

Gulf War Illness and Health of GW Veterans

Updated Scientific Findings and
Recommendations

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Research Advisory Committee on Gulf War Veterans' Illnesses
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Approach to Research Review

- The Committee periodically releases reports that summarize research to date on the health of veterans of the 1990-1991 Gulf War. The most recent report was published in 2008.
- The current report updates knowledge from that time by reviewing published scientific papers that appeared after the last report and through December 2013.

Approach to Research Review and Consensus Approval

- The report was drafted by Committee members and staff.
- Draft reports were reviewed by Committee members who were active at the time the report was begun in 2013 and active members in 2014.
- This report reflects consensus conclusions from active Committee members who provided input during prior in-person and teleconference meetings.

Sections of the Report

Research Review:

- **Epidemiological Research:** Gulf War Illness and Other Health Issues Affecting 1990-1991 Gulf War Veterans
- **Etiological Investigations:** Research on Persistent Health Effects of Gulf War Experiences and Exposures
 - Human studies
 - Animal models
- **Pathobiology of Gulf War Illness:** Physiological Findings in Gulf War Veterans
- **Gulf War Illness Treatment Research**

Research Recommendations

Epidemiological Research

- Prevalence estimates of GWI
- Prognosis studies
- Other health issues associated with GW service

How many veterans have Gulf War Illness?

- All population-based studies conducted since the Gulf War have continued to identify a significant excess rate of chronic symptomatic illness, variously defined, in 1990-1991 Gulf War veterans.
- While prevalence estimates differ with the case definitions used, seven of ten population-based studies indicate that 25 – 32 percent of 1991 Gulf War veterans are affected by this illness, over and above symptom levels documented in nondeployed era veterans.

Prevalence of GWI before 2008

Study	GW Veterans Assessed	Year(s) of Assessment	Case Definition Used	Prevalence in GW Veterans	Prevalence in Nondeployed Veterans	Excess Illness in GW Veterans
Prevalence estimates published before 2008						
Fukuda et al., 1998	1,155 Air Force veterans	1995	CMI	45%	15%	30%
Proctor et al., 2001	180 New England Army veterans	1994-1996	CMI (modified)	65%	33%	32%
Unwin et al., 1999	4,428 U.K. male veterans	1998	CMI (modified)	62%	36%	26%
Unwin et al., 2002	226 U.K. female veterans	1998	CMI (modified)	64%	35%	29%
Steele, 2000	1,548 Kansas veterans	1998	Kansas GWI	34%	8%	26%
			CMI	47%	20%	27%
Blanchard et al., 2006	1,035 U.S. veterans	1999-2001	CMI (modified) ¹	29%	16%	13%

Prevalence Studies of GWI Since 2008

Study	GW Veterans Assessed	Year	Case Definition Used	Prevalence in GW Veterans	Prevalence in Nondeployed Veterans	Excess Illness in GW Veterans
Prevalence estimates published since 2008						
King et al., 2008	357 U.S. veterans	2001	CMI	54%	not evaluated	-
Kang et al., 2009	6,111 U.S. veterans	2005	VA-defined multisymptom illness ²	37%	12%	25%
Kelsall et al., 2009	1,381 Australian veterans	2000-2002	Australian factor definition	26%	16%	10%
Iannacchione et al., 2011	5,699	2007-2009	Haley factors (3 syndromes combined)	14%	4%	10%
Steele et al., 2012	646 Kansas veterans	2000	CMI	45%	not evaluated	-
Smith et al., 2012	317 U.S. veterans	2001	CMI	50%* 34%*	not evaluated	-
King et al., 2008	357 U.S. veterans	2001	CMI	54%	not evaluated	-

How many veterans have Gulf War Illness?

- Differences in excess prevalence rates reported by different studies provide a clear illustration of the importance of case definition in Gulf War illness research.
- Broad case definitions (CMI, Kansas) produce higher rates of the disorder than narrowly defined factor-based definitions (e.g., Haley)
- A data-based case definition should and can be developed; the report recommends a process for this.

