Research Advisory Committee on Gulf War Veterans' Illnesses (RAC-GWVI) —PubMed Research Citations for April, May, June 2021

Prepared by Staff of the RAC-GWVI.

RAC-GWVI: Gulf War Illness—PubMed Citations for Apr May Jun 2021

The following is a list of published research projects that focus on Gulf War Illness (GWI) for the months of April, May and June 2021.

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A Placebo-Controlled, Pseudo-Randomized, Crossover Trial of Botanical Agents for Gulf War Illness: Reishi Mushroom (Ganoderma lucidum), Stinging Nettle (Urtica dioica), and Epimedium (Epimedium sagittatum)

Jarred Younger [1], Emily K Donovan [2], Kathleen S Hodgin [1], Timothy J Ness [3]

- Int J Environ Res Public Health. 2021 Apr 1;18(7):3671. doi: 10.3390/ijerph18073671.

Affiliations

- [1]Department of Psychology, University of Alabama at Birmingham, CH 233, 1300 University Boulevard, Birmingham, AL 35233, USA.
- [2]Department of Psychology, Virginia Commonwealth University, White House, 806 West Franklin Street, Richmond, VA 23284, USA.
- [3]Department of Anesthesiology and Perioperative Medicine, University of Alabama at Birmingham, BMR2-208, 901 19th Street South, Birmingham, AL 35205, USA.

Abstract

This report is third in a three-part clinical trial series screening potential treatments for Gulf War Illness (GWI). The goal of the project was to rapidly identify agents to prioritize for further efficacy research. We used a placebo-controlled, pseudo-randomized, crossover design to test the effects of reishi mushroom (*Ganoderma lucidum*), stinging nettle (*Uritca dioica*), and epimedium (*Epimedium sagittatum*) in 29 men with GWI. Participants completed 30 days of symptom reports for baseline, then a botanical line consisting of 30 days of placebo, followed by 30 days each of lower-dose and higher-dose botanical. After completing a botanical line, participants were randomized to complete the protocol with another botanical, until they completed three botanical trials. GWI symptom severity, pain, and fatigue were contrasted between the four conditions (baseline, placebo, lower-dose, higher dose) using linear mixed models. GWI symptom severity was unchanged from placebo in the reishi lower-dose condition ($p = 0.603$), and was higher in the higher-dose condition ($p = 0.012$). Symptom severity was not decreased from placebo with lower-dose stinging nettle ($p = 0.604$), but was significantly decreased with higher-dose stinging nettle ($p = 0.048$). Epimedium showed no significant decreases of GWI symptoms in the lower ($p = 0.936$) or higher ($p = 0.183$) dose conditions. Stinging nettle, especially at higher daily dosages, may help reduce the symptoms of GWI. Epimedium does not appear to beneficially affect GWI symptom severity, and reishi may exaggerate symptoms in some GWI sufferers. These results are in a small sample and are preliminary. Further research is required to determine if stinging nettle is indeed helpful for the treatment of GWI, and what dosage is optimal. This trial was registered on ClinicalTrials.gov (NCT02909686).

Gulf War Illness: Mechanisms Underlying Brain Dysfunction and Promising Therapeutic Strategies

Brandon Dickey[1], Leelavathi N Madhu[2], Ashok K Shetty[3]

- Pharmacol Ther. 2021 Apr; 220:107716. doi: 10.1016/j.pharmthera.2020.107716. Epub 2020 Oct 24.

Affiliations

- [1]Institute for Regenerative Medicine, Department of Molecular and Cellular Medicine, Texas A&M University Health Science Center College of Medicine, College Station, TX, USA; Texas A&M University Health Science Center College of Medicine, Temple, TX, USA.
- [2]Institute for Regenerative Medicine, Department of Molecular and Cellular Medicine, Texas A&M University Health Science Center College of Medicine, College Station, TX, USA.
- [3]Institute for Regenerative Medicine, Department of Molecular and Cellular Medicine, Texas A&M University Health Science Center College of Medicine, College Station, TX, USA. Electronic address: akskrs@tamu.edu.

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.

The First Gulf War: Operations Desert Shield and Desert Storm (17 January-28 February 1991)

Br Dent J. 2021 Apr;230(7):435-443. doi: 10.1038/s41415-021-2733-5. Epub 2021 Apr 9.

Authors
Ewan B Carmichael [1], Quentin Anderson [2]

Affiliations
- [1] Major General (Retired) Late Royal Army Dental Corps, Retired Dental Officer, London, UK. ewancarmichael@yahoo.com.
- [2] Colonel Commandant Royal Army Dental Corps, Regimental Headquarters Royal Army Dental Corps, Surrey, UK.

Abstract
The First Gulf War was triggered by Iraq, led by Saddam Hussein, invading and brutally occupying Kuwait, triggering an international response. A coalition of UN-sponsored allies, led by the USA, assembled to liberate Kuwait. The forces in the region included a British contingent, initially focusing on an Armoured Brigade, but eventually expanding to an Armoured Division, supported by maritime and air components. The Army presence included Royal Army Dental Corps officers and soldiers in clinical roles, but also as medical sub-unit commanders. A brief account of the field organisation of the Army Medical Services and the varied roles played by dental personnel leads into a short clinical report which provides epidemiological information on the dental health of the force and data on the treatment carried out. A description of the preparation for war is followed by a personal narrative of the land campaign.

Post-traumatic stress impact on health outcomes in Gulf War Illness

BMC Psychol. 2021 Apr 20;9(1):57. doi: 10.1186/s40359-021-00561-2.

