The Gulf War Illness Landscape

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I. Gulf War Illness Primary Features and Prevalence

I.1. Symptoms of Gulf War Illness

Within a short time after the 1990-1991 Gulf War (GW), Veterans who served in and around the theater of operations developed enduring, chronic conditions and/or constellations of symptoms and illnesses that could not be explained by established medical/psychiatric diagnoses or standard laboratory tests.

Symptoms experienced and reported by GW Veterans vary widely. However, the reported symptoms are similar clinically and usually include combinations of widespread pain, muscle aches, headache, persistent problems with memory and thinking, fatigue, breathing problems, stomach and intestinal symptoms, and skin abnormalities. In addition to the physical symptoms, changes in behavior and problems with interpersonal relationships frequently occurred.

Initially, this constellation of disorders was referred to as "Gulf War Syndrome." Other names given to these problems included chronic multi-symptom illness (CMI), undiagnosed illness, Gulf War illness (GWI), and other terms. Currently, "Gulf War illness" is the term recommended by the National Academy of Medicine (formerly the Institute of Medicine [IOM]) and is most commonly used by scientists, clinicians, Veterans organizations, and the U.S. Department of Defense (DoD).

I.2. Prevalence

GWI is estimated to affect 175,000 to 250,000 of the nearly 700,000 troops deployed to the 1990-1991 GW theater of operations. Twenty-seven of the 28 Coalition country members participating in the GW conflict have reported GWI in their troops. Epidemiologic studies indicate that rates of GWI vary in different subgroups of GW Veterans. GWI affects Veterans who served in the U.S. Army and Marines Corps at higher rates than those who served in the Navy and Air Force, and U.S. enlisted personnel are affected more than officers. Studies also indicate that GWI rates differ by where Veterans were located during deployment, with the highest rates among troops who served in areas in proximity to combat.

II. Risk Factors

II.1. GW Exposures

During the GW, Service members were exposed to low levels of chemicals, including chemical warfare agents released by the destruction of Iraqi facilities, widespread spraying and use of pesticides, prophylactic medications to protect against hazardous exposures, constant dust and sand storms, and effluent from oil well fires ignited by Iraqi troops.

Cholinergic agents represent the class of compounds with the broadest exposures experienced by Service members deployed to the GW. Of these, the organophosphates, including the chemical warfare agents sarin, cyclosarin, soman, and the pesticides permethrin (PER) and chlorpyrifos (CPF), have received considerable attention. Other cholinergic agents to which GW Veterans were exposed include pyridostigmine bromide (PB) pills, which were given as a prophylaxis against nerve agents, and the insect repellant N,N-diethyl-meta-toluamide (DEET). Virtually all deployed troops were exposed to the pesticide PER, which was used on clothing to kill insects, the area pesticide CPF, which was used in no-pest strips in mess and residential areas, and the insect repellant DEET, which was applied directly to skin. Many troops were given PB pills regularly in anticipation of a nerve agent attack, and many troops were likely exposed to vapor plumes resulting from destruction of chemical weapons, including sarin, cyclosarin, and possibly mustard gas and soman.

Exposures to other agents that may be related to development of GWI include airborne particulates and emissions from Kuwaiti oil well fires, desert dust, multiple vaccinations (including anthrax vaccination), depleted uranium (DU), chemical agent-resistant coating (CARC) paint, psychological and physiological stress, heat, and miscellaneous petroleum products such as cleaners, lubricants, and fuels. It is generally assumed that individuals meeting the criteria for GWI were likely exposed to multiple chemical agents.

II.2. Other Etiologic Considerations

Uncertainties regarding types and doses of chemical exposures, as well as a lack of scientific knowledge about the synergistic effects of combined agent exposures, have impeded the development of a consistent theory of GWI etiology. Genetics, epigenetics, and gene-environment interactions are being investigated for potentially contributing to GWI.

Multiple studies have examined the role of Paraoxonase 1 (PON1), particularly the $PON1_{192}$ subtype, and its association with susceptibility for GWI. PON1 is responsible for the metabolism of organophosphates that are thought to be primary contributors to GWI (Haley, 1999). The combination of certain less common genotypes of the enzyme butyrylcholinesterase (BChE), another gene involved in organophosphate detoxification, with PB use (common during the GW) has been shown to confer greater risk for developing GWI (Steele, 2015). Studies are underway to assess DNA damage from exposures present in the GW theater by measuring somatic mutation frequency, overall genome instability, and chronic alterations in global DNA methylation.

Traumatic brain injury (TBI) was not considered to be common in the 1990-1991 GW. Therefore, the relationship between TBI and chronic health symptoms experienced by GW Veterans is unknown. However, GW Veterans' self-reported experience of TBI has been shown to be related to increased rates of chronic health symptoms and CMI (Yee, 2016) (Yee, 2017).

Preclinical research studies funded by Gulf War Illness Research Program (GWIRP) are now investigating the influence of TBI on outcomes following exposure to GW agents.

III. Pathobiology of Gulf War Illness

Because exposures to various neurotoxicants were known to occur in the GW and many of the symptoms of GWI clearly relate to nervous system dysfunction, much GWI research has focused on nervous system pathobiology. Other physiological systems that have been and are actively being investigated include the immune/inflammatory and gastrointestinal (GI) systems and molecular mechanisms for respiration and management of oxidative potential. Studies that have included female GW Veterans suggest that sex differences may play a role in the underlying pathobiology of GWI.

III.1. Preclinical Investigations

Several animal models have been developed to elucidate possible molecular and physiological mechanisms underlying GWI. These models have been used to characterize molecular, cellular, and functional effects associated with chemical exposures similar to those encountered by Veterans during the GW. These animal studies have provided evidence on brain, autonomic, behavioral, neuroendocrine, immune, and epigenetic abnormalities and support the conclusion that relevant chemical and non-chemical (stress induction, heat) exposures are associated with the physiological and behavioral characteristics of GWI in Veterans.

White, et al., summarized a number of rat and mouse studies evaluating the effects of exposures including combinations of PB, PER, CPF, sarin, diisopropyl fluorophosphates (DFP, a sarin surrogate), and stress. In many cases, exposures were administered at dosage levels that do not produce overt symptoms of toxicity (White, 2016). Beginning with the work of Abou-Donia and colleagues with a rat model of PB, DEET, and CPF exposures (Abou-Donia, 1996), these models recapitulate certain of the features of GWI patients, such as cognitive dysfunction and immune and inflammatory disruption. Furthermore, these studies have shown that absorption, metabolism, and biological functions following exposure to a combination of chemicals are different than the absorption, metabolism, and biological functions of the individual exposures when studied separately (RAC-GWVI Scientific Findings and Recommendations, 2008). The findings from research utilizing several rodent GWI models are described here; however, this is not a comprehensive list of GWI models. Further animal model development supported by the DoD GWIRP can be found at (http://cdmrp.army.mil/gwirp/resources/gwirpresources.shtml). Importantly, preclinical studies are now directed toward investigating the chronic outcomes, and underlying pathobiology, from relatively acute exposures to GW agents, which holds greater translational relevance for identifying effective treatments for the current human patient population.

Several investigators have exposed rodents to a combination of PB, PER, DEET, and restraint stress (used as a surrogate for combat stress) in doses that do not immediately produce observable toxic effects. However, animals ultimately displayed depressive behavior, lack of motivation, and memory defects (Hattiangady, 2014; Parihar 2013); abnormal lipid metabolism and increased immune signaling (Abdullah, 2012); and long-term epigenetic alterations (Pierce, 2016). Other rodent models have shown various types of delayed central nervous system (CNS) abnormalities that appear sometime after exposures to combinations of CPF with DEET or PB or PB plus PER (Nutter, 2015; Cooper, 2016; Torres-Altoro, 2011; Ojo 2014).

Evidence of CNS inflammation was reported early on (Bozkurt, 2010) and recently has been the subject of extensive animal research. A series of studies has established a model based on dual exposure to PB and PER (Abou-Donia, 2004). Using this model, researchers have documented neurobehavioral, neuropathological, and neuroinflammatory effects, as well as evidence for mitochondrial dysfunction, in the short, mid-, and long term post-exposure (up to 22 months). Genomic and proteomic studies were used to discern many features of neuroinflammation (Abdullah, 2011 and 2013; Zakirova, 2015 and 2016).

O'Callaghan, et al., reported compelling results using a single chemical agent, DFP (O'Callaghan, 2015); however, this exposure was preceded by pretreatment with corticosterone (CORT), a stress hormone that would normally be expected to suppress inflammatory responses produced by external stressors. Exposure to a single dose of the acetylcholinesterase (AChE) inhibitor DFP, a surrogate for the chemical warfare agent sarin, was found to result in inflammation in the brain, but pretreatment with CORT was found to exacerbate the CNS inflammatory response and produce a persistent "priming" of the immune system, continuing to generate exacerbated responses to subsequent irritant challenges. Priming was maintained for months in the mouse model (equivalent of 20 years in humans) by periodic low dosing with CORT. This model has been expanded in research being carried out by two research consortia funded by the GWIRP to identify new features of GWI pathobiology and new targets for treatment (Morris, Fiscal Year [FY] 2012; Sullivan, 2012). In 2017, O'Callaghan, et al., showed that the model's neuroinflammatory effects do not appear to be related to the AChE inhibition induced by these organophosphate agents, but these exposures may exert their effects on the brain through the "organophosphorylation" of other neuroimmune targets (Locker, 2017). Joshi and colleagues in 2019 showed that a PER metabolite is associated with adaptive immune responses in the PB+PER mouse model of GWI and that autoantibodies against the haptenated metabolite were evident in the mice at up to 7 months post-exposure and were also present in a small clinical sample of GWI cases versus controls. Such work suggests an adaptive immune mechanism underlying the persistence and chronicity of pathobiology long after the original exposure.

Other studies have focused on additional cellular and subcellular targets of GW chemical agents and suggest abnormalities associated with cholinesterases, tubulin (Grigoryan, 2008 and 2009,

Jiang, 2010), axonal transport (Rao, 2017), and mitochondrial function (Middlemore-Risher, 2011). Microtubule dysfunction has also been investigated (Rao, 2017), and mitochondrial defects have been the target of experimental treatment approaches (Golomb, 2014).

GWIRP-funded investigators have generated induced pluripotent stem cell cultures from skin fibroblast cells from deployed GW Veterans who have GWI symptoms, as well as those who did not develop GWI. These cells are being made available to the research community with the intent to foster rapid-throughput studies of novel therapeutic approaches (Qiang, 2017).

Tau pathology has also been investigated as a potential contributor to GWI pathobiology. To date, GW-relevant organophosphate neurotoxicants have been shown to lead to significantly decreased microtubule width in neurons (Jiang, 2010).