9

Prognosis: Are Veterans Getting Better or Worse with Time?

- In 2008 report, Committee reviewed longitudinal evaluation results from four studies of GW veterans, all of which indicated that the symptomatic illness affecting GW veterans had not improved with time and the frequency of symptoms reported by GW veterans remained relatively stable over time.
- Little additional information on the long-term prognosis of Gulf War illness has become available since 2008

10

Prognosis: Are Veterans Getting Better or Worse with Time?

- Boston investigators are currently conducting a follow-up assessment of the longitudinally followed Ft. Devens cohort, which will provide more current insights on the course and prognosis of Gulf War illness.
- The third wave follow-up of the largest U.S. national cohort, the VA's National Survey of Gulf War era veterans, is also currently underway
- Unfortunately, this large national study does not include the questions necessary to assess GWI by any case definition rather it assessed unexplained multi-symptom illness as one self-report question

11

General Health Status of GW Veterans

- Studies published since 2008 have continued to document poorer general health status and greater disability among Gulf War veterans

<i>Study</i>	<i>Groups Studied</i>	<i>Outcome(s)</i>	<i>Key Findings</i>
Horn et al., 2010	4,257 U.K. GWV and 4,295 U.K. IWV	HSC, GHQ-12	Symptom reporting increased over 7 years across all symptom dimensions for U.K. veterans, and increase was greater in analyses adjusting for psychological morbidity. Results not specific for deployment era.
Kang et al., 2009	6,111 GWV, 3,859 NDV	SF-12	GWV had significantly lower mean scores on both PF and MF summary scales.
Iannacchione et al., 2011	3,442 deployed GWV, 765 NDV	SF-12	Deployed GWV with GWI had significantly lower mean functional status than nonsymptomatic GWV.
Ismail et al., 2011	3626 U.S. GWV and 5573 U.K. GWV	SF-36, GHP and PF	PF scores did not differ between U.S. and U.K. GWV.
Smith et al., 2013	311 deployed GWV	Fukuda et al. (1998) GWI case definition	Most common symptom was fatigue, followed by memory impairment, joint issues, sleep difficulty, and mood lability.

12

Other Medical Conditions Affecting GW Veterans

- Neurological disorders
- Cancer
- Sleep dysfunction
- Adverse reproductive outcomes

Neurological Conditions in Gulf War Veterans: 2009-2013

Study	Outcomes	Results Summary
Barth, 2009	Mortality due to brain cancer, MS, PD, ALS	Significantly higher rates of brain cancer mortality in nerve agent and oil well fire exposed groups
Kang, 2009	Diagnosed medical conditions	Significantly higher rates of seizures, neuralgia/neuritis, stroke
Kasarskis, 2009	ALS age on onset, site of onset, atypical symptom features, ventilator-free survival time	Ventilator-free survival time significantly shorter in deployed GWV. No difference between ALS symptoms, age and site of onset between groups
Rayhan, 2013	Structured headache evaluations	Statistically similar proportions of GWV and CFS patients affected by migraines; both significantly greater than controls
Wallin, 2012	MS incidence	No determination of MS rates in GWV

Significant findings in 4/5 studies

Cancer in Gulf War Veterans: 2009-2013

	Outcomes	Results Summary
Kang, 2009	Self-reported diagnosed cancer	GWV and NDV similar rates of cancers
Young, 2010	Proportional incidence ratios of cancer diagnoses	Proportional incidence of lung cancer significantly higher in GWV compared to NDV. Proportional incidence of testicular cancer and Kaposi's sarcoma significantly lower in GWV.

Significant findings in 1/2 studies

Sleep Disturbances in Gulf War Veterans: 2009-2013

Study	Outcomes	Results Summary
Amin, 2011	Sleep apnea, hypopnea, airflow limitation	Symptomatic GWV showed significantly increased numbers of arousals, sleep disordered breathing and flow-limited breathing during NREM stage 2 sleep, indicating more collapsible upper airways.