Authors

Mary Jeffrey [1 2 3], Fanny Collado [3], Jeffrey Kibler [4], Christian DeLucia [4], Steven Messer [4], Nancy Klimas [1 3 5], Travis J A Craddock [6 7 8 9]

Affiliations

- [1] Institute for Neuro-Immune Medicine, Nova Southeastern University, Fort Lauderdale, FL, USA.
- [2] Department of Psychology and Neuroscience, Nova Southeastern University, Fort Lauderdale, FL, USA.
- [3] Miami Veterans Affairs Medical Center, Miami, USA.
- [4] Department of Clinical and School Psychology, Nova Southeastern University, Fort Lauderdale, FL.
- [5] Department of Clinical Immunology, Nova Southeastern University, Fort Lauderdale, FL, USA.
- [6] Institute for Neuro-Immune Medicine, Nova Southeastern University, Fort Lauderdale, FL, USA. tcraddock@nova.edu.
- [7] Department of Psychology and Neuroscience, Nova Southeastern University, Fort Lauderdale, FL, USA. tcraddock@nova.edu.
- [8] Department of Clinical Immunology, Nova Southeastern University, Fort Lauderdale, FL, USA. tcraddock@nova.edu.
- [9] Department of Computer Science, Nova Southeastern University, Fort Lauderdale, FL, USA. tcraddock@nova.edu.

Abstract

Background: Gulf War Illness (GWI) is a chronic, multi-symptomatic disorder affecting an estimated 25-32% of the returning military veterans of the 1990-1991 Persian Gulf War. GWI presents with a wide range of symptoms including fatigue, muscle pain, cognitive problems, insomnia, rashes and gastrointestinal issues and continues to be a poorly understood illness. This heterogeneity of GWI symptom presentation complicates diagnosis as well as the identification of effective treatments. Defining subgroups of the illness may help alleviate these complications. Our aim is to determine if GWI can be divided into distinct subgroups based on PTSD symptom presentation.

Methods: Veterans diagnosed with GWI (n = 47) and healthy sedentary veteran controls (n = 52) were recruited through the Miami Affairs (VA) Medical Health Center. Symptoms were assessed via the RAND short form health survey (36), the multidimensional fatigue inventory, and the Davidson trauma scale. Hierarchal 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: Overall analyses returned two symptom-based subgroups differing significantly across all health and trauma symptoms. These subgroups supported PTSD symptomatology as a means to subgroup veterans. Hierarchical models showed that GWI and levels of PTSD symptoms both impact measures of physical, social, and emotional consequences of poor health ($\Delta R^2 = 0.055$-0.316). However, GWI appeared to contribute more to fatigue measures. Cut-point analysis retained worse health outcomes across all measures for GWI with PTSD symptoms compared to those without PTSD symptoms, and healthy controls. Significant differences were observed in mental and emotional measures.

Conclusions: Therefore, this research supports the idea that comorbid GWI and PTSD symptoms lead to worse health outcomes, while demonstrating how GWI and PTSD symptoms may uniquely contribute to clinical presentation.

Gulf War Illness Clinical Trials and Interventions Consortium (GWICTIC): A collaborative research infrastructure for intervention and implementation

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Authors

Amanpreet K Cheema [1], Rebecca B McNeil [2], Travis Craddock [3], Gordon Broderick [4], Maria M Abreu [5], Kristina Aenlle [5], Drew A Helmer [6], J Wesson Ashford [7], Kimberly Sullivan [8], Alison Bested [9], Devra E Cohen [5], Dikoma Shungu [10], Helena Chandler [11], Mary Ann Fletcher [12], Maxine Krengel [13], Nancy Klimas [5]

Affiliations

- [1] Institute for Neuro Immune Medicine, Dr. Kiran C. Patel College of Osteopathic Medicine, Nova Southeastern University, Fort Lauderdale, FL, United States; Department of Nutrition, Dr. Kiran C. Patel College of Osteopathic Medicine, Nova Southeastern University, Fort Lauderdale, FL, United States; Halmos College of Natural Sciences and Oceanography, Nova Southeastern University, Fort Lauderdale, FL, United States. Electronic address: acheema@nova.edu.
- [2] RTI International, Research Triangle Park, NC, United States.
- [3] Institute for Neuro Immune Medicine, Dr. Kiran C. Patel College of Osteopathic Medicine, Nova Southeastern University, Fort Lauderdale, FL, United States; Department of Psychology and Neuroscience, Nova Southeastern University, Fort Lauderdale, FL, United States; Department of Computer Science, Nova Southeastern University, Fort Lauderdale, FL, United States.
- [4] Center for Clinical Systems Biology, Rochester General Hospital, Rochester, NY, United States.
- [5] Institute for Neuro Immune Medicine, Dr. Kiran C. Patel College of Osteopathic Medicine, Nova Southeastern University, Fort Lauderdale, FL, United States; Miami VA Healthcare System, Miami, FL, United States.
- [6] Center for Innovations in Quality, Effectiveness and Safety, Michael E. DeBakey VA Medical Center, Houston, TX, United States; Department of Medicine, Baylor College of Medicine, Houston, TX, United States.
- [7] War Related Illness & Injury Study Center, VA Palo Alto Health Care System, Palo Alto, CA, United States; Department of Psychiatry & Behavioral Sciences, College of Medicine, Stanford University, Palo Alto, CA, United States.
- [8] Department of Environmental Health, Boston University School of Public Health, Boston, MA, United States.
- [9] Department of Integrative Medicine, Nova Southeastern University College of Osteopathic Medicine, Fort Lauderdale, FL, United States.
- [10] Department of Radiology, Weill Cornell Medical College, New York, NY, United States.
- [11] War Related Illness and Injury Study Center, Department of Veterans Affairs New Jersey Health Care System, East Orange, NJ, United States.
- [12] Institute for Neuro Immune Medicine, Dr. Kiran C. Patel College of Osteopathic Medicine, Nova Southeastern University, Fort Lauderdale, FL, United States.
- [13] VA Boston Healthcare System, Boston, MA, United States; Department of Neurology, Boston University School of Medicine, Boston, MA, United States.