III.2. Clinical Investigations

III.2.1. Case Definitions

Research on GWI has relied on a number of differing definitions of the disorder, including CMI (Fukuda, 1998), the Kansas GWI definition (Steele, 2000), the Haley syndrome criteria (Haley, 1997 and 2001), and adaptations of these approaches. An IOM panel recommended the use of the CMI definition in clinical settings, as it is somewhat inclusive (IOM, 2014). In the same report, the panel recommended use of the Kansas definition in research settings because it is more selective and includes exclusionary criteria. Current best practice in research is to use one of the two IOM-recommended case definitions (CMI or Kansas) for primary analyses that best fit a study and also include the criteria that allow use of the other definition to facilitate cross-comparison of study results.

III.2.2. Imaging Studies

Consistent differences between GWI cases and controls have been demonstrated using various brain imaging technologies to measure brain structure and function.

Structural magnetic resonance imaging (MRI) techniques have been employed in GW Veteran populations to define structural changes in the brain, such as a reduction in brain size, that are associated with specific exposures in theater or are associated with GWI diagnosis. MRI-based measurements of specific brain areas and their volumes (segmentation and volumetry techniques) have revealed frank reductions of white and gray matter volumes in Veterans with suspected sarin/cyclosarin exposure when compared to controls (Chao 2010, 2011, and 2014). Using diffusion tensor imaging, which assesses the integrity and connectivity of white matter structures to other parts of the brain, Rayhan and Stevens reported increased axial diffusivity in subjects with GWI compared to controls. These results suggest that the white matter in GWI patients functions less effectively. Furthermore, they reported that increased diffusivity seen in the GWI patients was associated with increased fatigue, pain, and hyperalgesia (Rayhan, 2013b).

Chao, et al., also observed increased axial diffusivity in GWI patients and found that the increased diffusivity correlated with poorer neurobehavioral performance (Chao, 2015). In functional MRI (fMRI) studies, where activation of brain structures in response to cognitive and other behavioral challenges can be visualized, Calley, et al., reported case/control differences in specific brain regions during a Semantic Object Retrieval Test (Calley, 2010).

fMRI studies using a pre-/post-exercise protocol have shown that brain regions activated in response to innocuous heat stimulus following exercise were different among Veterans diagnosed with the three subtypes of GWI defined by the Haley criteria (Haley, 2001) and that, as a whole, the GWI group had distinct responses post-exercise when compared to the control group (Gopinath, 2012). Furthermore, the Haley-defined GWI subgroups showed atrophy in different brain regions and exhibited compensation in different brain regions during a verbal working memory task following exercise. Another MRI study revealed case/control differences in regional brain activation during memory encoding and memory recall (Hubbard, 2013).

Brain functional patterns measured by magnetoencephalography showed that patterns of synchronous neural interactions (SNI) were distinctly different in participants with GWI compared to healthy controls. Moreover, GWI-SNIs did not differ significantly from known immune-related diseases (rheumatoid arthritis, Sjogren's syndrome), but did differ significantly from Alzheimer's, schizophrenia, and post-traumatic stress disorder (PTSD) SNIs (Georgopoulos, 2017).

III.2.3. Neurocognitive Findings

Because the neurocognitive and affective symptoms reported by GW Veterans commonly include problems in memory, concentration, and mood, psychological tests are often used to quantify neurobehavioral function in this Veteran group.

A large study comparing deployed GW Veterans versus non-deployed GW-era Veterans found that deployed participants performed worse than their non-deployed counterparts on tests that assess short-term memory attention, visuospatial abilities, executive function, and fine motor coordination and speed (Toomey, 2009). Differences in performance on specific cognitive tasks were associated with self-reported exposures to specific chemical agents in theater. Self-reported exposure was found to predict poorer performance outcomes on measures of short-term memory, attention, and affective functions (White, 2001) and was also associated with poorer executive function and greater mood complaints (Sullivan, 2003). In a number of studies, researchers reported poorer visuospatial and memory functions and greater dysphoria in Veterans meeting the criteria for GWI versus controls (Anger, 1999; Axelrod, 1997; Binder, 1999; Bunegin, 2001; Lange, 2001; Storzbach 2000 and 2001; Odegard, 2013; Sullivan, 2003). One study showed little difference between cases and controls in cognitive domains, but did find significantly poorer reports of mood and quality of life (QoL) in those with GWI (Wallin, 2009);

this study involved a very small sample of GW-deployed Veterans and lacked the statistical power to detect subtle but significant differences in cognitive outcomes.

III.2.4. Autonomic and Neuroendocrine Systems

Studies have linked autonomic dysregulation to symptoms experienced by GW Veterans. In these studies, important differences in function among ill GW Veterans, controls, and Veterans with differing Haley syndromes were not apparent during resting or work, but rather emerged following some type of physiological challenge. The challenge used in these studies was most often physical exercise, but could take other forms. In animal models, pharmacological challenges have been used (e.g., drugs that increase heart rate).

Tests of parasympathetic and sympathetic nervous system regulation in GW Veterans have demonstrated that some symptoms, such as chronic diarrhea, dizziness, and fatigue, as well as changes in cardiovascular indices, may be caused by subtle autonomic system dysfunction (Haley 2004; Rayhan, 2013a).

Due to the extreme conditions of deployment and possible exposure to pathogenic agents during the GW, it has been suggested that the neuroendocrine control system may have been pushed beyond its normal operating capacity. Thus, neuroendocrine dysregulation as a result of GW deployment has been reported, including demonstrations of pronounced differences between GWI Veterans and controls after exercise and other challenges. Specific patterns of altered hypothalamic-pituitary-adrenal (HPA) axis functioning that are distinct from other conditions such as PTSD have been identified (Ben-Zivi, 2009; Golier, 2007 and 2009). A GWIRP-funded project (Craddock, 2014) found that regulation of sex hormones through the hypothalamic-pituitary-gonad (HPG) axis and components of innate and adaptive immunity undergo distinct and significant remodeling following exercise challenges in Veterans with GWI (Broderick, 2011).

Further investigation into altered regulation of these systems is ongoing. Research under a GWIRP-supported consortium has integrated basic and clinical research to identify the metabolic signaling mechanisms involved in disruption of autonomic cardiovascular function and endocrine functions in GWI (Morris, FY 2012). Results to date suggest there are changes in cardiac regulation associated with GW-era chemical exposures.

III.2.5. Neuroimmune Response

Multiple channels of communication between the brain and the immune system have been identified in prior neuroscientific research, and brain-immune interrelationships have been investigated in GWI. In the short term, inflammatory responses generated by the immune system are helpful to the organisms in responding to infectious agents and other physiological insults, eliciting self-preserving physical responses; however, chronic inflammation can be maladaptive. This observation led to recent interest in chronic neuroinflammatory activation of the brain's

glial cells as a potential cause of chronic symptoms in GWI. Chronic glial activation results in the synthesis and release of pro-inflammatory cytokines and chemokines (O'Callaghan, 2008) and is particularly relevant to GWI because the effects are seen in both gray and white brain matter. Gray and white matter volumes have both been shown to be reduced in neurotoxicant-exposed and symptomatic GW Veterans (see Brain Imaging Studies above). In addition to lower white matter volumes, studies have shown reduced information processing speeds in symptomatic GW Veterans exposed to low-dose sarin, a neurotoxicant (Proctor, 2006). Taken together, the findings of reduced white matter volumes and poorer information processing suggest that glial cells may have an important role in the development of (and ongoing) health symptoms and the cognitive complaints of GW Veterans.

A GWIRP-funded project (Klimas, FY 2008) used comprehensive molecular profiling combined with control theory, to link a stress-potentiated neuro-inflammatory response with symptom severity. This project identified changes in immune cell abundance, function, and signaling (Broderick, 2013). Further investigation into whether GWI is related to chronic brain-immune activation and inflammation is ongoing under a GWIRP-supported consortium (Sullivan, 2012). A pilot study conducted by this group showed that serum antibodies for a series of neuronal and glial-specific proteins (CaMKII, GFAP, tau, tubulin, MAG, MBP, NFP, and MAP-2) were significantly elevated in a GWI cohort. The results must be validated further, but they support continued study into glial signaling, white matter alterations, and neuronal degeneration. These findings may also contribute to development of a panel of objective diagnostic biomarkers of GWI.

III.2.6. Mitochondrial Dysfunction

Exposures linked to GWI are known to impair cell energy, and adverse cell energetics have been shown to contribute to symptoms consistent with GWI. Given these observations and because the mitochondrion is the source of chemical energy for the cell, the potential relationship between mitochondrial dysfunction and GWI has been subject to investigation. A GWIRP-funded study recently provided the first objective evidence of mitochondrial dysfunction in Veterans with GWI. Compared to controls, Veterans with GWI exhibited prolonged post-exercise recovery of phosphocreatine, a compound used as a backup energy store and a robust index of mitochondrial function (Koslik, 2014). This finding supports the presence of mitochondrial pathology in GWI.

GWI clinical trial investigators are regularly challenged to complete enrollment of both symptomatic and healthy GW Veterans and GW-era Veterans. The GWIRP has prepared a document to assist investigators in this process. The document, General Guidance for Gulf War Veteran Outreach and Recruitment, can be found on the GWIRP website

http:/cdmrp.army.mil/gwirp/pdfs/General%20_Guidance_for_Gulf_War_Veteran_Outreach_and_Recruitment.pdf

IV. Treatments

Clinical trials with the potential to have significant impacts on the health and lives of Veterans with GWI continue to be an ongoing priority. A primary focus of the GWIRP has been to fund research studies that identify treatment targets and test interventional approaches to alleviate symptoms. While most of these studies remain in progress, several have already shown varying levels of promise as GWI treatments.

IV.1. Treatments Using Alternative or Mind-Body Interventions

IV.1.1. Why This Strategy for GWI

Alternative or mind-body interventions utilize the interactions among brain, mind, body, and behavior, with the intention to use the mind to affect the body and its physiological responses to positively influence health. In theory, these interventions could act by quelling inflammatory processes by way of effects on the HPA homeostatic hormonal axis. These types of interventions are symptom-based and target improvement in the QoL of the patient. Alternative or mind-body interventions include acupuncture, acupressure, tai chi, yoga, and detoxification protocols to name a few. These techniques have been previously used to treat general pain, back and neck pain, headaches, and sleep disturbances. Since many of these manifestations are also experienced by GW Veterans, researchers believed that they could be implemented as an intervention to potentially improve the QoL of this population.

IV.1.2. Potential Impact

Despite self-reported evidence in reduction of fatigue, headaches, general pain ailments, there has been no definitive evidence for their effectiveness mainly due to the lack of objective markers of improvement. These types of treatments have the potential to be widely applicable due to the fact that they relatively non-invasive, free of side effects, and do not require special technology. Studies funded by the GWIRP and the Department of Veterans Affairs (VA) address these type of interventions to hopefully identify markers of improvement and provide further evidence in support of these techniques to develop more effective treatment options for Veterans with GWI.