Significant findings in 1/1 studies

Adverse Reproductive and Birth Outcomes in Gulf War Veterans: 2009-2013

Study	Outcomes	Results Summary
Bukowinski, 2012	Birth defects	No increased overall risk of birth defects; paternal deployment length (between 153 and 200 days) was significantly associated with higher birth defect rate when compared to paternal deployment length (<92 days)
Verret, 2008	Fertility disorders, miscarriages, birth defects, preterm birth	No evidence of an association between paternal GW deployment and adverse reproductive or birth outcomes
Kang, 2009	Fertility disorders, miscarriages	Sig. higher rates of fertility disorders in women GWV than NDV. No difference in miscarriage

Significant findings in 2/3 studies

Multisymptom Illnesses

- Chronic fatigue syndrome
- Fibromyalgia
- Multiple chemical sensitivity

Multisymptom Conditions in Gulf War Veterans: 2009-2013

Study	Outcomes	Results Summary
Ciccone, 2008	CFS screening questionnaire	CFS characteristics differed between GWV and civilian controls. Civilian CFS more likely to have sudden flu-like onset and be comorbid with FM and psychiatric disorders
Ismail, 2008	CFS, FM	Disabled GWV more likely to meet CFS criteria, but similar rates of FM to comparison group.
Kang, 2009	MSI, CFS, FM	Sig. higher rates of MSI, CFS, FM
Li, 2011	CFS-like illness	Sig. higher prevalence of CFS-like illness, greater increase in CFS-like illness between 1995-2005

While there is some overlap between GWI symptoms and symptoms reported by CFS and FM patients, criteria for these conditions do not adequately describe GWI and do not account for the large majority of cases.

Psychiatric and Psychological Disorders in GW Veterans

- Follow up studies on deployed Gulf War veterans and psychological and psychiatric morbidity since 2008 continue to show that combat and other stressors are associated with PTSD, anxiety, depression and alcohol abuse in this population. However, these disorders do not explain GWI and occur at far lower rates than GWI in GW veterans

Psychiatric and Psychological Disorders in Gulf War Veterans: 2009-2013

Outcomes	Results Summary
Hippocampal volume by MRI	GWV with current PTSD had smaller hippocampal volume than GWV without PTSD
Alcohol use, PTSD, MDD, MSI, CFS-like illness	Problem drinking was significantly and positively associated with PTSD, MDD, unexplained MSI and CFS.
MCS	Exposure to war casualties but not combat overall was associated with mental health decline.
PSS, DSS, alcohol misuse	Combat exposure was significantly associated with PSS, DSS and alcohol misuse.
DRRI, PTSS	High PT and DLWE scores on the DRRI and PTSS were significantly stronger for active duty women and NG/R men.
PSS, PCL, PHS	Sig. associations between post-deployment physical health and PSS in all symptom categories.
Cortical volume measured using MRI	Subjects with combat-related PTSD showed sig. smaller cerebral cortical volume, thickness and area
Plasma ACTH changes, declarative memory, MRI, PET, DST	PTSD+ group showed sig. greater cortisol and ACTH suppression. Hippocampal volume difference and greater hippocampal metabolic activity seen in PTSD+ GWV.

Significant findings in 8/8 studies associated with GW service but NOT with GWI

Hospitalization Rates in Gulf War Veterans: 2009-2013

Study	Outcomes	Results Summary
Hooper, 2008	Hospitalization Rates	Most common hospitalizations involved musculoskeletal, digestive, injury related, ill-defined and circulatory conditions. Hospitalizations related to mental health disorders were under-represented in this study population compared to U.S. Armed Forces overall.