Abstract

Aims: There is an inadequate portfolio of treatments for Gulf War Illness (GWI), a complex disease involving multiple organ systems, and early-phase clinical trials are hampered by many logistical problems. To address these challenges, the Gulf War Illness Clinical Trials and Interventions Consortium (GWICTIC) was formed with the aims of (i) creating a collaborative consortium of clinical and scientific researchers that will rapidly implement rigorous and innovative phase I and II clinical trials for GWI, (ii) perform at least four phase I or II clinical trials, (iii) provide a foundation of scalable infrastructure and management in support of the efficient and successful operation of the GWICTIC, and (iv) partner with the Boston Biorepository, Recruitment & Integrated Network for GWI and other GWI investigators to develop a common data element platform for core assessments and outcomes. **Main methods:** The GWICTIC brings together a multidisciplinary team of researchers at several institutions to provide scientific innovation, statistical and computational rigor, and

logistical efficiency in the development and implementation of early-phase low-risk clinical trials for GWI. The GWICTIC core trials adhere to a Veteran-centered philosophy and focus on interventions with multiple mechanistic targets to maximize the likelihood of efficacy. To support rapid and efficient study startup and implementation across the GWI research community, the GWICTIC will share infrastructure with investigator-initiated research studies funded under separate mechanisms. **Significance:** The GWICTIC will leverage the efficiencies of centralized research support and innovative trial designs to address several longstanding needs in the GWI interventions research community.

Effect of the low glutamate diet on inflammatory cytokines in veterans with Gulf War Illness (GWI): A pilot study

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Authors
Kathleen F Holton [1], Shalini S Ramachandra [2], Sidney L Murray [3], Michael Baron [4], James N Baraniuk [5]

Affiliations
- [1] Department of Health Studies, American University, Washington, DC 20016, United States of America; Center for Neuroscience and Behavior, American University, Washington, DC 20016, United States of America. Electronic address: holton@american.edu.
- [2] Department of Health Studies, American University, Washington, DC 20016, United States of America; Department of Mathematics and Statistics, American University, Washington, DC 20016, United States of America.
- [3] Behavior, Cognition, and Neuroscience Program, American University, Washington, DC 20016, United States of America.
- [4] Department of Mathematics and Statistics, American University, Washington, DC 20016, United States of America.
- [5] Department of Medicine, Georgetown University, Washington, DC 20057, United States of America.

Abstract
Aim: To examine the effects of the low glutamate diet on inflammatory cytokines in veterans with Gulf War Illness (GWI).
Main methods: Forty veterans with GWI were recruited from across the country. Anthropometric measurements and blood samples were collected at baseline and after one month on the low glutamate diet. Dietary adherence was measured with a glutamate food frequency questionnaire (FFQ). Inflammatory cytokines (IL-1β, IL-6, IFN-γ, and TNF-α) were measured in pre- and post-diet serum (N = 34). Improvement was defined as being "much" or "very much" improved on the patient global impression of change scale (PGIC), or as having ≥30% of their symptoms remit. Correlations of the FFQ and the cytokines were calculated, followed by multivariable linear regression for significant findings. Mann Whitney U tests were used to compare cytokine levels according to improvement on the diet, and then logistic regression was used to estimate the association after adjustment for potential confounders. Classification trees were also produced to determine the ability of change in the inflammatory cytokines to predict improvement on the diet.
Key findings: Dietary adherence was significantly associated with reduction in TNF-α, and PGIC improvement was significantly associated with reduced IL-1β, after adjustment for potential confounders. Classification trees demonstrated that IL-1β, TNF-α, and IL-6 can predict improvement on the diet with 76.5% accuracy.
Significance: Finding suggests that the low glutamate diet may be able to reduce systemic inflammation in veterans with GWI.

Neurotoxicant exposures and rates of Chronic Multisymptom Illness and Kansas Gulf War illness criteria in gulf war deployed women veterans

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Authors
Maxine Krengel [1], Kimberly Sullivan [2], Vahé Heboyan [3], Clara G Zundel [4], Col Candy Wilson [5], Nancy Klimas [6], Steven S Coughlin [7]

Affiliations
- [1] Boston University School of Medicine, United States of America; VA Boston Healthcare System, Boston, MA, United States of America. Electronic address: mhk@bu.edu.
- [2] Boston University School of Public Health, Boston, MA, United States of America.
- [3] Health Economics and Modeling Division, Population Health Sciences Department, Medical College of Georgia, Augusta University, Augusta, GA, United States of America.
- [4] Boston University School of Medicine, United States of America; VA Boston Healthcare System, Boston, MA, United States of America.
- [5] Uniformed Services University Graduate School of Nursing, Bethesda, MD, United States of America.
- [6] Miami VA Healthcare System, Miami, FL, United States of America; Institute for Neuro-Immune Medicine, Dr. Kiran C. Patel College of Osteopathic Medicine, Nova Southeastern University, Fort Lauderdale, FL, United States of America.
- [7] Department of Population Health Sciences, Medical College of Georgia, Augusta University, Augusta, GA, United States of America; Research Service, Charlie Norwood Veterans Administration Medical Center, Augusta, GA, United States of America.

Abstract
Aims: This study analyzed deployment-related exposures and risk of Persian Gulf War Illness (GWI) in women veterans from the Veterans Affairs (VA) Cooperative Studies Program 585 Gulf War Era Cohort and Biorepository (GWECB CSP#585).
Main methods: We examined the associations between GW deployment-related exposures and case definitions for GWI in deployed GW women. Multivariate regression analyses controlling for demographic outcomes were performed.
Key findings: Surveys were obtained from 202 GW deployed women veterans. Self-reported exposure to smoke from oil well fires as well as chemical and biological warfare were the only exposures significantly associated with the Center for Disease Control and Prevention (CDC) GWI criteria. Seventy-nine women were excluded from the rest of the analyses as they met Kansas GW illness exclusion criteria. Eligible women who self-reported deployment-related exposure to smoke from oil wells, pyridostigmine bromide (PB) pills, pesticide cream, pesticide treated uniforms, and insect baits were significantly more likely to meet the Kansas GWI criteria (n = 123) than those unexposed and exposures were related to Kansas symptom subdomain endorsements.
Significance: These results suggest that women GW veterans reporting deployment related exposures of pesticide, oil well fire and PB pills are significantly more likely to meet the Kansas GWI criteria in this national cohort of GW women suggesting its utility in future studies. In addition, based on these results it appears that women exposed to particular toxicants during the war may benefit from more targeted treatment strategies dependent upon the mechanism of exposure of their toxicant induced outcomes.

