters responses to palmitoylethanolamide in a mouse model of Gulf War Illness.](#)

Neuropharmacology. 2020 Nov 15;179:108264. doi: 10.1016/j.neuropharm.2020.108264. Epub 2020 Aug 3.

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Abstract

Gulf War Illness (GWI) is a chronic multisymptom illness that includes gastrointestinal disorders. Although the exact etiology of GWI is unknown, exposure to the drug pyridostigmine bromide (PB) is considered a major factor. Exposure to PB drives enteric neuroinflammation, promotes immunosuppression, and alters physiological functions of the colon in the short term but whether exposure to PB is sufficient to promote long term dysfunction is not known. Here, we tested whether exposure to PB is sufficient to drive long term changes that reflect GWI, and whether the endogenous anti-inflammatory mediator palmitoylethanolamide (PEA) is sufficient to reduce the detrimental effects of PB in the gut and brain of mice. Exposure to PB alone was not sufficient to cause major changes in neuromuscular transmission but did drive major changes by altering the effects of PEA. Calcium imaging data show that the mechanisms responsible include a shift in receptor signaling mediated by TRPV1, endocannabinoids, and peroxisome proliferator-activated receptors alpha (PPAR α). Additional mechanisms include the development of glial reactivity and changes in enteric neurochemical coding and survival. PB and PEA caused major shifts in pro-inflammatory cytokines/chemokines in the brain and colon that persisted up to 5 months following exposure. Many of the effects of PB and PEA exhibit significant sex differences. Together, these results highlight novel mechanisms whereby PB promotes long-lasting changes in nervous system and immune function by inducing occult neuroplasticity that is revealed by subsequent exposure to unrelated drugs in a sex dependent manner.

[The peroxisome proliferator-activated receptor gamma \(PPARgamma\) agonist, rosiglitazone, ameliorates neurofunctional and neuroinflammatory abnormalities in a rat model of Gulf War Illness.](#)

PLoS One. 2020 Nov 13;15(11):e0242427. doi: 10.1371/journal.pone.0242427. eCollection 2020. PMID: 33186383

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Abstract

Background: Gulf War (GW) Illness (GWI) is a debilitating condition with a complex constellation of immune, endocrine and neurological symptoms, including cognitive impairment, anxiety and depression. We studied a novel model of GWI based on 3 known common GW exposures (GWE): (i) intranasal lipopolysaccharide, to which personnel were exposed during desert sand storms; (ii) pyridostigmine bromide, used as prophylaxis against chemical warfare; and (iii) chronic unpredictable stress, an inescapable element of war. We used this model to evaluate prophylactic treatment with the PPAR γ agonist, rosiglitazone (ROSI).

Methods: Rats were subjected to the three GWE for 33 days. In series 1 and 2, male and female GWE-rats were compared to naïve rats. In series 3, male rats with GWE were randomly assigned to prophylactic treatment with ROSI (GWE-ROSI) or vehicle. After the 33-day exposures, three neurofunctional domains were evaluated: cognition (novel object recognition), anxiety-like behaviors (elevated plus maze, open field) and depression-like behaviors (coat state, sucrose preference, splash test, tail suspension and forced swim). Brains were analyzed for astrocytic and microglial activation and neuroinflammation (GFAP, Iba1, tumor necrosis factor and translocator protein). Neurofunctional data from rats with similar exposures were pooled into 3 groups: naïve, GWE and GWE-ROSI.

Results: Compared to naïve rats, GWE-rats showed significant abnormalities in the three neurofunctional domains, along with significant neuroinflammation in amygdala and hippocampus. There were no differences between males and females with GWE. GWE-ROSI rats showed significant attenuation of neuroinflammation and of some of the neurofunctional abnormalities.

Conclusion: This novel GWI model recapitulates critical neurofunctional abnormalities reported by Veterans with GWI. Concurrent prophylactic treatment with ROSI was beneficial in this model.

[Multiple Vaccinations and the Enigma of Vaccine Injury.](#)

Mawson AR, Croft AM. Mawson AR, et al. *Vaccines (Basel)*. 2020 Nov 12;8(4):676. doi: 10.3390/vaccines8040676.

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Abstract

A growing number of vaccines are administered at the same time or in close succession, increasing the complexity of assessing vaccine safety. Individual vaccines are assumed to have no other effect than protection against the targeted pathogen, but vaccines also have nonspecific and interactive effects, the outcomes of which can be beneficial or harmful. To date, no controlled trials and very few observational studies have determined the impact of vaccination schedules on overall health. The balance of the risks and benefits from mass vaccination therefore remains uncertain. Recent studies worryingly suggest links between multiple vaccinations and increased risks of diverse multisystem health problems, including allergies, infections, and neuropsychiatric or neurodevelopmental disorders. Here, we propose that, in susceptible persons, multiple vaccinations activate the retinoid cascade and trigger apoptotic hepatitis, leading to cholestatic liver dysfunction, in which stored vitamin A compounds (retinyl esters and retinoic acid) enter the circulation in toxic concentrations; this induces endogenous forms of hypervitaminosis A, with the severity of adverse outcomes being directly proportional to the concentration of circulating retinoids. In very low concentrations, vitamin A and its major metabolite retinoic acid contribute to immune function and to the process of immunization, whereas excess vitamin A increases the risk of adverse events, including common "side-effects" as well as chronic adverse outcomes. The increasing rates of allergy, ear infections, and neurodevelopmental disorders (NDDs) in countries with high rates of vaccination could be related to mass vaccination and to its impact on liver function and vitamin A metabolism, collectively representing endogenous manifestations of hypervitaminosis A. Further studies of health outcomes in vaccinated and unvaccinated groups are urgently needed, to increase understanding of the pathophysiology and treatment of vaccine injury, to identify the risk factors and screen for vaccine injury, to inform public health policy on potential hazards related to vaccination schedules, and to optimize the safety and benefits of vaccines.