IV.1.3. Completed Clinical Trials

- ***Effectiveness of Acupuncture in the Treatment of Gulf War Illness***

  Veterans with GWI report suffering from chronic multi-symptoms including, but not limited to, headaches, muscle and joint pain, and fatigue. This study aimed to identify whether individualized acupuncture could be used as a cost-effective treatment for the reduction of GWI symptoms. Acupuncture has successfully been used to treat key symptoms experienced by Veterans with GWI, making it a potential intervention for its treatment. Several studies have shown this technique to be effective, safe, and cost-effective. This study found positive

improvements in the severity of Veterans' self-reported complaints, overall health, and fatigue. A positive improvement in the bi-weekly treatment group was statistically significant when compared to the weekly treatment group. In addition to the aforementioned outcomes, the Principal Investigator also reported significant improvements on pain scores on the McGill Pain Scale from the 2-month time point to the 6-month. Finally, study participants reported a favorable experience and would recommend acupuncture to family and friends. The primary outcome was the Physical Functioning Subscale of the Quality of Life Scale, from the Short Form 36 Health Survey (SF-36). (Conboy, 2012) https://clinicaltrials.gov/ct2/show/NCT01305811

- ***Gulf War Illness: Evaluation of an Innovative Detoxification Program***

  This study hypothesized that a detoxification program can improve the general physical and mental health and/or the QoL of Veterans with GWI. The detoxification program is a rehabilitative therapy that uses a combination of exercise, nutritional supplements, and sauna sessions to improve the QoL of individuals diagnosed with multi-symptom illnesses. This detoxification program has been used as a treatment protocol for individuals affected by environmental exposure to toxic substances. This research group assessed improvements in pain and fatigue levels and overall symptom burden post-treatment in subjects who met the Kansas case criteria for GWI. Published results from this study noted that the patient-reported outcomes indicated health improvements in pain and fatigue scores (Kerr, 2019). The procedure was deemed as safe and well-tolerated by the participants. An intervention showing overall QoL improvements is needed to provide these Veterans relief from their disease. This research offers preliminary data in the hope to advise efforts in the health improvement of GW Veterans. Clinical outcome measures used include the SF36-V Forms of Quality of Life, Physical and Mental Status; the Multidimensional Fatigue Inventory; the McGill Pain Questionnaire; the Trail Making Test A and B; the Grooved Pegboard Test; the Wechsler Memory Scale III-a Test, the Stroop Color Word Test, the Symptom Checklist 90 Test; and the State-Trait Anxiety Inventory Test. Data analysis was not completed due to lack of resources. https://clinicaltrials.gov/ct2/show/NCT01672710

- ***Investigating Clinical Benefits of a Novel Sleep-Focused, Mind-Body Program on Gulf War Illness Symptoms: An Exploratory Randomized Controlled Trial***

  Sleep problems are a common concern for GW Veterans. Given the diverseness of this population, data that could enhance our knowledge of the impact of sleep disturbances and other comorbid symptoms are essential. This study sought to evaluate the positive impact of mind-body bridging (MBB) in GW Veterans that suffer from the aforementioned conditions. Upon completion of the study, the results showed MBB to be more efficacious in improving sleep quality when compared to the control condition, sleep education (Nakamura, 2017). Additionally, GW Veterans reported an improvement in PTSD, depression, and fatigue

symptoms post-treatment. The primary outcome measure used in this study is the Medical Outcomes Study - Sleep Scale (MOS-SS). https://clinicaltrials.gov/ct2/show/NCT01543997

- ***Effectiveness of Acupressure Treatment for Pain Management and Fatigue Relief in Gulf War Veterans***

  Acupressure is a traditional Chinese medicine therapy that uses localized massage that provides relief from pain, nausea, and fatigue. Published data indicate that this intervention has been proven effective in reducing fatigue in cancer patients and those with neck pain. Given the existing scientific support of acupressure in relieving these symptoms, a study evaluating this intervention and its potential impact on GW Veterans would have a powerful impact on the field if successful. This study sought to assess the efficiency of acupressure – routine care combination versus reiki – as routine clinical care for the management of pain and fatigue. The clinical outcomes showed fatigue reduction and pain relief. The data provide further basis for the potential implementation or refinement of this treatment for alleviation of specific symptoms presented by Veterans with GWI. Clinical outcome measures included Study Short Form 36 (SF-36) for QoL evaluation; revised Piper Fatigue Scale for fatigability evaluation (rPFS); and Brief Pain Inventory (BPI) for pain evaluation. https://clinicaltrials.gov/ct2/show/NCT02075489

- ***A Randomized, Multi-Center, Controlled Trial of Multi-Modal Therapy in Veterans with Gulf War Illness (Exercise and Behavioral Therapy Trial)***

  This project studied GW Veterans who present unexplained pain, fatigue, or cognitive difficulties. Cognitive behavioral therapy (CBT), aerobic exercise, and their combination were evaluated to determine their impact on the unexplained physical symptoms report by these subjects. Published outcomes from this project showed that exercise alone and in combination with CBT significantly improved cognitive and mental health functioning, fatigue, and distress, while CBT alone only improved cognitive and mental health functioning. However, neither treatment, either alone or in combination, resulted in a positive impact to pain. (Donta, 2003). https://clinicaltrials.gov/ct2/show/NCT00007748

- ***Testing the Feasibility of MC CBT for Veterans with IBS Alliance***

  GI disorders are among the unexplained illnesses reported by many Veterans with GWI. In order to find an effective treatment for irritable bowel syndrome (IBS), in particular, this trial sought to test the feasibility of minimal contact cognitive behavioral therapy (MC CBT). This psychological therapy attempts to teach patients skills for managing and controlling negative thoughts and the ability to cope with daily stressors. Data from this trial suggested that GW Veterans diagnosed with IBS may have significantly different characteristics from civilians with IBS. GW subjects were older, mostly male, and presented higher rates of PTSD versus other psychological disorders. It was also reported that this trial was unable to

produce significant treatment effects of MC CBT due to small sample size, high dropout rates, and lack of motivation. This study has been completed.

IV.1.4. Ongoing Clinical Trials

- ***A Multimodal Evaluation of the Comparative Efficacy of Yoga Versus a Patient-Centered Support Group for Treating Chronic Pain in Gulf War Illness***

  Chronic pain is one of the most common and debilitating symptoms reported by Veterans suffering from GWI. Yoga is a practice that involves breathing and relaxation techniques, physical exercise, and positive thinking to promote well-being. There is evidence indicating that this technique is a safe, cost-effective, and self-sustaining practice that has the potential to alleviate chronic pain. This study is assessing yoga for the treatment of this condition in Veterans with GWI. Positive outcomes from the study would be relevant to Veterans with GWI and could potentially increase adoption of this practice. Data analyses and result findings are pending. https://clinicaltrials.gov/ct2/show/NCT02378025

- ***Pilot Test of Telephone-Delivered Cognitive Behavioral Therapy for Insomnia for Veterans with Gulf War Illness***

  One of the common symptoms reported by Veterans who suffer from GWI is sleep disturbances such as insomnia. Published reports associate insomnia with fatigue and psychological disorders. This trial seeks to investigate the efficacy of a telephone-delivered CBT (CBT-I) for sleep in GW Veterans. If successful, this trial may be a significant first step toward identifying a non-invasive treatment to improve the QoL for the estimated 175,000 Veterans with GWI. This trial is still ongoing.
  https://clinicaltrials.gov/ct2/show/NCT02782780

- ***Impact of Exercise Training on Pain and Brain Function in Gulf War Veterans***

  Reports show that resistant exercise training has a moderate impact on the improvement of pain, tenderness, and muscle strength in women with fibromyalgia (FM). Both FM and GWI patients are known to suffer from widespread chronic musculoskeletal pain. This group of scientists is evaluating the potential benefit of this intervention on Veterans with GWI and the brain's response to pain during training. This study is still ongoing.
  https://clinicaltrials.gov/ct2/show/NCT01350492

- ***Telemedicine Treatment for Veterans with Gulf War Illness***

  Despite evidence showing CBT as an effective treatment for the alleviation of GWI symptoms, the number of Veterans seeking this treatment is limited. One of the main issues raised by Veterans include the requirement for in-person treatment sessions, which makes it challenging for some. This study aims to determine if CBT delivered by phone could be an

efficient delivery method for this treatment by eliminating in-person sessions. If successful, this delivery method would minimize the resources used by the VA and provide readily available resources to GW Veterans regardless of geographic location. Data from this study are currently being analyzed. No findings have been reported to date. https://clinicaltrials.gov/ct2/show/NCT00129454

- ***Evaluation of a Mindfulness-Based Intervention for Gulf War Illness (A Randomized Controlled Trial of a Mindfulness-Based Intervention for Gulf War Syndrome)***

  Mindfulness-based interventions (MBIs) use meditation techniques to increase moment awareness, manage physical pain, and relieve stress, among others. This VA study seeks to evaluate two MBIs, Mindfulness-Based Stress Reduction (MBSR) and treatment as usual, to determine which intervention results in a greater improvement on chronic muscle pain. If MBSR proves to be successful, it would offer support for the implementation of MBIs across the GWI population. Data collection is currently ongoing. No findings have been reported to date. https://clinicaltrials.gov/ct2/show/NCT01267045

- ***Problem-Solving Therapy for Gulf War Illness (Cognitive Rehabilitation Therapy for Gulf War Veterans)***

  While the etiology of GWI remains unknown, GW Veterans continue to report unexplained and life-limiting ailments. This VA study seeks to determine whether problem-solving therapy, a patient-centered cognitive rehabilitation treatment that teaches patients tactics to address real-life problems in hopes to improve day-to-day life, can reduce disability by compensating for problem-solving deficits. If positive results are obtained, problem-solving therapy would be an innovative approach to improve the QoL of GW Veterans. Findings and/or results are not yet available.