In 2008, Committee reviewed 14 hospitalization studies. Overall, few differences were identified in disease-specific hospitalizations, although individual studies found that GW veterans had higher hospitalization rates due to fibromyalgia, musculoskeletal conditions, respiratory conditions, and gastrointestinal conditions

Mortality in Gulf War Veterans

- A study conducted by VA and published since the 2008 RACGWVI report found that when Gulf War veterans were compared to nondeployed era veterans, no significant differences in deaths due to any neurological disease were identified, including deaths due to brain cancer, amyotrophic lateral sclerosis (ALS), and Parkinson's disease
- However, when brain cancer mortality rates were evaluated in subgroups of veterans who were potentially exposed to nerve agents resulting from the Khamisiyah demolitions and Kuwaiti oil fires, both were associated with significantly increased risk for brain cancer deaths in exposed Gulf War veterans

23

Mortality in Gulf War Veterans

- The 2009 VA mortality study results provide a clear example of the importance of assessing mortality and other health outcomes in veteran subgroups defined by deployment locations, exposures, and other characteristics of importance.
- The overall picture of mortality among U.S. Gulf War veterans remains unclear. Issues of current concern include apparent increases in brain cancer deaths among veterans exposed to oil fire smoke and low-level nerve agents.
- Additional areas of possible concern, raised by crude mortality data reported in VA's 2011 *Gulf War Era Veterans Report: Pre 9/11*, relate to whether overall mortality through 2009 was higher among Gulf War personnel in particular locations in theater.

24

Mortality in Gulf War Veterans

- In summary, a primary issue of concern is the lack of current information on overall and disease-specific mortality among U.S. Gulf War veterans. No comprehensive information has been published on the mortality experience of U.S. Gulf War era veterans after the year 2000.

25

Epidemiological Recommendations

Recommendations

Case definitions: evidence-based, expert consensus-driven case definition should be developed.

Terminology for Illness: VA should adopt the name '**Gulf War illness**' for the symptomatic condition associated with GW military service in 1990-1991 Gulf War

Surveillance: ongoing monitoring and surveillance is critical as Gulf War veterans age. VA's longitudinal survey can be effectively used to assess rates of physician diagnosed medical conditions. Survey data should be used to flag conditions of possible importance and followed up to determine potential rates of increased medical diagnoses affecting GW veterans at excess rates.

Prevalence Studies: A study on the prevalence of MS, Parkinson's disease and brain cancers, as well as CNS abnormalities that are difficult to diagnose was required by Congress in 2008 and should be carried out.

Epidemiological Recommendations 2

Recommendations

Mortality Studies: Systematic assessment of overall and disease-specific mortality in all GW veterans and in specific subgroups of interest (Khamisiyah) is essential. These results should be published in 5-year intervals.

Morbidity Studies: VA's longitudinal survey should be used to assess rates of medical conditions, including immunological and behavioral disorders and birth defects, in children of GW veterans. Survey data can be used to flag conditions of possible concern and followed up. It is also important that VA publish results from studies of Veteran's children that were conducted over 10 years ago.

Subgroups of Importance: Evaluation of health outcomes in subgroups of potential importance is critical as some health outcomes are related to specific exposures and experiences or locations in theater.

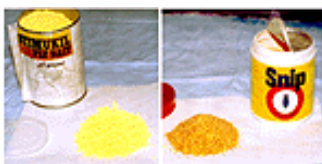
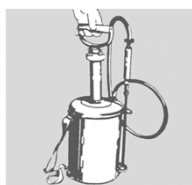
Improved Methodology Guidelines for Epidemiological Research: Should include systematic methods for assessing symptoms and other health outcomes, evaluation of health outcomes in subgroups of importance (exposure, location), consideration of subpopulations with multiple health outcomes, use of analytic methods that control for multiple exposures (confounding effects and synergistic effects)

Etiological Investigations



Etiological Research findings

- Epidemiological studies continue to support the conclusion from the 2008 RACGWVI report that chemical exposures (particularly pesticides and pyridostigmine bromide), not psychological stressors or psychiatric disorders, are the cause of Gulf War illness and other health and functional disorders in Gulf War veterans.