[Impact of Air Pollution and Weather on Dry Eye.](#)

J Clin Med. 2020 Nov 20;9(11):3740. doi: 10.3390/jcm9113740. PMID: 33233863

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Abstract

Air pollution has broad effects on human health involving many organ systems. The ocular surface is an excellent model with which to study the effects of air pollution on human health as it is in constant contact with the environment, and it is directly accessible, facilitating disease monitoring. Effects of air pollutants on the ocular surface typically manifest as dry eye (DE) symptoms and signs. In this review, we break down air pollution into particulate matter (organic and inorganic) and gaseous compounds and summarize the literature regarding effects of various exposures on DE. Additionally, we examine the effects of weather (relative humidity, temperature) on DE symptoms and signs. To do so, we conducted a PubMed search using key terms to summarize the existing literature on the effects of air pollution and weather on DE. While we tried to focus on the effect of specific exposures on specific aspects of DE, environmental conditions are often studied concomitantly, and thus, there are unavoidable interactions between our variables of interest. Overall, we found that air pollution and weather conditions have differential adverse effects on DE symptoms and signs. We discuss these findings and potential mitigation strategies, such as air purifiers, air humidifiers, and plants, that may be instituted as treatments at an individual level to address environmental contributors to DE.

[Effects of Incubation of Human Brain Microvascular Endothelial Cells and Astrocytes with Pyridostigmine Bromide, DEET, or Permethrin in the Absence or Presence of Metal Salts.](#)

Int J Environ Res Public Health. 2020 Nov 11;17(22):8336. doi: 10.3390/ijerph17228336. PMID: 33187257

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Abstract

Gulf War Illness (GWI) is a chronic, multi-symptom illness suffered by over one-third of American military veterans who served in the Persian Gulf War between 1990 and 1991. No current single-exposure scenario accounts for all the symptoms observed in GWI, and instead may be due to a multi-exposure scenario. As a larger effort to understand how one category of multi-exposure scenarios of organic compounds such as nerve gas prophylactic pyridostigmine bromide, or insecticides/pesticides such as N,N-diethyl-*m*-toluamide (DEET) and permethrin, plus heavy metals found in inhaled dust particles (Al, Fe, Ni, Sr, DU, Co, Cu, Mn, and Zn) might play a role in neural aspects of GWI, we begin this initial study to examine the toxicity and oxidative damage markers of human brain endothelial cell and human astrocyte cell cultures in response to these compounds. A battery of cytotoxicity assessments, including the MTT assay, Neutral Red uptake, and direct microscopic observation, was used to determine a non-toxic dose of the test compounds. After testing a wide range of doses of each compound, we chose a sub-toxic dose of 10 μ M for the three organic compounds and 1 μ M for the nine metals of interest for co-exposure experiments on cell cultures and examined an array of oxidative stress-response markers including nitric oxide production, formation of protein carbonyls, production of thiobarbituric acid-reactive substances, and expression of proteins involved in oxidative stress and cell damage. Many markers were not significantly altered, but we report a significant increase in nitric oxide after exposure to any of the three compounds in conjunction with depleted uranium.

Ocular Manifestations of Sarcoidosis in a South Florida Population.

Clin Ophthalmol. 2020 Nov 2;14:3741-3746. doi: 10.2147/OPTH.S278373. eCollection 2020. Clin Ophthalmol. 2020. PMID: 33173272

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Abstract

Objective: To describe the ocular manifestations of sarcoidosis in a South Florida population and identify risk factors for the presence of ocular disease.

Design: Retrospective consecutive case series.

Methods: Medical charts of individuals with sarcoidosis seen in the University of Miami pulmonary department were reviewed for ocular disease. Odds ratios were used to identify risk factors for ocular sarcoidosis.

Results: Fourteen of 108 individuals with sarcoidosis had ocular involvement. The mean age of the 14 individuals was 56±15 years. Seventy-one percent were female, 50% were black, and 21% were Hispanic. Twelve had uveitis of which panuveitis was the most common subtype. Five had ≤20/70 vision in at least one eye due to uveitis. Neurosarcoidosis was a risk factor for ocular sarcoidosis (OR 6.14, p=0.03, 95% CI 1.21-31.09).

Conclusion: Ocular manifestations occurred in a minority of individuals in a pulmonary sarcoidosis clinic in South Florida. Uveitis was the most common ocular manifestation. Neurosarcoidosis was a risk factor for ocular involvement.