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

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Authors
Bani Malhotra [1], Rebekka Dieterich-Hartwell [2], Bryann DeBeer [3], Christina Burns [2], Girija Kaimal [2]

Affiliations
- [1] Department of Creative Arts Therapies, Drexel University, Philadelphia, PA, United States of America. Electronic address: bm3223@drexel.edu.
- [2] Department of Creative Arts Therapies, Drexel University, Philadelphia, PA, United States of America.
- [3] Rocky Mountain Mental Illness, Research, Education and Clinical Center (MIRECC) for Suicide Prevention, Rocky Mountain Regional VHA Medical Center, Aurora, CO and Department of Physical Medicine and Rehabilitation, University of Colorado Anschutz Medical Campus, Aurora, CO, United States of America.

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.

Emerging role of glutamate in the pathophysiology and therapeutics of Gulf War illness

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Authors
Xueqin Wang [1], Noor Ali [1], Chien-Liang Glenn Lin [2]

Affiliations
- [1] Department of Neuroscience, College of Medicine, The Ohio State University, Columbus, OH, USA.
- [2] Department of Neuroscience, College of Medicine, The Ohio State University, Columbus, OH, USA. Electronic address: lin.492@osu.edu.

Abstract
Gulf War illness (GWI) is a chronic and multi-symptomatic disorder affecting veterans who served in the Gulf War. The commonly reported symptoms in GWI veterans include mood problems, cognitive impairment, muscle and joint pain, migraine/headache, chronic fatigue, gastrointestinal complaints, skin rashes, and respiratory problems. Neuroimaging studies have revealed significant brain structure alterations in GWI veterans, including subcortical atrophy, decreased volume of the hippocampus, reduced total grey and white matter, and increased brain white matter axial diffusivity. These brain changes may contribute to or increase the severities of the GWI-related symptoms. Epidemiological studies have revealed that neurotoxic exposures and stress may be significant contributors to the development of GWI. However, the mechanism underlying how the exposure and stress could contribute to the multi-symptomatic disorder of GWI remains unclear. We and others have demonstrated that rodent models exposed to GW-related agents and stress exhibited higher extracellular glutamate levels, as well as impaired structure and function of glutamatergic synapses. Restoration of the glutamatergic synapses ameliorated the GWI-related pathological and behavioral deficits. Moreover, recent studies showed that a low-glutamate diet reduced multiple symptoms in GWI veterans, suggesting an important role of the glutamatergic system in GWI. Currently, growing evidence has indicated that abnormal glutamate neurotransmission may contribute to the GWI symptoms. This review summarizes the potential roles of glutamate dyshomeostasis and dysfunction of the glutamatergic system in linking the initial cause to the multi-symptomatic outcomes in GWI and suggests the glutamatergic system as a therapeutic target for GWI.

Heart rate and heart rate variability as outcomes and longitudinal moderators of treatment for pain across follow-up in Veterans with Gulf War illness

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Authors
Danielle C Mathersul [1], Kamini Dixit [2], Timothy J Avery [3], R Jay Schulz-Heik [2], Jamie M Zeitzer [4], Louise A Mahoney [2], Rachael H Cho [2], Peter J Bayley [5]

Affiliations
- [1] War Related Illness and Injury Study Center (WRIISC), Veterans Affairs Palo Alto Health Care System, Palo Alto, CA 94304, United States of America; Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305, United States of America; Discipline of Psychology, Murdoch University, Murdoch, WA 6150, Australia. Electronic address: danielle.mathersul@murdoch.edu.au.
- [2] War Related Illness and Injury Study Center (WRIISC), Veterans Affairs Palo Alto Health Care System, Palo Alto, CA 94304, United States of America.
- [3] War Related Illness and Injury Study Center (WRIISC), Veterans Affairs Palo Alto Health Care System, Palo Alto, CA 94304, United States of America; Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305, United States of America; National Centre for Posttraumatic Stress Disorder (NCPTSD), Veterans Affairs Menlo Park Health Care System, Menlo Park, CA 94025, United States of America.
- [4] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305, United States of America; Mental Illness Research, Education and Clinical Center (MIRECC), Veterans Affairs Palo Alto Health Care System, Palo Alto, CA 94304, United States of America.
- [5] War Related Illness and Injury Study Center (WRIISC), Veterans Affairs Palo Alto Health Care System, Palo Alto, CA 94304, United States of America; Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305, United States of America.

Abstract
Aims: Accumulating evidence suggests Gulf War illness (GWI) is characterized by autonomic nervous system dysfunction (higher heart rate [HR], lower heart rate variability [HRV]). Yoga - an ancient mind-body practice combining mindfulness, breathwork, and physical postures - is proposed to improve autonomic dysfunction yet this remains untested in GWI. We aimed to determine (i) whether HR and HRV improve among Veterans with GWI receiving either yoga or cognitive behavioural therapy (CBT) for pain; and (ii) whether baseline autonomic functioning predicts treatment-related pain outcomes across follow-up.
Main methods: We present secondary analyses of 24-hour ambulatory cardiac data (mean HR, square root of the mean squared differences between successive R-R intervals [RMSSD], high frequency power [HF-HFV], and low-to-high frequency ratio [LF/HF] extracted from a 5-min window during the first hour of sleep) from our randomised controlled trial of yoga versus CBT for pain among Veterans with GWI (ClinicalTrials.govNCT02378025; N = 75).
Key findings: Veterans who received CBT tended towards higher mean HR at end-of-treatment. Better autonomic function (lower mean HR, higher RMSSD/HF-HRV) at baseline predicted greater reductions in pain across follow-up, regardless of treatment group. Better baseline autonomic function (mid-range-to-high RMSSD/HF-HRV) also predicted greater pain reductions with yoga, while worse baseline autonomic function (higher mean HR, lower RMSSD/HF-HRV) predicted greater pain reductions with CBT.
Significance: To our knowledge, this is the first study to suggest that among Veterans with GWI, HR may increase with CBT yet remain stable with yoga. Furthermore, HR and HRV moderated pain outcome across follow-up for yoga and CBT.