Exposures and Health Outcomes: Neurological/Neuropsychological

Study	Exposure	Method	Health Outcomes
Chao, 2010	Sarin and cyclosarin	MRI, neuropsychological testing	Sig. reduced gray matter and hippocampal volumes
Chao, 2011	Sarin and cyclosarin	MRI, neuropsychological testing	Sig. reduced total gray and white matter volume
Toomey, 2009	PB, pesticides, vaccines, IG injections, oil well fire smoke	Neuropsychological testing	Deployed GWV had sign. lower scores on tests of verbal memory, verbal learning, motor speed, and attention

Significant findings in 3/3 studies

Exposures and Health Outcomes: Cancer mortality

Study	Exposure	Method	Health Outcomes
Barth, 2009	Sarin/cyclosarin Oil well fire contaminants	Brain cancer mortality, brain cancer, ALS, MS, PD	Sig. increase in brain cancer mortality among GWV in sarin exposure area ≥ 2 days; sign. dose response effect for number of days of exposure. Oil fire associated with sig. increase in brain cancer mortality among exposed Army GWV, compared to non-exposed.

Significant findings in 1/1 studies

Exposures and Health Outcomes: Health status

Study	Exposure	Method	Health Outcomes
Kelsall, 2009	Vaccines	Total symptom number, SF-12 physical component, GHQ-12 case status	Number of self-reported vaccines weakly associated with total number of symptoms and poorer health; relationship not seen with recorded vaccination number.

Significant findings in 0/1 studies

Exposures and Health Outcomes: GWI and CMI

Study	Exposure	Method	Health Outcomes
Haley, 2013	Chemical alarms, DoD-modeled Kham exposure area	GWI	GWI was significantly associated with hearing chemical alarms but not with exposure to Khamisiyah plume
Phillips, 2009	Vaccines (squalene antibodies)	CMI	Similar proportions of CMI (55%) and healthy (51%) GWV were positive for squalene antibodies (p = 0.71).
Steele, 2012	PB, pesticides, vaccines, oil well fire smoke	GWI	Pesticide use sig. associated with GWI for veterans who were in Iraq or Kuwait and for veterans in support areas. Use of PB, close proximity to exploded SCUD missiles and exposure to oil well fire smoke sig. associated with GWI for personnel in forward areas only; GWI not associated with serving in combat, hearing chemical alarms.

Significant findings in 2/3 studies

Studies Evaluating Depleted Uranium Exposure in Gulf War Veterans

Parameter(s) Evaluated	Key Findings
Urine U and cytogenic endpoints	Chromosomal damage not associated with urinary uranium levels.
KPA Isotopic ratio of U in urine	Only subjects who retained DU embedded fragments showed detectable depleted isotopic uranium signatures in urine.
Total urine uranium and U urine ratio	No differences in pulmonary or respiratory function were seen between high and low uranium groups.
ICP-DRC-MS urine U/g creatinine	No statistically significant differences in biomarkers of genotoxicity or cognitive function between high and low U groups
ICP-MS total U/g creatinine, isotopic ratio of uranium in urine, PET-CT	DU-related effects on renal function seen only in subjects with multiple metal fragments; pulmonary function in normal range
Uranyl acetate and extended metal match testing	No uranyl acetate patch test reactions were observed in veterans or control group, indicating few memory effector T-cells sensitive to dermal DU exposure.
ICP-MS total U/g creatinine,	42% showed excreted urine U concentrations above normal U excretion cutoff values. No clinically significant health effects found in DU-exposed GWV.
ICP-MS U quantification in semen	Wide variation in semen uranium in DU-exposed GWV and GWV with unknown exposure

Depleted Uranium



Significant findings in 0/8 studies for reporting clinically significant differences between exposed and unexposed groups.

Etiological Research Using Animal Models

- Animal studies have confirmed hypotheses that exposures to chemicals and pharmaceutical agents that were present in the Gulf War theater are important in the development and expression the types of symptoms observed in Gulf war illness
- Health effects due to exposures and exposure mixtures are often delayed; persistent effects can be seen after exposure has ended.