- ***Novel Interventions for Gulf War Veterans' Illnesses***

  Tai chi is a traditional Chinese mind-body therapy that can improve both physical health and psychological well-being in patients with a variety of chronic conditions. This study seeks to determine the effectiveness of tai chi on Veterans with GWI. If this therapy shows to have positive impact on the reduction of GWI symptoms, it could be an easy-to-implement, non-pharmaceutical treatment that Veterans could practice in clinic and/or independently within their own homes. Providing Veterans some relief from the debilitating symptoms of GWI would have a significant impact on the QoL of these Veterans. This trial is currently recruiting. No data are available at this time. https://clinicaltrials.gov/ct2/show/NCT02661997

- ***Complementary and Alternative Medicine (CAM) in Veterans with Gulf War Illnesses***

  Integrative restoration (iRest(R)) yoga nidra is a type of meditation that induces deep relaxation through breathing, body sensing, imaging, and relaxation techniques. This VA

trial aims to determine whether combined auricular acupuncture and iRest(R) yoga nidra will lead to improved overall health functioning, sleep quality, and stress in Veterans with GWI compared to GW Health Education. Positive outcomes from this trial would provide basis to include CAM interventions in the standard of care for GWI. In addition, the benefits of these interventions would also have a potential positive impact on Veterans of all wars. This study is currently recruiting. No data are available at this time (Hull, 2014). https://clinicaltrials.gov/ct2/show/NCT02180243

- ***Predictors of Response to Insomnia Treatments for Gulf War Veterans***

  While alternative treatments for insomnia, such as CBT, have been identified, the specific target population that would benefit from this intervention remains unclear. The purpose of this study is to evaluate the efficacy and effectiveness of sleep restriction (SR) and cognitive therapy (CT) in GW Veterans suffering from insomnia. If successful, this trial would address the need for a non-pharmacological treatment and/or develop tools for clinicians to identify the best insomnia treatment for individual GW Veterans. This study is currently recruiting. No data are available at this time. https://clinicaltrials.gov/ct2/show/NCT03208049

IV.2. Anti-Inflammatory/Immune Effector Therapies

IV.2.1. Why This Strategy for GWI

Chronic neuroinflammation is the sustained activation of glial cells, the resident innate immune cells in the CNS, and recruitment of other immune cells into the brain. It is initiated in response to a variety of cues, including infection, TBI, toxicant and toxic metabolite exposure, or autoimmunity. Typically the CNS is an immunologically privileged site because peripheral immune cells are blocked by the blood–brain barrier (BBB). However, sustained glial cell activation can compromise the BBB, allowing circulating immune cells to pass, perpetuating the immune response. Published findings of reduced white matter volumes in ill GW Veterans compared to controls suggest that activated glial cells may play an important role in the development of (and ongoing) health symptoms. This has led to interest in neuroinflammatory chronic glial activation as a potential cause of chronic symptoms in GWI and strategies to intervene.

IV.2.2. Potential Impact

A successful trial with improved clinical outcomes and reduced proinflammatory biomarkers would validate the hypothesis that chronic inflammation is part of the underlying pathophysiology of GWI. This could lead to a new paradigm for the diagnosis and treatment of GWI – targeting the underlying cause of disease and not just ameliorating symptoms.

IV.2.3. Completed Clinical Trials

- ***A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial of Mifepristone in Gulf War Veterans with Chronic Multisymptom Illness***

  Distinct biological alterations reflective of disturbances in central processes that regulate neuroendocrine systems have been associated with GW deployment. In particular, enhanced negative feedback inhibition of the HPA axis and lower 24-hour plasma ACTH (adrenocorticotropic hormone, adrenocorticotrophic hormone) levels have been found in deployed GW Veterans vs. controls. Since dysregulation of the HPA axis can have deleterious effects on multiple systems including the immune system, the autonomic nervous system, and the CNS, this system is a useful target of treatment. This GWIRP-supported trial sought to determine whether mifepristone, a glucocorticoid receptor antagonist, can reverse the neuroendocrine alterations described in GWI, by reducing glucocorticoid sensitivity, and in so doing, improve the health of these Veterans. Mifepristone has previously been safely used to treat physical symptoms and disturbances of memory and mood in other medical and neuropsychiatric disorders associated with disturbances in the HPA axis. The primary outcome measure was improvement in physical health as measured by the Veterans Rand 36-item health survey. This study was negative with respect to all clinical outcomes. However, the data suggested a moderate dose of mifepristone may have circumscribed cognitive-enhancing effects in ill GW Veterans. Future studies are needed to further explore neuroendocrine approaches to treating GWI with a focus on cognitive outcomes. Results were published in 2016 (Golier, 2016).

- ***Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf War Syndrome***

  Symptoms of chronic rhinosinusitis (CRS) and fatigue are the first and third most common symptoms of GWI, respectively, and are biologically characterized by interrelated proinflammatory cytokines. This GWIRP-supported, 26-week, three-arm trial compared saline nasal irrigation (S-NI) or xylitol nasal irrigation (X-NI) plus routine care with routine care alone on outcomes including sinus symptoms, fatigue, overall QoL, cost-effectiveness, and proinflammatory biomarkers and cell types. S-NI was hypothesized to improve sinus symptoms by thinning and clearing mucus and inflammatory mediators, decreasing mucosal edema, and improving ciliary function. X-NI has been shown to change the salinity of the mucosal surface, resulting in enhanced antimicrobial properties. Enrollment of 48 participants met an 80% enrollment target. Statistically positive results on health-related QoL outcome measures suggested that nasal irrigation can provide effective adjunct therapy for CRS and fatigue in Veterans with GWI. Results were published in 2015 (Hayer, 2015).

- ***Treating Gulf War Illness with Novel Anti-Inflammatories: A Screening of Botanical Microglia Modulators***

  Inflammatory processes may be critical in the maintenance of multisymptom illnesses characterized by pain and fatigue, and microglia modulators may be a novel and effective approach to treating those disorders. The overall objective of this GWIRP-supported Phase I/II screening trial was to screen nine botanical microglia-modulating and central anti-inflammatory agents to identify those that would be most promising for further study in treating GWI. To accommodate the various symptom profiles, the primary outcome was a single item measure of overall GWI severity. Out of the nine botanical agents tested, four showed a significant impact on GWI symptoms over both baseline and placebo conditions. These agents are: reserveratrol, stinging nettle, pycnogenol, and CurcumaSorb. The other botanical agents (epimedium, luteolin, boswellia, fisetin, reishi) showed no appreciable effect on GWI symptoms. This screening study therefore identified four botanical agents that should be tested further for efficacy in treating GWI. Full results will be available when manuscripts are published and will be made open-access.

- ***Randomized Control Trial of Duloxetine and Pregabalin for the Treatment of GWI in Veterans***

  The goal of this VA-supported trial was to evaluate the efficacy of a Duloxetine and Pregabalin for the treatment of pain, sleep, fatigue, mood, and safety and tolerability of the medications in Veterans with GWI. The primary outcome was clinically relevant reduction in pain and symptom improvements. This trial has completed.

- ***Neurosteroid Intervention***

  The goals of this VA-supported trial were to characterize the metabolic profile of pregnenolone, obtain valuable pharmacokinetic data, and identify possible windows of optimal therapeutic efficacy and potential neurosteroid predictors of clinical response. This trial has completed.

IV.2.4. Ongoing Clinical Trials

- ***Gulf War Illness Inflammation Reduction Trial***

  Pilot studies comparing blood samples from GW Veterans with and without multiple symptoms of pain, fatigue, and cognitive dysfunction demonstrate plasma from symptomatic Veterans has significantly higher levels of inflammatory proteins and blood cells, indicating the presence of chronic inflammation. The efficacy of glucocorticoids (GCs) as anti-inflammatory and immunosuppressive drugs is clearly established. Their pleiotropic effects on immune system functions make them attractive as potential treatments for the inflammation associated with GWI. Prednisone is an effective and widely prescribed synthetic GC. The goal of this GWIRP-supported proof-of-principle trial is to determine if

reducing inflammation is an effective treatment for GWI. The treatment group will receive a low dose of delayed-release (DR)-prednisone for 8 weeks versus the placebo group receiving matching placebo for 8 weeks. The study will determine if treating GWI Veterans for 8 weeks with DR-prednisone improves physical health functioning as measured by SF-36 vitality and physical function subscores and reduces inflammation parameters compared to Veterans receiving placebo. The recruitment phase of this trial has closed, and data analysis is underway. If proven safe and efficacious, a change in clinical practice that focuses on inflammation could be implemented immediately.

- ***Testing the Model: A Phase I/II Randomized Double-Blind Placebo Control Trial of Targeted Therapeutics: Liposomal Glutathione and Curcumin***

  Using data from previous studies in a dynamic computational model of GWI, investigators identified five prime targets, NF-κB being "upstream" of several others. This GWIRP-supported trial will evaluate two nutraceuticals known to downregulate NF-κB, comparing each to placebo. It is anticipated that this intervention will impact many cellular functions, including the antioxidant and methylation-related metabolic function of peripheral blood mononuclear cells (PBMCs). Depending upon the results of this study, feasibility, efficacy, and safety data could support a Phase III clinical trial of the most effective of the treatments examined in this trial.

- ***The Use of B-Cell Depletion Therapy (BCDT) in Gulf War Illness: A Phase I/II Study***

  Immune inflammatory biomarkers, which have been implicated in GWI, can be used as biomarkers to identify targeted therapeutic interventions or biologic response modifiers. This GWIRP-supported trial aims to target two different immune pathways, the pro-inflammatory cytokine cascade as well as interfering with autoantibody production. Using the B-cell depleting therapy rituximab, investigators not only hope to decrease the presence of autoantibodies but also decrease pro-inflammatory cytokine expression and reset underlying mechanisms of disease by wiping out B-cell memory cells to prevent future autoantibody production. The primary outcome variable in this trial is changes in SF-36 vitality and physical function subscores. This study is ongoing. The use of a BCDT may prove that the autoantibodies seen in GWI are mediators of illness persistence. This study may provide an understanding of disease onset and progression and provide a targeted therapy for at least a subgroup of patients with GWI.

- ***A Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Oleoylethanolamide for Targeting Lipid Metabolism in Gulf War Illness***

  Recent research has shown that one of the pathogenic mechanisms in GWI involves impaired lipid metabolism, which corresponds with brain glia activation and inflammation. These lipid alterations are detected in the blood of Veterans with GWI and point to an abnormal function of peroxisomes, which regulate lipids required for cellular signaling. Preclinical

studies targeting peroxisomal lipid metabolism with oleoylethanolamide (OEA), a natural dietary supplement that activates peroxisome proliferation, found that OEA treatment reduced glia activation, inflammation, and neurobehavioral deficits and promoted mitochondria biogenesis in GWI mice. This GWIRP-supported pilot clinical trial will test whether OEA can correct the underlying lipid disturbances and inflammation associated with GWI in a Veteran cohort. Although the primary objectives are based on biological outcomes related to lipid parameters associated with GWI, data collected on general health and symptoms of GWI will help guide the design of a future Phase III clinical trial to develop OEA as a treatment of GWI. This trial is ongoing.