Nociceptive stress interferes with neural processing of cognitive stimuli in Gulf War Veterans with chronic musculoskeletal pain

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Authors
Jacob B Lindheimer [1], Aaron J Stegner [2], Stephanie M Van Riper [2], Jacob V Ninneman [2], Laura D Ellingson [3], Dane B Cook [2]

Affiliations
- [1] William S. Middleton Memorial Veterans Hospital, Madison, WI, USA; Department of Kinesiology, University of Wisconsin-Madison, Madison, WI, USA; Department of Medicine, University of Wisconsin-Madison, Madison, WI, USA. Electronic address: lindheimer@wisc.edu.
- [2] William S. Middleton Memorial Veterans Hospital, Madison, WI, USA; Department of Kinesiology, University of Wisconsin-Madison, Madison, WI, USA.
- [3] Division of Health and Exercise Science, Western Oregon University, Monmouth, OR, USA.

Abstract
Aims: Disrupted cognition and chronic musculoskeletal pain (CMP) are prevalent experiences among Gulf War Veterans (GWV). A negative association between CMP and cognition (i.e., chronic pain-related cognitive interference) has been observed in some chronic pain populations but has not been evaluated in GWV. Additional research suggests that disrupted cognition in GWV with CMP may be exacerbated by stressing the nociceptive system. Therefore, we compared cognitive performance and related neural activity between CMP and healthy control (CO) GWV in the absence and presence of experimental pain.
Main methods: During functional magnetic resonance imaging (fMRI), Veterans (CMP = 29; CO = 27) completed cognitive testing via congruent and incongruent conditions of a modified Stroop task (Stroop-only). A random subset (CMP = 13; CO = 13) also completed cognitive testing with experimental pain (Pain+Stroop). Yuen's modified t-test and robust mixed-model analysis of variance (ANOVA) models were used for analyzing cognitive performance data. Independent t-tests and repeated-measures ANOVA models were employed for fMRI data with thresholding for multiple-comparisons ($p < 0.005$) and cluster size (> 320 mm^3).
Key findings: Functional MRI analysis revealed significant between-group differences for the incongruent but not congruent-Stroop run. Neither correct responses nor reaction time differed between groups in either Stroop condition (all $p \geq 0.21$). Significant group (CMP, CO) by run (Stroop-only, Pain+Stroop) interactions revealed greater neural responses in CMP Veterans during Pain+Stroop runs. No significant interactions were observed for correct responses or reaction time ($p \geq 0.31$).
Significance: GWV with CMP require a greater amount of neural resources to sustain cognitive performance during nociceptive stress.

Lacto-N-fucopentaose-III (LNFPIII) ameliorates acute aberrations in hippocampal synaptic transmission in a Gulf War Illness animal model

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Authors
Kyle A Brown [1], Collin J Preston [1], Jessica M Carpenter [2], Helaina D Ludwig [1], Thomas Norberg [3], Donald A Harn [4], Nikolay M Filipov [5], John J Wagner [6]

Affiliations
- [1] Department of Physiology and Pharmacology, University of Georgia, Athens, GA, United States; Interdisciplinary Toxicology Program, University of Georgia, Athens, GA, United States.
- [2] Department of Physiology and Pharmacology, University of Georgia, Athens, GA, United States; Neuroscience PhD Program, University of Georgia, Athens, GA, United States.
- [3] Department of Chemistry, University of Uppsala, Uppsala, Sweden.
- [4] Department of Infectious Diseases, University of Georgia, Athens, GA, United States; Center for Tropical and Emerging Infectious Diseases, University of Georgia, Athens, GA, United States.
- [5] Department of Physiology and Pharmacology, University of Georgia, Athens, GA, United States; Interdisciplinary Toxicology Program, University of Georgia, Athens, GA, United States; Neuroscience PhD Program, University of Georgia, Athens, GA, United States. Electronic address: filipov@uga.edu.
- [6] Department of Physiology and Pharmacology, University of Georgia, Athens, GA, United States; Interdisciplinary Toxicology Program, University of Georgia, Athens, GA, United States. Electronic address: jwagner@uga.edu.

Abstract
Approximately one-third of Persian Gulf War veterans are afflicted by Gulf War Illness (GWI), a chronic multisymptom condition that fundamentally presents with cognitive deficits (i.e., learning and memory impairments) and neuroimmune dysfunction (i.e., inflammation). Factors associated with GWI include overexposures to neurotoxic pesticides and nerve agent prophylactics such as permethrin (PM) and pyridostigmine bromide (PB), respectively. GWI-related neurological impairments associated with PB-PM overexposures have been recapitulated in animal models; however, there is a paucity of studies assessing PB-PM-related aberrations in hippocampal synaptic plasticity and transmission that may underlie behavioral impairments. Importantly, FDA-approved neuroactive treatments are currently unavailable for GWI. In the present study, we assessed the efficacy of an immunomodulatory therapeutic, lacto-N-fucopentaose-III (LNFPIII), on ameliorating acute effects of in vivo PB-PM exposure on synaptic plasticity and transmission as well as trophic factor/cytokine expression along the hippocampal dorsoventral axis. PB-PM exposure resulted in hippocampal synaptic transmission deficits 48 h post-exposure, a response that was ameliorated by LNFPIII coadministration, particularly in the dorsal hippocampus (dH). LNFPIII coadministration also enhanced synaptic transmission in the dH and the ventral hippocampus (vH). Notably, LNFPIII coadministration elevated long-term potentiation in the dH. Further, PB-PM exposure and LNFPIII coadministration uniquely altered key inflammatory cytokine and trophic factor production in the dH and the vH. Collectively, these findings demonstrate that PB-PM exposure impaired hippocampal synaptic responses 48 h post-exposure, impairments that differentially manifested along the dorsoventral axis. Importantly, LNFPIII ameliorated GWI-related electrophysiological deficits, a beneficial effect indicating the potential efficacy of LNFPIII for treating GWI.