36

Studies Using Animal Models of Gulf War Illness and Related Diseases: 2009-2013

Effect Evaluated	Key Findings
<i>Altered behavior, cognitive function, neurotransmission and intracellular signaling in OP (CPF) PB, DEET, permethrin exposures</i>	Sig findings in 9/9 studies
<i>Molecular and cellular disruptions of axonal transport in OP exposures (CPF, sarin surrogate DPF)</i>	Sig. findings in 5/5 studies
<i>Liver and cardiovascular effects in OP exposures (dichlorvos and sarin)</i>	Sig. findings in 2/2 studies
<i>Genomic and proteomic profiling to identify novel targets of Gulf War exposure in PB, permethrin, DEET exposures</i>	Sig. findings in 2/2 studies
<i>Depleted uranium: Mitochondria and oxidative stress and gestational and post-weaning effects</i>	Sig. findings in 2/2 study

Significant findings in 20/20 studies

Pathobiology of Gulf War Illness: Physiological Findings in Gulf War Veterans

EEG and Brain Imaging Findings in Gulf War Veterans: 2009-2013

Methods	Key Findings
MRI and SPECT	Significant findings in 2/3 studies
Physostigmine challenge test	Significant findings in 2/2 studies
Structural MRI	Significant findings in 5/5 studies
fMRI	Significant findings in 3/3 studies
EEG	Significant findings in 2/2 studies

Significant findings in 14/15 studies

Studies Assessing Neuroendocrine Function in Gulf War Veterans: 2009-2013

Study	Parameters evaluated	Key Findings
Golier, 2009	Metyrapone stimulation, cortisol, 11-deoxycortisol, ACTH	PTSD- group had significantly lower ACTH response to metyrapone stimulation and significantly lower post-metyrapone ACTH levels compared to PTSD+ and healthy controls. ACTH response to metyrapone was significantly associated with six health symptom scales (neurological, psychological, musculoskeletal, neuropsychological, pulmonary, cardiac) for both GWV groups, but not healthy controls.
Golier, 2012	CRF stimulation, ACTH, cortisol, DHEA, CBG	PTSD- group from OEF/OIF showed elevated ACTH compared to non-exposed group, but not in GWV. PTSD+ ACTH levels were higher than non-exposed in GWV and OIF/OEF. Robust differences between PTSD+, PTSD- and non-exposed were found in GWV. ACTH response greater in PTSD+ GWV than PTSD- or non-exposed GWV, and also greater than VV and OEF/OIF PTSD+ subjects. ACTH AUC was associated with self-reported exposure to PB.

Significant findings in 2/2 studies

Studies of Autonomic Function in Gulf War Veterans: 2009-2013

Study	Autonomic Tests	Key Findings
Haley, 2013	ASP, CAS, 24-hour HRV with ECG	GWV in all symptom groups reported significantly more symptoms on the ASP than controls. CAS varied significantly between syndrome groups and controls, and was highest in Haley syndrome 2. Syndrome groups had significantly reduced sudomotor function. High frequency increases in HRV was significantly blunted in syndrome groups.

Significant findings in 1/1 study

Immunological function:
8 studies

Study	Groups Evaluated	Immune Findings
Broderick, 2011	9 symptomatic GWV, 11 veteran controls	Majority of immune markers show significant differences in node extent, a novel metric of immune marker influence over time across GWV groups.
Broderick, 2012	26 symptomatic GWV matched to 13 sedentary GWV, 9 CFS	Symptomatic GWV showed higher expression of immune markers IL-6 in plasma and IL-5 and TNF- α and INF- γ in PHA-stimulated culture.
Broderick, 2013	20 symptomatic GWV, 22 GWV controls, 7 CFS/ME	19 significant immunological gene expression pathway activation differences found in symptomatic GWV compared to controls and CFS/ME.
Johnson, 2013	43 Ill GWV, 21 healthy GWV controls	Ill GWV and healthy control GWV had similar platelet functioning. Ill GWV had elevated platelet counts and higher rates of spontaneous aggregation, as well as elevated responses to thrombin receptor agonist peptide 6 and CRP.
Smylie, 2013	30 Ill GWV, 22 subjects with CFS/ME, 30 healthy sedentary GWV	Male GWV participants had higher IL-13 and IL-10 and IL-23 at rest, and elevations in IL-13 in the context of IL-10, IL-23, and IL-1b post-exercise. Male CFS participants had elevations of IL-23 at rest, and IL-2 in context of IL-16, 10, and 15 at peak effort. Female GWV subjects had elevations in IL-8 and IL-5, and decreases of IL-10 were seen at peak effort, and decreases in IL-23 and IL-1a were observed post-exercise.
Whistler, 2009	9 symptomatic GWV, 11 nondeployed veterans	Statistically significant differences in NK cell subsets CD3-CD56+, CD3-16+ and CD3-CD16+. Hierarchical clustering distinguished between cases and controls based on PRF and KLR complex receptors. Significant differences found between CD4/CD8 ratios between cases and controls. Salivary cortisol decreased in symptomatic GWV in response to exercise.