- ***Understanding Gulf War Illness: An Integrative Modeling Approach***

  Computer models of the neuroendocrine system suggest that tumor necrosis factor (TNF)-α silencing followed separately by glucocorticoid receptor blockade might be able to shift the neuroendrocrine system from an abnormal state of dynamic equilibrium characterized by the GWI phenotype to a normal, healthy state. This GWIRP-supported trial is using a combination treatment strategy using a tumor necrosis factor (TNF) receptor antagonist, followed by a glucocorticoid receptor blockade in a Phase I study of GW Veterans. The research team plans to repeat the dynamic modeling before treatment and during the trial to further inform the computation model and evaluate impact of the intervention. Results of this pilot study will be used to inform interventions under a newly established FY17 Clinical Consortium (see Section V, Research Infrastructure and Collaborative Efforts).

- ***A Translational Medicine Approach to Gulf War Illness: From Cells to Therapy***

  The goal of this VA-supported trial is to determine if intervening at therapeutic targets selected via computational modeling will act as predicted and normalize the balance of systems in GWI, using selected drugs in vitro in peripheral blood mononuclear cell cultures. Outcome measures include significant treatment effect ($p<0.05$) in the majority of cell populations, cytokine expression, and NK cell functional markers that are abnormally expressed in GWI. This study is currently enrolling.

- ***A Randomized Clinical Trial of Duloxetine and Pregabalin for the Treatment of Gulf War Illness in Veterans***

  The purpose of this trial is to find out if duloxetine (an SSRI, or selective serotonin reuptake inhibitor) and pregabalin (an anti-seizure medication), two U.S. Food and Drug Administration (FDA)-approved medications for treating FM syndrome, can provide relief to Veterans who suffer from GWI. This study is currently enrolling through 2019.

IV.3. CNS Stimulants or Depressants

IV.3.1. Why This Strategy for GWI

Exposures to various neurotoxicants were known to occur in the GW. Neurotoxicants are capable of causing adverse effects and major functional changes in the CNS. CNS impairment affects a wide range of different capabilities, from motor skills to memory. Cognitive complaints have been particularly troublesome to Veterans with GWI, and studies have suggested that a slowing of CNS response speed is present affecting function across multiple cognitive domains. CNS stimulants are substances that work to activate the CNS, increasing attention and focus. Depressants are substances that reduce function of the CNS, increasing feelings of relaxation while lowering levels of awareness in the brain. CNS stimulants or depressants are known to have profound effects on memory, attention, and mood.

IV.3.2. Potential Impact

Use of CNS stimulants or depressants to treat neurotoxicant induced cognitive impairments in ill GW Veterans holds promise. Identification of an effective treatment or a biological target for treatment that has the advantage of direct access to the brain has the potential to be widely applicable. Providing Veterans even moderate relief from these chronic and debilitating symptoms could have a profound impact on improving their overall sense of well-being and QoL.

IV.3.3. Completed Clinical Trials

- ***Trial of Naltrexone and Dextromethorphan for Gulf War Veterans' Illness***

  Dextromethorphan is a CNS depressant while naltrexone blocks opioid receptors and reverses subjective and analgesic effects. A study supported by the GWIRP sought to determine if naltrexone and dextromethorphan were efficacious in relieving cognitive symptoms in ill GW Veterans. A secondary impact was to determine if pro-inflammatory cytokines and markers of neurogenic inflammation are elevated in the Veterans participating in the study, providing evidence for a biomarker of disease and insight into the mechanism. The trial showed responders and non-responders at the doses used; however, no statistical benefit was apparent when averaged over all participants. A nerve growth factor and cytokine panel showed no consistent pattern of variability, and empirical pharmacology demonstrated no benefit relative to those using no medications. These results were presented at the September 2014 VA Research Advisory Committee on Gulf War Veterans' Illnesses (RAC-GWVI) Meeting.

- ***Intranasal Insulin: A Novel Treatment for Gulf War Multisymptom Illness***

  Intranasal delivery of therapeutics offers direct access to the CNS. Treatment advances in other cognitive disorders and in normal subjects suggest that intranasal insulin is a safe, effective, inexpensive, and tolerable treatment that can improve memory, attention, and

mood, reduce neuroinflammation, and modulate catecholamines and cortisol levels. Therefore, intranasal insulin has been identified as a treatment strategy with potential to alter leading pathobiological correlates of GWI, including neuroinflammation, synaptic function, and HPA axis dysregulation. This GWIRP-supported intervention will assess the efficacy of two different doses (10 IU BID and 20 IU BID) of daily intranasal insulin for 8 weeks on memory and attention functioning in GW Veterans with CMI. The primary outcome measure is neuropsychological outcome (verbal memory and selective attention). This trial has now closed. If data demonstrate efficacy, intranasal insulin could be quickly deployed for use since insulin is already FDA-approved.

- ***D-Cycloserine: A Novel Treatment for Gulf War Illness***

  Advances in other neurodegenerative diseases, including Alzheimer's disease, suggest that d-cycloserine (DCS) is a safe, effective, and tolerable treatment that can improve memory, attention, and mood; reduce neuroinflammation; and modulate glutamate levels. DCS has been identified as a treatment that alters many of the leading pathobiological correlates of GWI (i.e., neuroinflammation, proinflammatory cytokines, synaptic functions in hippocampus and frontal lobes). Treatment-induced changes could result in significant functional improvements in memory, attention, mood, and fatigue in Veterans with GWI. The overall objective of the GWIRP-supported treatment was to evaluate the efficacy of the randomized double-blind clinical treatment of DCS vs. placebo for GWI. The primary clinical outcome measures were change in declarative and procedural memory performance from treatment baseline across time. Non-memory cognitive tasks were also primary clinical outcomes, including attention and working memory, executive functions, visuospatial and motor functions. DCS is currently FDA-approved and therefore, if found effective, could be quickly deployed for use. This intervention is closed.

IV.3.4. Ongoing Clinical Trials

- ***Glutamate Neuroexcitotoxicity in GWI***

  Glutamate is the most ubiquitous neurotransmitter in the human body. Excess glutamate is well known to cause excitotoxicity, resulting in hyperexcitation and death of neurons. Glutamate is not only produced endogenously, but is also used as a flavor enhancer in food. Dietary exposure to glutamate may be able to mediate excitatory neurotransmission in the nervous system, leading to a myriad of symptoms throughout the body. The rationale for this GWIRP-funded treatment trial stems from the effectiveness of a low-glutamate diet in FM patients. In prior research in FM patients, 84% had >30% remission of symptoms after 1 month on the diet and 8 subjects had complete remission of symptoms. Symptoms that showed the greatest improvement included fatigue, headache, diarrhea, muscle pain, concentration, difficulty with words/numbers/math, and problems sleeping. Due to symptom overlap between FM and GWI, this intervention is being tested in GWI patients. Endpoints will include symptom score, cognitive function measured by computerized cognitive testing

and N-back fMRI testing, as well as change in brain glutamate levels pre-/post-diet. A randomized, double-blind, placebo-controlled crossover challenge trial is currently ongoing. If found to be similarly beneficial in GWI patients, a training program to educate dietitians in VA hospitals across the country is planned.

IV.4. Physical CNS or Neural Stimulation

IV.4.1. Why This Strategy for GWI

Some GWI researchers are testing therapies using non-invasive direct stimulation of either neural networks in the brain or individual neurons. These treatments use low-level, non-detectable electrical impulses delivered to specific areas of the head to provide plastic changes (improvements) in impaired brain circuitry. The treatments seek to address symptoms like headache, widespread pain, memory loss, and cognitive deficits (e.g., word retrieval).

IV.4.2. Potential Impact

These treatments have the potential to benefit ill GW Veterans by improving neural circuit communication and performance. Most of these treatment modalities have been proven effective in other areas like TBI and neurodegenerative diseases. Some are also FDA-approved for various conditions like depression, and all are non-invasive. These treatments could represent accessible symptom relief for Veterans suffering from some of the biggest components of GWI.

IV.4.3. Completed Clinical Trials

- ***rTMS for the Treatment of Chronic Pain in GW1 Veterans***

  This VA study aimed to evaluate the ability of repetitive Transcranial Magnetic Stimulation (rTMS) to resolve chronic pain in Veterans from the first GW. The trial did not meet recruitment goals and was therefore terminated.

- ***Use of a Portable Stimulator to Treat GWI***

  The War Related Illness and Injury Study Center found that GW Veterans commonly report symptoms of nausea and dizziness, both associated with vestibular (balance system) damage. Dizziness and vertigo can result in poor balance, which contributes to the threat of falls, significantly reducing QoL. This study of 31 impaired Veterans used a novel stochastic noise stimulator to enhance vestibular function and demonstrated that low levels of random electrical noise can improve both vestibular function and balance in Veterans. The study paved the way for more development of this technology and vestibular hypofunction in GW Veterans.

IV.4.4. Ongoing Clinical Trials

- ***Treatment of Memory Disorders in Gulf War Illness with High-Definition Transcranial Direct Cortical Stimulation***

  Key cognitive symptoms described by Veterans with GWI extend from disruption in the cognitive process of verbal retrieval. This team has evidence to support that a neural circuit of the Pre-Supplementary Motor Area (preSMA)-caudate-thalamus is essential for effective retrieval of verbal information. This study uses high-definition transcranial direct current stimulation (HD tDCS) over the preSMA region to strengthen the connections of this retrieval circuit and address this cognitive dysfunction, including improving word retrieval and verbal fluency. Also from this study, the team will formalize procedures for the treatment and generate the training and standard operating procedures to set up and perform the treatment in a clinical setting in order to quickly transition this treatment to the clinic.

- ***Vagus Nerve Stimulation: A Noninvasive Treatment to Improve the Health of Gulf Veterans with Gulf War Illness***

  This innovative new treatment, currently FDA-approved for two disease processes – epilepsy and major depressive disorder – directly stimulates the vagus nerve. Vagus nerve stimulation (VNS) has shown efficacy to reduce widespread pain and tenderness in non-Veteran women with FM. This study aims to provide pilot data where, if successful, VNS to relieve GWI-related widespread pain can move quickly to a multi-site clinical trial.

- ***Long-Term Efficacy of Neuronavigation-Guided rTMS in Alleviating Headache and Pain in GWI and rTMS in Alleviating Pain and Comorbid Symptoms in Gulf War Veterans' Illness***

  Headaches and muscle and joint pain are some of the most common debilitating symptoms in military personnel who served in the GW. Migraine-like headaches and diffuse body pain were detected in 64% of GW Veterans diagnosed with GWI. Transcranial magnetic stimulation (TMS) is currently FDA-approved for treatment of major depression and migraine headache. Building on a successful pilot trial, these Phase II studies of TMS aim to reduce headache pain and general pain in symptomatic GW Veterans. Neuronavigation guided rTMS non-invasively stimulates the brain utilizing electromagnetic principles to produce small focal electrical currents in the cortex, directed at a precise location. These clinical trials will provide outcome and preliminary mechanistic evidence to validate rTMS as a low-risk, non-invasive therapy for GWI headache pain and neuropsychological dysfunction. One multi-site trial is funded by the DoD GWIRP and the other, which additionally focuses on Veterans with depression, is funded by the VA.