The Carbamate, Physostigmine does not Impair Axonal Transport in Rat Cortical Neurons

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Sean X Naughton[1], Wayne D Beck[1], Zhe Wei[1], Guangyu Wu[1], Peter W Baas[2], Alvin V Terry Jr[1]

Affiliations

- [1]Department of Pharmacology and Toxicology, Medical College of Georgia, Augusta University, Augusta, GA, USA.
- [2]Department of Neurobiology and Anatomy, Drexel University, College of Medicine, Philadelphia, PA, USA.

Abstract

Among the various chemicals that are commonly used as pesticides, organophosphates (OPs), and to a lesser extent, carbamates, are most frequently associated with adverse long-term neurological consequences. OPs and the carbamate, pyridostigmine, used as a prophylactic drug against potential nerve agent attacks, have also been implicated in Gulf War Illness (GWI), which is often characterized by chronic neurological symptoms. While most OP- and carbamate-based pesticides, and pyridostigmine are relatively potent acetylcholinesterase inhibitors (AChEIs), this toxicological mechanism is inadequate to explain their long-term health effects, especially when no signs of acute cholinergic toxicity are exhibited. Our previous work suggests that a potential mechanism of the long-term neurological deficits associated with OPs is impairment of axonal transport (AXT); however, we had not previously evaluated carbamates for this effect. Here we thus evaluated the carbamate, physostigmine (PHY), a highly potent AChEI, on AXT using an *in vitro* neuronal live imaging assay that we have previously found to be very sensitive to OP-related deficits in AXT. We first evaluated the OP, diisopropylfluorophosphate (DFP) (concentration range 0.001-10.0 µM) as a reference compound that we found previously to impair AXT and subsequently evaluated PHY (concentration range 0.01-100 nM). As expected, DFP impaired AXT in a concentration-dependent manner, replicating our previously published results. In contrast, none of the concentrations of PHY (including concentrations well above the threshold for impairing AChE) impaired AXT. These data suggest that the long-term neurological deficits associated with some carbamates are not likely due to acute impairments of AXT.

Adaptive Immune Responses Associated with the Central Nervous System Pathology of Gulf War Illness

Aurore Nkiliza[1], Utsav Joshi[1], James E Evans[1], Ghania Ait-Ghezala[1], Megan Parks[1], Fiona Crawford[1], Michael Mullan[1], Laila Abdullah[1]

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Affiliation

- [1]Roskamp Institute, Sarasota, FL, USA.

Abstract

Gulf War Illness is a multisymptomatic condition which affects 30% of veterans from the 1991 Gulf War. While there is evidence for a role of peripheral cellular and humoral adaptive immune responses in Gulf War Illness, a potential role of the adaptive immune system in the central nervous system pathology of this condition remains unknown. Furthermore, many of the clinical features of Gulf War Illness resembles those of autoimmune diseases, but the biological processes are likely different as the etiology of Gulf War Illness is linked to hazardous chemical exposures specific to the Gulf War theatre. This review discusses Gulf War chemical-induced maladaptive immune responses and a potential role of cellular and humoral immune responses that may be relevant to the central nervous system symptoms and pathology of Gulf War Illness. The discussion may stimulate investigations into adaptive immunity for developing novel therapies for Gulf War Illness.

Vagus Nerve Stimulation Ameliorates Cognitive Impairment and Increased Hippocampal Astrocytes in a Mouse Model of Gulf War Illness

Lavanya Venkatasamy[1], Damir Nizamutdinov[1], Jaclyn Jenkins[1], Lee A Shapiro[1]

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Affiliation

- [1]Department of Neuroscience and Experimental Therapeutics, Texas A&M University, Bryan, TX, USA.

Abstract

Gulf war illness (GWI), is a chronic multi-symptom illness that has impacted approximately one-third of the veterans who served in the 1990 to 1991 Gulf War. GWI symptoms include cognitive impairments (eg, memory and concentration problems), headaches, migraines, fatigue, gastrointestinal and respiratory issues, as well as emotional deficits. The exposure to neurological chemicals such as the anti-nerve gas drug, pyridostigmine bromide (PB), and the insecticide permethrin (PER), may contribute to the etiologically related factors of GWI. Various studies utilizing mouse models of GWI have reported the interplay of these chemical agents in increasing neuroinflammation and cognitive dysfunction. Astrocytes are involved in the secretion of neuroinflammatory cytokines and chemokines in pathological conditions and have been implicated in GWI symptomology. We hypothesized that exposure to PB and PER causes lasting changes to hippocampal astrocytes, concurrent with chronic cognitive deficits that can be reversed by cervical vagus nerve stimulation (VNS). GWI was induced in CD1 mice by injecting the mixture of PER (200 mg/kg) and PB (2 mg/kg), i.p. for 10 consecutive days. VNS stimulators were implanted at 33 weeks after GWI induction. The results show age-related cognitive alterations at approximately 9 months after exposure to PB and PER. The results also showed an increased number of GFAP-labeled astrocytes in the hippocampus and dentate gyrus that was ameliorated by VNS.