Studies Assessing Immunological Function in Gulf War Veterans: 2009-2013

Study	Groups Evaluated	Immune Functions
Bakhtmutsky 2009	35 GWV, 15 GWV with embedded DU fragments	No significant differences in micronuclei frequency in peripheral blood lymphocytes in GWV with high versus low urine U.
Philips, 2009	579 GWV Seabees	No association found between squalene antibody status and multisymptom illness.

Significant findings in 6/8 studies

Pathobiology Research Recommendations

Recommendations

Clear, operational case definitions are important for this work

Theater exposures, age and other variables likely moderate pathobiological effects and should be carefully addressed in research

Gender differences may play a role in pathobiological expression of GWI and its effects. Gender should be considered whenever possible in mechanistic/treatment research of GWI

Exploratory probes in genetics, metabolomics, lipidomics and proteomics may yield useful information that can lead to more focused research

Epigenetic and genetic approaches to research on GWI pathobiology likely to be informative

Standard protocols for sample collections should be established and followed in research that uses biological specimens in order to expedite exploratory and hypothesis-driven research.

Increased emphasis should be placed on the study of alterations in regulatory dynamics both within and across the principal regulatory axes, including the endocrine, immune and nervous systems. These should include response to standardized challenges at different time scales, i.e., acute response to exercise, circadian rhythm, and monthly cycles as well as long-term illness progression.

Animal models may be appropriate to investigate mechanistic hypotheses and illness or exposure effects.

Gulf War Illness Treatment Research

- Published studies
- Ongoing studies
- Treatment studies using animal models of Gulf War illness

Published GWI Treatment Research

Study	Treatment Evaluated	Parameters Evaluated	Key Findings
Amin, 2011	CPAP	Pain VAS, FSS, cognition VAS, PQSI, general health short form 36	CPAP group showed significant improvements in pain, sleep, fatigue, cognitive function, and physical and mental health. Sham subjects exhibited significant levels of symptom worsening.
Baraniuk, 2013	L-carnosine	Self-report on pain, fatigue, psychosocial variables, gastrointestinal distress, activity level, WAIS-R	Digit symbol substitution scores increased significantly with L-carnosine treatment, indicating cognitive improvement, and a decrease in IBS- associated diarrhea.

Ongoing Treatments for GWI

Investigator	Treatment	Group
Cook	Exercise Resistance Training	GWV with chronic musculoskeletal pain
Kearney & Hunt	Mindfulness	GWV with GWI
Lin	Antibiotic	GWV with IBS
Conboy	Acupuncture	GWV with GWI
Rabago	Nasal Irrigation	GWV with rhinosinusitis/fatigue
Tuteja	Probiotics	GWV with IBS
Carpenter	Hubbard detox program	GWV with GWI
Nakamura	Sleep focused mind-body program	GWV with GWI
Lin	Acupressure	GWV with pain/fatigue

Ongoing Treatments for GWI

Investigator	Treatment	Group
Golier	Intranasal Insulin	GWV with GWI
Golier	Mifepristone	GWV with GWI
Golomb	Co-Q10	GWV with GWI
Meggs	Low Dose Naltrexone and Dextromethorphan	GWV with GWI
Naeser	LED therapy	GWV with GWI
Reinhard	Acupuncture, restorative sleep, yoga	GWV with CMI
McAndrew	Problem Solving Cognitive Therapy	GWV with GWI
Ashford	rTMS	GWV with chronic pain