- ***Transcranial Direct Current Stimulation for Pain Treatment of Gulf War Illness***

  Based on research on FM, it is expected that tDCS pain treatment can be effective for Veterans with GWI. tDCS stimulates the greater occipital nerve field (on the back of the neck) to provide relief from chronic pain. This study aims to demonstrate the efficacy of tDCS as a novel, targeted, non-pharmacological treatment for pain in GWI with few known side effects or drug interactions and an easy translation to a clinical setting or even at-home treatment.

IV.5. Treatments Targeting the Gut-Brain Axis

IV.5.1. Why This Strategy for GWI

Since the digestive system is the body's largest interface with foreign agents in the environment, it is profoundly connected with the immune system, and the "gut-brain axis" is a complex, bi-directional communication system between the CNS and the enteric (gut) nervous system. This system encompasses the sympathetic and parasympathetic arms of autonomic nervous system, the endocrine hormonal system (HPA axis), and of course, the immune system. An ecosystem of microbes lives inside the gut, and this is called the "gut microbiome" or "gut microflora." Not surprisingly, the composition and health of this ecosystem has a significant impact on the immune system and thus, the gut-brain axis. Changes in the microbiome have been observed in a number of diseases, and while in the past these changes have been thought to be a result of disease, it has slowly become clear that therapeutic manipulation of the gut microbiome can alter some diseases and perhaps produce cures. Since many manifestations of GWI are related to endocrine/autonomic dysregulation and exaggerated immune/inflammatory responses, researchers felt there was a good possibility that GWI might be abated or at least quelled by manipulation of the gut microbiome.

IV.5.2. Potential Impact

Many symptoms of GWI are thought to directly involve exaggerated immune/neuroinflammatory responses and hormonal imbalance including headache, joint/body pain, GI symptomatology, and some aspects of fatigue. It is thought that individuals suffering symptoms such as these would be the most likely to benefit from treatments affecting the gut microbiome and gut-brain axis. Other symptoms like sleep, skin, or respiratory disorders are not so obviously connected to immunity or inflammation; however, an underlying component related to inflammation is not unreasonable, so gut-brain axis treatments may be useful in those cases as well. It is unknown whether treatments aimed at the gut microbiome could provide a persistent cure or would simply abate symptoms and still require periodic treatments.

IV.5.3. Completed Clinical Trials

- ***Bacterial Overgrowth Associated with Chronic Multi-Symptom Illness Complex***

  Rifaximin is a minimally absorbed antibiotic thought to reduce IBS by helping to restore normal gut microflora. A double-blind, placebo-controlled study was carried out to compare the effects of 2 weeks of rifaximin treatment with placebo. Endpoints included various self-reported QoL measures and other measures specifically related to bowel function including an overall Bowel Symptom Score. The study was ended with 44 subjects completing the protocol. Rifaximin was not found to be effective in improving IBS symptoms and QoL in GW Veterans with non-constipated IBS. (Tuteja, 2019)

IV.5.4. Ongoing Clinical Trials

- ***Probiotic (Bifidobacterium infantis) for Gulf War Illness***

  Altered gut flora may be the etiological factor for IBS and GWI. Probiotics are living organisms that improve health by re-establishing a normal gut flora. Probiotics also have anti-inflammatory properties. Probiotics have been claimed to be of some benefit in non-Veterans with IBS. This study will demonstrate the safety and effectiveness of *B. infantis* in the treatment of IBS and non-intestinal symptoms of IBS that are indistinguishable from GWI. The knowledge gained from this study may also benefit other travelers who develop IBS on return. Endpoints measured include changes in bowel flora and various self-reported QoL measures and other measures specifically related to bowel function including an overall Bowel Symptom Score. Sixty Veterans have been enrolled in the study, and 55 have completed to date. Stool samples have been sent for analysis, and the investigators are currently preparing data for analysis.

- ***Effect of Diet on Gulf War Illness: A Pilot Study***

  FODMAPs (Fermentable Oligo-, Di and Mono-saccharides And Polyols) are carbohydrates that are poorly absorbed in the small intestine. Undigested FODMAPs are fermented in the colon by microbiota, increase osmotic load, increase delivery of water into the colon, and can produce gas/distension of the colon. FODMAP ingestion does not produce symptoms in most people but can produce GI symptoms in people with IBS. A diet low in FODMAPs has been shown to reduce symptoms and may do so (1) by changing the gut microbiota and/or (2) by production of metabolities which can indirectly influence host physiology. A low FODMAP diet has also been shown to improve cognitive functions and depression, which are symptoms common in GWI. This study is designed to demonstrate the safety and effectiveness of a low FODMAP diet in the treatment of GWI. In addition to changes in bowel flora and measures specifically related to bowel function and QoL, endpoints include improvements in a broad assortment of non-bowel-related GWI symptoms. This trial is in progress. Thirty-three of the target amount of 80 subjects have been enrolled. https://clinicaltrials.gov/ct2/show/NCT02881944

IV.6. Treatments Targeting Mitochondria and Reactive Oxygen Species

IV.6.1. Why This Strategy for GWI

Mitochondria are the subcellular organelles that produce a large proportion of the cell's energy, and basic research studies have shown that mitochondrial dysfunction and deficiencies in physiological energy availability are associated with GWI. These deficiencies can have two types of effects. One would be a direct impact on energy requiring actions such muscle contraction, nerve conduction, or chemical processes like synthesis of proteins or RNA synthesis. The other would be a more indirect effect on cellular oxidation state exposing cells to the detrimental oxidative effects of reactive oxygen species (ROS). Either of these effects could produce fatigue directly and contribute to inflammation, which is thought to give rise to many of the symptoms associated with GWI. Because of this, drugs, vitamins, and dietary supplements that are known to improve energy production and scavenge ROS are being assessed for relief of GWI symptomatology. These substances interact with the cell's energy production machinery to obtain high-energy electrons, which they then transfer to ROS to detoxify them. They can then be recharged by the cell with more high-energy electrons to engage in further ROS detoxification. Some of these compounds like the vitamin coenzyme Q10 (CoQ10) can also boost mitochondrial throughput of by providing a shunt that moves high-energy electrons past bottlenecks in the mitochondrial energy production machinery. These substances do not produce their effects by possessing high-energy electrons when they are administered but rather by being capable of participating in a reaction cycle where they obtain electrons from the cell's energy-producing machinery, put them to good use in detoxification or energy production, and then go back and obtain more high-energy electrons from the cell once again.

IV.6.2. Potential Impact

These treatments would be expected to reduce inflammation and affect many symptoms of GWI but especially chronic fatigue and body pain. Such treatments would provide abatement of symptoms rather than a cure and would be expected to be administered on an ongoing basis.

IV.6.3. Completed Clinical Trials

- ***A Prospective Open-Label Clinical Trial of Methylphenidate plus a GWI-Specific Nutrient Formula in Patients with Gulf War Illness and Concentration Disturbances***

  This treatment combines a proprietary cocktail dubbed KPAX002, which combined antioxidants with the CNS stimulant methylphenidate. The impact of a safe and effective treatment for the fatigue, alertness, and cognitive symptoms faced by GWI patients would be substantial to this long-suffering population. The primary clinical efficacy assessment was the GWI Symptoms Assessment Tool (SAT). A secondary efficacy assessment tool utilized was the Checklist Individual Strength (CIS) total score. The study has been completed and published. A patent application is pending. GWI Veterans taking KPAX002 for 12 weeks had a significant reduction in overall symptom severity as demonstrated by reductions in

SAT and CIS total scores, as well as improved Visual Analog Scale scores for concentration disturbance symptoms, fatigue, sleep, and pain. There was also a significant reduction in serum lipid peroxide levels. (Holodniy, 2019, Kaiser, 2016)

- ***Q10 for Gulf War Veterans***

  A double-blind placebo-controlled crossover study was used to assess whether administration of CoQ10 administration (in the oxidized form called ubiquinone) would reduce symptoms and improve subjective health in GW Veterans. Endpoints included a general self-rated health (GSRH) score, symptom score (self-rated scores on 20 GWI-associated symptoms), systolic blood pressure, and the summary performance score (SPS). The study was completed with 23 placebo controls and 11 and 12 Veterans each receiving 100 or 300 mg CoQ10 three times daily respectively for 3 months. Data analysis indicated an improvement in GSRH scores with Q10 treatment regardless of dose, although neither was significantly different than placebo. Q100 mg treatment seemed to generally improve the overall symptoms of GWI, whereas Q300 mg produced mixed results. Moreover, Q300 mg was associated with sleep disturbances, which may have contributed to the mixed results. (Golomb, 2014)

- ***CNDP1 Polymorphisms and Carnosine Therapy in GWI***

  The dipeptide carnosine (β-alanyl-L-histidine) is a compound found in high concentrations in brain and muscle and has antioxidant and neuromodulatory properties. Studies found that an enzyme called carnosine dipeptidase 1 (CNDP1) that cleaves and destroys carnosine was present in elevated amounts in Veterans with GWI, so investigators undertook this randomized double-blind placebo-controlled 12-week dose escalation study in 25 subjects to assess the effects of carnosine administration on GWI symptoms and try to assess whether subjects possessed mutations in CNDP1 that might affect carnosine metabolism. Outcomes included subjective fatigue, pain, and psychosocial questionnaires as well as instantaneous fatigue and activity levels recorded by ActiWatch Score devices. Cognitive function was evaluated by WAIS-R (Wechsler Adult Intelligence Scale – Revised) digit symbol substitution test. Significant increases WAIS-R scores and a decrease in diarrhea associated with IBS were observed in subjects taking carnosine. (Baraniuk, 2013)

IV.6.4. Ongoing Clinical Trials

- ***Development of Dietary Polyphenol Preparations for Treating Veterans with Gulf War Illness***

  Polyphenols are a class of antioxidant molecule found in common plants and fruits, which have been shown to improve fatigue and preserve cognitive function in other disorders. Researchers designed a 6-month, randomized, double-blind placebo-controlled study to assess safety, tolerability, feasibility, and efficacy of high-polyphenol dietary supplementation to treat cognitive deficits and chronic fatigue in Veterans with GWI.

Primary outcome measures are short- and longer-term safety/compliance/tolerability evaluation, and changes in cognition and chronic fatigue. Secondary outcomes and covariates include measures of pain, sleep quality, and bioavailability of polyphenols in the blood. The study was closed to recruitment in July 2018 with a total of 32 subjects enrolled. Analysis and publication are pending.