Altered hippocampal function and cytokine levels in a rat model of Gulf War illness

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Authors
Nathan M Gargas [1], Victoria T Ethridge [2], Molly K Miklasevich [3], Joyce G Rohan [4]

Affiliations
- [1] Naval Medical Research Unit Dayton, 2728 Q Street, Area B, Building 837, WPAFB, OH 45433, USA; Henry M. Jackson Foundation for the Advancement of Military Medicine, 6720A Rockledge Drive, Bethesda, MD 20817, USA; Odyssey Systems Consulting Group, Ltd, 201 Edgewater Drive Suite 270, Wakefield, MA 01880, USA.
- [2] Naval Medical Research Unit Dayton, 2728 Q Street, Area B, Building 837, WPAFB, OH 45433, USA; Oak Ridge Institute for Science and Education, 1299 Bethel Valley Rd, Oak Ridge, TN 37830, USA.
- [3] Naval Medical Research Unit Dayton, 2728 Q Street, Area B, Building 837, WPAFB, OH 45433, USA; Henry M. Jackson Foundation for the Advancement of Military Medicine, 6720A Rockledge Drive, Bethesda, MD 20817, USA.
- [4] Naval Medical Research Unit Dayton, 2728 Q Street, Area B, Building 837, WPAFB, OH 45433, USA. Electronic address: Joyce.Rohan.1@us.af.mil.
- PMID: 33705732
- DOI: 10.1016/j.lfs.2021.119333

Abstract
Aims: Gulf War illness (GWI) is a disorder affecting military personnel deployed in the Gulf War (GW) from 1990 to 1991. Here, we will use a rat model of GWI to evaluate hippocampal function and cytokine levels.
Materials and methods: Rats were exposed to diethyltoluamide and permethrin via dermal absorption and pyridostigmine bromide via gavage with or without a 5-min restraint for 28 days. Immediate and delayed effects of GW chemical exposure were evaluated using electrophysiology to quantitate hippocampal function, behavioral tests to assess cognitive effects and biochemical assays to measure neurotransmitter and cytokine levels.
Key findings: Behavioral data revealed a statistically significant increase in motor activity at 3 months following completion of exposures, potentially indicating increased excitability, and/or restlessness. Electrophysiology data revealed statistically significant changes in paired pulse facilitation and input-output function of CA1 hippocampal neurons within 24 h and 3 months following completion of exposures. There was also a statistically significant reduction in the frequency of spontaneous firing activity of hippocampal neurons within 24 h following exposures. Naïve hippocampal slices directly incubated in GW chemicals also resulted in similar changes in electrophysiological parameters. Biochemical measurements revealed reduced hippocampal glutamate level at 3 months post-exposure. Furthermore, there was a statistically significant increase in plasma and hippocampal levels of IL-13, as well as decrease in plasma level of IL-1β.
Significance: Our data support an effect on glutamate signaling within the hippocampus as indicated by changes in PPF and hippocampal level of glutamate, with some activation of T helper type 2 immune response.

Surveillance of Depleted Uranium-exposed Gulf War Veterans: More Evidence for Bone Effects

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Authors

Melissa A McDiarmid, Joanna M Gaitens, Stella Hines, Marianne Cloeren, Richard Breyer [1], Marian Condon [1], Marc Oliver, Tracy Roth, Patricia Gucer, Bruce Kaup [1], Lawrence Brown, Clayton H Brown [2], Moira Dux [1], Danielle Glick [3], Michael R Lewin-Smith [4], Frederick Strathmann [4], Hanna Xu [4], Maria A Velez-Quinones [4], Elizabeth Streeten [3]

Affiliations

- [1] Department of Veterans Affairs Medical Center Baltimore, MD.
- [2] Biophysical Toxicology, The Joint Pathology Center, Silver Spring, MD.
- [3] Department of Medicine, University of Maryland School of Medicine, Baltimore, MD.
- [4] Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, 655 W Baltimore S, Baltimore, MD 21201.

Abstract

Gulf War I veterans who were victims of depleted uranium (DU) "friendly-fire" incidents have undergone longitudinal health surveillance since 1994. During the spring of 2019, 36 members of the cohort were evaluated with a monitoring protocol including exposure assessment for total and isotopic uranium concentrations in urine and a comprehensive review of health outcomes, including measures of bone metabolism and bone mineral density (BMD) determination. Elevated urine U concentrations were observed in cohort members with retained depleted uranium (DU) shrapnel fragments. In addition, a measure of bone resorption, N-telopeptide, showed a statistically significant increase in those in the high DU subgroup, a finding consistent with a statistically significant decrease in bone mass also observed in this high DU subgroup compared to the low DU subgroup. After more than 25 y since first exposure to DU, an aging cohort of military veterans continues to show few U-related health effects in known target organs of U toxicity. The new finding of impaired BMD in the high DU subgroup has now been detected in two consecutive surveillance visits. While this is a biologically plausible uranium effect, it is not reflected in other measures of bone metabolism in the full cohort, which have largely been within normal limits. However, ongoing accrual of the U burden from fragment absorption over time and the effect of aging further impairing BMD suggest the need for future surveillance assessments of this cohort.