Two 'treatments tried' survey studies also currently funded (Golomb, Krengel/Sullivan)

Ongoing Animal Model Treatment Studies

Investigator	Treatment	Treatment type	Animal Group
Abou-Donia	Flupirtine	Non-opioid analgesic	Rats
O'Callaghan	Minocycline	Antibiotic	Mice
Morris	Alzheimer's medications	Cognitive enhancers	Rats
Shetty	Fluoxetine, resveratrol, curcumin, exercise	Antidepressants, antioxidants, and exercise	Rats

Two 'Consortia' Studies also currently funded which will address the full spectrum of treatment development, including pilot treatment studies in animal models

Treatment Research Recommendations

Recommendations

The Committee believes that the first priority of federal Gulf War illness research must be the identification of effective treatments to improve the health of Gulf War veterans and to protect the health of current and future American servicemen and women at risk of similar exposures. This research should include a number of critical elements:

- Clear, operationalized case definitions for Gulf War illness and other diagnostic subgroups for whom treatments are designed are essential.
- Clear, operationalized definitions of the clinical targets for treatment must be included in the research plan.
- Treatment outcomes must be clearly defined so that it is possible to quantify quantified improvements associated with interventions.
- Where possible, treatment outcomes should include improvement in measures associated with expressions of underlying pathology (abnormal laboratory and functional assays).

Treatment Research Recommendations2

Recommendations

Treatment approaches based on **known mechanistic pathways** of GWI should be pursued. Effective treatments of GWI could also lead to significant breakthroughs in the treatment of other exposure-related occupational health problems.

Although the perfect animal model of GWI has not yet been developed, preclinical animal models can and should be used to develop and test new treatments focused on pathobiological mechanisms of GWI and the effects of Gulf War theater exposures.

Center- and consortium based treatment research efforts can capitalize on multi-disciplinary expertise and multi-pronged approaches to treatment targets and pre-clinical trials. The DoD CDMRP treatment consortia are an important step in developing integrated treatments for ill GW veterans as an initial assessment of treatment safety and efficacy. Validation studies through the VA Cooperative Studies Program (CSP) or similar large, multi-site, government sponsored programs are necessary to provide final confirmation validation of safety and efficacy from initial Phase I/II trials.

When a pilot treatment study funded by VA or CDMRP shows promising results and is judged to have scientific merit, VA should follow up with a larger trial or other systematic assessment of the treatment's potential benefits.

Summary

- 23 years after the war, epidemiologic and other research continues to document the occurrence of poorer health and greater disability among GW veterans
- The constellation of health problems known as Gulf War illness affects approximately 25-30% of Gulf war veterans
- Gulf War illness is the term that should be used for this disorder

Summary-2

- Gulf War illness and other sources of dysfunction and ill health among Gulf War veterans are related to exposures to chemicals and pharmaceuticals in theater:
 - Pesticides and PB: GWI, neurological outcomes
 - Sarin/cyclosarin: neurological outcomes, ?cancer
 - Oil well fire smoke exposure: ?cancer

Summary-3

- Human and animal studies are beginning to identify the underlying pathobiology of Gulf War illness: central and autonomic nervous systems, immune system, endocrine function all appear to be important
- Gulf War illness is a complex disorder with multiple downstream effects related to exposure to Gulf War theater
- It is hoped that –omics, genetic/epigenetic and other probes will provide more insight into the pathobiology of the disorder

Summary-4

- Treatment studies are finally in place and multiple small treatment trials are under way that approach Gulf War illness symptoms and underlying pathology through multiple pathways
- Emphasis should be placed on mechanistically based approaches; animal models are appropriate and encouraged for treatment development
- Promising treatments should be followed up as quickly as possible with full scale treatment trials
- Improved health for GW veterans is the ultimate goal and should be urgently pursued!

Thank you