- ***Extending Benefits of Q10: Mitochondrial Cocktail for Gulf War Illness***

  Having proven some benefit to Veterans with GWI from CoQ10 treatment in the study described above, the same researchers conceived a further study to attempt combining CoQ10 administration (in the oxidized form called ubiquinone) with a cocktail of other antioxidants and metabolites, which would be adjusted for each subject on an individual basis to achieve optimal metabolic balance and mitochondrial function. In a double-blind, randomized, sham-controlled trial of 6 months duration, researchers will measure balance of amino acids and citric acid cycle metabolites in addition to a large number of validated and non-validated measures of fatigue, cognition and memory, lower extremity function, QoL, pain, and sleep quality. This trial has not begun because of delays associated with one investigator's change of institution. https://clinicaltrials.gov/ct2/show/NCT02804828?

- ***A Pilot Randomized Control Trial on the Effect of Resveratrol on Mood, Memory Deficits, Hippocampal Inflammation, and Neurogenesis in Veterans with Gulf War Illness***

  The polyphenols resveratrol and quercetin are known antioxidant and anti-inflammatory substances found in abundance in grapes and berries and other fruits, nuts, and seeds. Researchers will conduct a three-armed, placebo-controlled, 26-week study of the effects of resveratrol alone or resveratrol plus quercetin in 93 Veterans with GWI. This study is ongoing. Of 40 subjects initially enrolled, 25 withdrew, 9 are currently active, and 6 have completed. https://clinicaltrials.gov/ct2/show/NCT03665740

- ***Liposomal Glutathione Versus CoQ10***

  Glutathione is a very well-characterized antioxidant, and the researchers involved in this study want to do a head-to-head comparison of the abilities of CoQ10 and liposomal glutathione to penetrate the CNS and presumably relieve oxidative stress. In this study, subjects will receive either liposomal glutathione or CoQ10, and levels of glutathione or CoQ10 in the CNS will be measured by magnetic resonance spectroscopy. In trials of CoQ10 for other neurological conditions, the non-oxidized form of CoQ10, called ubiquinol, was found to be more effective than the oxidized form, called ubiquinone, so the researchers are using the non-oxidized form, ubiquinol, in this study. This study is ongoing and in its earliest stages. https://clinicaltrials.gov/ct2/show/NCT02865460

- ***Randomized, Double-Blind Placebo-Controlled Phase III Trial of Coenzyme Q10 in Gulf War Illness***

  Based on the success of the prior small trial of CoQ10 (described above), researchers embarked on a large-scale Phase III trial of CoQ10. This is double-blind, placebo-controlled four-site trial with a target subject pool of 200 Veterans with GWI. The protocol duration is 24 weeks. Endpoints include SF-36 physical function score and fatigue, pain, sleep subscales; neurocognitive testing; activity monitor data;, and laboratory assessments of cytokines, hormones, and other measurements in blood, urine, and saliva. In trials of CoQ10 for other neurological conditions, the non-oxidized form of CoQ10, called ubiquinol, was found to be more effective than the oxidized form, called ubiquinone, so the researchers are using the non-oxidized form ubiquinol in this study. This study is ongoing. All data and results will remain blinded until the conclusion of the study. https://clinicaltrials.gov/ct2/show/NCT02865460?

IV.7. Other Treatments

IV.7.1. Why This Strategy for GWI

Some GWI research projects fall outside the major focus areas of research. These studies have targeted individual symptoms, like sleep quality, fatigue, and impaired cognitive performance, or explored a different theory of the nature of GWI or applied a known therapy practice to the illness.

IV.7.2. Potential Impact

These studies encompass early attempts to address treating GWI at its essence and applying either an established treatment or more recent technology to the disease. Some were shown to be effective while others pointed researchers in a different direction. Study results are being analyzed for one therapy that has yet to realize its potential to help Veterans with GWI, but could lead to relief of cognitive problems.

IV.7.3. Completed Clinical Trials

- ***Sleep Disordered Breathing in Gulf War Illness and the Effect of Nasal CPAP Treatment***

  This pilot study investigated sleep disordered breathing in 17 Veterans with GWI and assessed the effect of treatment with continuous positive airway pressure (CPAP) to alleviate the symptoms of GWI. Participants received 3 weeks of treatment with either therapeutic nasal CPAP or sham nasal CPAP. Beyond improved sleep quality, those receiving therapeutic nasal CPAP exhibited significant improvement in pain, fatigue, cognitive function, and physical and mental health. The results were published in 2011 (Amin, 2011a, 2011b).

- ***Antibiotic Treatment of GW Veterans' Illnesses (ABT)***

  This study was based on the concept that GWI resulted from systemic *Mycoplasma fermentans* infection. The Antibiotic Treatment Trial of GWVI was a randomized placebo-controlled trial to determine whether a 1-year course of doxycycline treatment in GW Veterans with GWI (and testing positive for *Mycoplasma* species) would improve their overall functional status by a self-reported measure (SF-36V Physical Component subscore). The VA-funded multi-site trial enrolled 491 deployed GW Veterans who took doxycycline or a matching placebo daily for 12 months. The study found no statistically significant difference between the doxycycline and placebo groups for the primary outcome measure, improvement in self-reported health status. The results were published in 2004 (Donta, 2004).

- ***Cognitive Behavioral Therapy and Aerobic Exercise for Gulf War Veterans' Illnesses: A Randomized Controlled Trial***

  Because there was originally no consensus etiology or basis for GWI, CBT and exercise were investigated to relieve symptoms experienced by Veterans. This study compared CBT and exercise, or either activity alone, to usual care to improve self-reported health status measured with the Veteran's SF-36 Physical Component subscore. CBT sessions (60 to 90 minutes) and exercise sessions (60 minutes) were conducted weekly for 12 weeks. After 1 year, 18.4% of the participating Veterans using CBT plus exercise showed improvement in physical function, 18.5% with CBT alone, 11.7% with exercise alone, and 11.5% with usual care. For secondary outcomes, exercise alone or in combination with CBT significantly improved fatigue, distress, cognitive symptoms, and mental health functioning. CBT alone significantly improved cognitive symptoms and mental health functioning. Neither treatment had a significant impact on pain. The study showed that CBT and/or exercise could provide modest relief for some of the symptoms of GWI. The results were published in 2003 (Donta, 2003).

- ***Transcranial, Light-Emitting Diode (LED) Therapy to Improve Cognition in GWVI***

  This study investigated whether application of LED in red (visible) and near-infrared (NIR) wavelengths to the scalp resulted in improvement in cognition in Veterans with GWI. These wavelengths had been shown to improve ATP production in cells, especially hypoxic or compromised cells. The treatment increased regional cerebral blood flow, which is associated with improved cognition, in chronic TBI. Impaired cognition is one of the major symptom areas of GWI. The procedure is considered non-invasive by FDA and is painless. The study incorporated a cross-over design where one group received two treatments of active light per week for 7.5 weeks followed by the same regimen with sham treatment. Another group received the sham treatment first for 7.5 weeks, followed by the same regimen with active treatment. The active phase of the study was recently completed, and results are being analyzed.

V. Research Infrastructure and Collaborative Efforts

V.1. Consortia and Biorepositories

In 2012, the GWIRP granted two Consortium Awards, one to a team of investigators led by Drs. Mariana Morris, Nancy Klimas, and Gordon Broderick at Nova Southeastern University and another led by Dr. Kimberly Sullivan at Boston University. These GWI consortia brought together a diverse group of experts with the goal of executing preclinical and clinical studies that would increase understanding of the mechanisms responsible for mediating GWI and lead to the discovery of potential therapeutics for Veterans with GWI. The Nova Southeastern consortium focused on identifying candidate treatments by merging preclinical animal model studies comparing cytokine, hormone, and neuropeptide expression profiles with advanced computer simulations of aberrant metabolic activity. Based on these findings, Dr. Klimas and her team selected a combination treatment strategy that targets the inflammation and endocrine dysfunction observed in GWI now being evaluated in a Phase I study of Veterans with GWI. The treatment consists of entanercept, a tumor necrosis factor receptor antagonist, and mifepristone, an anti-glucocorticoid. Major findings of the Boston University consortium include strong evidence for a neuroinflammatory component in GWI in animal models as well as significant differences between the immune cells of Veterans with GWI and controls. The results gathered by these consortia have provided a critical step forward in understanding the pathobiological mechanisms responsible for GWI and have produced key evidence to support the use of specific therapeutics to treat Veterans with GWI.

In September 2018, Dr. Klimas received a GWIRP Clinical Consortium Award. The objective of the Gulf War Illness Clinical Trials and Interventions Consortium (GWICTIC) is to combine the expertise and efforts of the two previous consortia and build upon their results by implementing early-phase clinical trials to evaluate candidate therapeutics for GWI. The GWICTIC aims to execute five Phase I or Phase II clinical trials in the 4-year period of performance. The first set of trials will extend the initial evaluation of the entanercept plus mifepristone treatment carried out by the original consortium. Subsequent interventions will target additional pathobiological mechanisms elucidated by the prior consortia efforts.

In addition to her participation as a co-investigator on Dr. Klimas' Clinical Consortium Award, Dr. Sullivan will use her 2017 GWIRP Biorepository Resource Network Award to work toward creating the Boston Biorepository, Recruitment, and Integrative Network (BBRAIN), which will house previously and newly collected biological specimens and clinical data from Veterans with GWI and control subjects. BBRAIN will harness the biorepository infrastructure created by Dr. Sullivan's previous consortium to create a resource for all GWI researchers.

Novel treatment strategies and objective markers of GWI are critical needs for the GWI community. The GWICTIC will help meet these needs by establishing a streamlined infrastructure for conducting Phase I and II clinical trials to evaluate potential GWI therapeutics,

while the new BBRAIN will provide a key resource for the exploration of mechanisms, identification of biomarkers, and selection of innovative treatment strategies for GWI. With these new projects, Drs. Klimas and Sullivan will continue fostering and creating a collaborative environment for researchers interested in understanding and tackling the pathology of GWI.

V.2. Common Data Elements

Through a collaboration among the National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), VA, DoD GWIRP, and GWI community, common data elements (CDE) recommendations are being developed for GWI. The goals of this effort are to increase the efficiency and effectiveness of clinical research studies and treatment, increase data quality, facilitate data sharing and aggregation of information across studies, and help educate new clinical investigators. Development of CDEs is an iterative process, and updates are expected as research progresses and feedback is received from the community.

V.3. Deep Phenotyping

Large-scale genotype and phenotype efforts are planned and/or are underway through collaborative efforts at the VA and NIH. These studies will examine relationships between genetic variations and the physical traits of ill GW Veterans.