Genomics of Gulf War Illness in U.S. Veterans Who Served during the 1990-1991 Persian Gulf War: Methods and Rationale for Veterans Affairs Cooperative Study #2006

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Krishnan Radhakrishnan[1,2], Elizabeth R Hauser[3,4], Renato Polimanti[5,6], Drew A Helmer[7,8], Dawn Provenzale[3,4], Rebecca B McNeil[3], Alysia Maffucci[5], Rachel Quaden[9], Hongyu Zhao[5,10], Stacey B Whitbourne[9,11,12], Kelly M Harrington[9,13], Jacqueline Vahey[3,14], Joel Gelernter[5,6], Daniel F Levey[15,16], Grant D Huang[17], John Michael Gaziano[9,11], John Concato[6,18], Mihaela Aslan[5,6]

Affiliations

- [1]Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Rockville, MD 20857, USA.
- [2]College of Medicine, University of Kentucky, Lexington, KY 40536, USA.
- [3]VA Cooperative Studies Program Epidemiology Center-Durham, Department of Veterans Affairs, Durham, NC 27705, USA.
- [4]Department of Biostatistics and Bioinformatics, Duke University, Durham, NC 27705, USA.
- [5]Cooperative Studies Program Clinical Epidemiology Research Center (CSP-CERC), VA Connecticut Healthcare System, West Haven, CT 06516, USA.
- [6]School of Medicine, Yale University, New Haven, CT 06511, USA.
- [7]Center for Innovations in Quality, Effectiveness, and Safety (IQuESt), Michael E. DeBakey VA Medical Center, Houston, TX 77030, USA.
- [8]Department of Medicine, Baylor College of Medicine, Houston, TX 77030, USA.
- [9]Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Healthcare System, Boston, MA 02130, USA.
- [10]Department of Biostatistics, Yale School of Public Health, New Haven, CT 06520, USA.
- [11]Department of Medicine, Harvard Medical School, Boston, MA 02115, USA.
- [12]Department of Medicine, Division of Aging, Brigham and Women's Hospital, Boston, MA 02115, USA.
- [13]Department of Psychiatry, Boston University School of Medicine, Boston, MA 02118, USA.
- [14]Computational Biology and Bioinformatics Program, Duke University, Durham, NC 27705, USA.
- [15]Division of Human Genetics, Department of Psychiatry, School of Medicine, Yale University, New Haven, CT 06511, USA.
- [16]Department of Psychiatry, Veterans Affairs Connecticut Healthcare Center, West Haven, CT 06516, USA.
- [17]Cooperative Studies Program, VA Office of Research and Development, Washington, DC 20420, USA.
- [18]Food and Drug Administration, Silver Spring, MD 20993, USA.

Abstract

Background: Approximately 697,000 members of the U.S. Armed Forces were deployed to the Persian Gulf in support of the 1990-1991 Persian Gulf War (GW). Subsequently, many deployed and some non-deployed veterans developed a chronic multi-symptom illness, now named Gulf War Illness (GWI). This manuscript outlines the methods and rationale for studying the genomics of GWI within the Million Veteran Program (MVP), a VA-based national research program that has linked medical records, surveys, and genomic data, enabling genome-wide association studies (GWASs).

Methods: MVP participants who served in the military during the GW era were contacted by mail and invited to participate in the GWI study. A structured health questionnaire, based on a previously tested instrument, was also included in the mailing. Data on deployment locations and exposures, symptoms associated with GWI, clinical diagnoses, personal habits, and health care utilization were collected. Self-reported data will be augmented with chart reviews and structured international classification of disease

codes, to classify participants by GWI case status. We will develop a phenotyping algorithm, based on two commonly used case definitions, to determine GWI status, and then conduct a nested case-control GWAS. Genetic variants associated with GWI will be investigated, and gene-gene and gene-environment interactions studied. The genetic overlap of GWI with, and causative mechanisms linking this illness to, other health conditions and the effects of genomic regulatory mechanisms on GWI risk will also be explored. **Conclusions:** The proposed initial GWAS described in this report will investigate the genomic underpinnings of GWI with a large sample size and state-of-the-art genomic analyses and phenotyping. The data generated will provide a rich and expansive foundation on which to build additional analyses.

A review of pre-clinical models for Gulf War Illness

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Ana C R Ribeiro[1], Laxmikant S Deshpande[2]

Affiliations

- [1]Departments of Neurology, School of Medicine, Virginia Commonwealth University, Richmond, VA, USA.
- [2]Departments of Neurology, School of Medicine, Virginia Commonwealth University, Richmond, VA, USA; Departments of Pharmacology and Toxicology, School of Medicine, Virginia Commonwealth University, Richmond, VA, USA. Electronic address: laxmikant.deshpande@vcuhealth.org.

Abstract

Gulf War Illness (GWI) is a chronic multisymptomatic disorder that afflicts over 1/3rd of the 1991 GW veterans. It spans multiple bodily systems and presents itself as a syndrome exhibiting diverse symptoms including fatigue, depression, mood, and memory and concentration deficits, musculoskeletal pain and gastrointestinal distress in GW veterans. The etiology of GWI is complex and many factors, including chemical, physiological, and environmental stressors present in the GW arena, have been implicated for its development. It has been over 30 years since the end of the GW but, GWI has been persistent in suffering veterans who are also dealing with paucity of effective treatments. The multifactorial aspect of GWI along with genetic heterogeneity and lack of available data surrounding war-time exposures have proved to be challenging in developing pre-clinical models of GWI. Despite this, over a dozen GWI animal models exist in the literature. In this article, following a brief discussion of GW history, GWI definitions, and probable causes for its pathogenesis, we will expand upon various experimental models used in GWI laboratory research. These animal models will be discussed in the context of their attempts at mimicking GW-related exposures with regards to the variations in chemical combinations, doses, and frequency of exposures. We will discuss their advantages and limitations in modeling GWI followed by a discussion of behavioral and molecular findings in these models. The mechanistic data obtained from these preclinical studies have offered multiple molecular pathways including chronic inflammation, mitochondrial dysfunction, oxidative stress, lipid disturbances, calcium homeostatic alterations, changes in gut microbiota, and epigenetic modifications, amongst others for explaining GWI development and its persistence. Finally, these findings have also informed us on novel druggable targets in GWI. While, it has been difficult to conceive a single pre-clinical model that could express all the GWI signs and exhibit biological complexity reflective of the clinical presentation in GWI, animal models have been critical for identifying molecular underpinnings of GWI and evaluating treatment strategies for GWI.