VI. Remaining Gaps in Our Understanding of GWI

VI.1. Prognostic Research Needs

Little is known about the long-term prognosis of GWI and the rates at which GW Veterans are affected by other diseases. The 2014 report by RAC-GWVI summarized investigations addressing health changes related to GWI (RAC-GWVI Research Update and Recommendations, 2014). The report states that Veterans of the 1990-1991 GW generally are in poorer health and present with greater disability than other Veterans of the same era that were not deployed to the Persian Gulf. Research suggests that the GWI symptomology experienced by Veterans has not improved over the last 25 years, with few experiencing improvement or recovery. Many GW Veterans will soon begin to experience the common comorbidities associated with aging. The effects that aging will have on this unique and vulnerable population remain a matter of significant concern, and population-based research to obtain a better understanding of mortality, morbidity, and symptomology over time is needed. Zundel et al. recently published a paper showing that GW Veterans have significantly greater odds of developing chronic conditions and that, as Veterans age, they will continue to develop these chronic conditions and other diseases associated with aging (Zundel, 2019).

VI.2. Etiologic Research Needs

Uncertainties regarding types and doses of agent exposures, as well as a lack of scientific knowledge about the synergistic effects of combined agent exposures, have precluded a consistent theory of GWI etiology. Identification of objective markers of GW-relevant exposures and downstream effects of those exposures, including latent effects that represent the current status of Veterans with GWI, are needed. In addition, comparative studies designed to identify additive effects of exposures to multiple toxic agents and stressors should be undertaken.

VI.3. Pathobiology Research Needs

As medical needs continue to evolve and as we improve our understanding of GWI, new research needs emerge. These research needs hold significant impact for the advancement of treatment, the cure, and/or management of GWI. Some of those research needs include the identification of novel pathways relevant to GWI, validation of targets by replication of previously identified system dysfunctions, research into sex and racial differences, and better understanding of relations between disease components, and concurrent assessment of different physiological systems within individual Veteran research subjects. Additionally, in the absence of a consensus case definition for GWI, the need continues for applied research aimed at producing a robust, evidence-based definition for both clinical and research applications. The creation and collaboration for a robust GWI repository to support validation and correlative research is also an important area that must also be addressed.

VI.4. Treatment Needs

Symptomatic treatments to improve QoL and objective treatment approaches aimed at dysregulated molecular pathways are needed. These approaches require validation of promising leads and a clear definition of mechanistic outcomes.

VII. Future Directions

VII.1. GWI Overarching Challenges

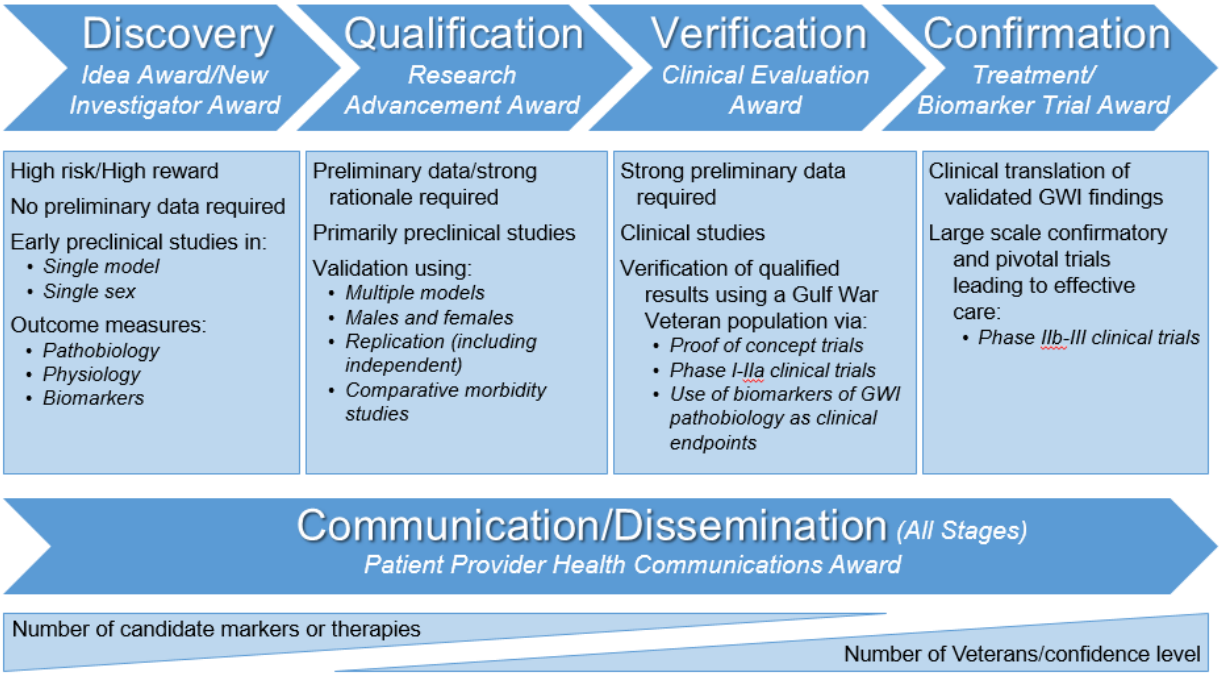
Considering the current Gulf War Illness Landscape and the GWIRP's mission, all GWIRP applications must address at least one of the following overarching challenges unless adequate justification for exception is provided.

- Treatments: Eliminate the health consequences associated with GWI and revolutionize treatment
- Diagnosis: Better define and diagnose GWI
- Subtyping: Distinguish symptom clusters to better target treatments, identify underlying causes, and elucidate differences in severity

- Determinants: Validate exposures associated with GWI and impacts on organs and systems
- Consequences: Determine whether GWI is associated with greater risk for developing other disease states including neurological diseases, cancers, or other life-threatening and severely debilitating conditions
- Communication: Help Veterans, their caregivers, and clinicians communicate effectively about GWI, its symptoms, and potential treatments

VII.2. GWIRP Four-Tiered Research Mechanism Pipeline

To address the overarching challenges in a step-wise and translational manner, the GWIRP award mechanisms are aligned to the different phases of the research pipeline.



VII.3. GWIRP Areas of Emphasis

- Replication and validation of treatments that have shown positive impact on GWI
- Identification, replication, and/or validation of the causes of and treatment targets for dysregulated biological system function. Emphasis should be placed on:
  - Cognitive difficulties to include memory deficits, mood and behavior disturbances
  - Non-restorative sleep or sleep disturbances
  - Chronic widespread pain

- Chronic debilitating fatigue
- Gastrointestinal effects including dietary intolerances, GERD and FGIDs
- Sinus and respiratory effects
- Headaches
- Dermatological issues
- Neurological dysfunction (central, peripheral, autonomic, and/or neuromuscular)
- Immune system dysfunction
- Endocrine, exocrine, and/or excretory system dysfunction, with special attention to kidney and liver (e.g., Cytochrome P450 abnormalities)
- Microbiome variants
- The impact of stresses (e.g., exertion, immune challenge) on the severity and duration of the symptoms
- Disordered system crosstalk (e.g., immunological dysfunction that alters the nervous system, autonomic dysfunction that impacts functioning of the GI tract) that contributes to malfunction in several physiological systems

- Identification of molecular signatures (e.g., genomic, proteomic, metabolic, and epigenetic) underlying symptoms and the grouping of symptom sets based on common underlying pathobiology
- Investigation of comorbidities, mortality, sex or ethnic differences

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IX. Acronyms

AChE	Acetylcholinesterase
ACTH	Adrenocorticotropic Hormone, Adrenocorticotrophic Hormone
BBB	Blood–Brain Barrier
BBRAIN	Boston Biorepository, Recruitment, and Integrative Network
BCDT	B-Cell Depletion Therapy
BChE	Butyrylcholinesterase
CAM	Complementary and Alternative
CARC	Chemical Agent-Resistant Coating
CBT	Cognitive Behavioral Therapy
CDC	Centers for Disease Control and Prevention
CDE	Common Data Elements
CIS	Checklist Individual Strength
CMI	Chronic Multi-Symptom Illness
CNDP1	Carnosine Dipeptidase 1
CNS	Central Nervous System
CORT	Corticosterone
CoQ10	Coenzyme Q10
CPAP	Continuous Positive Airway Pressure
CPF	Chlorpyrifos
CRS	Chronic Rhinosinusitis
CT	Cognitive Therapy
DCS	D-Cycloserine
DEET	N,N-Diethyl-Meta-Toluamide
DFP	Diisopropyl Fluorophosphates
DoD	Department of Defense
DR	Delayed Release
DU	Depleted Uranium
FDA	U.S. Food and Drug Administration
FGIDs	Functional Gastrointestinal Disorders
FM	Fibromyalgia
fMRI	Functional Magnetic Resonance Imaging
FODMAPs	Fermentable Oligo-, Di and Mono-saccharides And Polyols
GCs	Glucocorticoids

GERD	Gastroesophageal Reflux Disease
GI	Gastrointestinal
GSRH	General Self-Rated Health
GW	Gulf War
GWI	Gulf War Illness
GWICTIC	Gulf War Illness Clinical Trials and Interventions Consortium
HD tDCS	High-Definition Transcranial Direct Current Stimulation
HPA	Hypothalamic-Pituitary-Adrenal
HPG	Hypothalamic-Pituitary-Gonad
IBS	Irritable Bowel Syndrome
IOM	Institute of Medicine
iRest(R)	Integrative Restoration
LED	Light Emitting Diode
MBB	Mind-Body Bridging
MBIs	Mindfulness-Based Interventions
MBSR	Mindfulness-Based Stress Reduction
MC CBT	Minimal Contact Cognitive Behavioral Therapy
MOS-SS	Medical Outcomes Study - Sleep Scale
MRI	Magnetic Resonance Imaging
NIH	National Institutes of Health
NIR	Near-Infrared
OEA	Oleoylethanolamide
PBMCs	Peripheral Blood Mononuclear Cells
PER	Pesticides Permethrin
PON1	Paraoxonase 1
preSMA	Pre-Supplementary Motor Area
PTSD	Post-Traumatic Stress Disorder
QoL	Quality of Life
RAC-GWVI	Research Advisory Committee on Gulf War Veterans' Illnesses
ROS	Reactive Oxygen Species
rTMS	Repetitive Transcranial Magnetic Stimulation
SAT	Symptoms Assessment Tool
SNI	Synchronous Neural Interactions
S-NI	Saline Nasal Irrigation

SPS	Summary Performance Score
SR	Sleep Restriction
SSRI	Selective Serotonin Reuptake Inhibitor
TBI	Traumatic Brain Injury
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
TNF	Tumor Necrosis Factor
VA	Department of Veterans Affairs
VNS	Vagus Nerve Stimulation
WAIS-R	Wechsler Adult Intelligence Scale – Revised
X-NI	Xylitol Nasal Irrigation