Deliberation and Discussion:

Gulf War Illness and the Health of Gulf War Veterans: Research Update and Recommendations, 2009-2013

Updated Scientific Findings and Recommendation

Draft Report Review Process

Jan. 8-9, 2014:

--Review report by sections.

--Focus on Conclusions and Recommendations for each section

--Edits/revisions to be discussed

Jan. 22, 2014:

--Written edits and revision suggestions from RAC members due Jan. 22

--New draft will be prepared for review

Draft Report Review Process

Feb.-March, 2014:

--New draft edited and re-edited if necessary

April, 2014:

--Final report ready for release

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Abbreviations and Acronyms

REPORT REVIEW: Research Section 2, Etiology (Exposure effects)

Animal models (O'Callaghan)

Summary, animal models

Summary: Animal exposure studies
In aggregate, the data obtained using animal models of GWI are suggestive of the involvement of multiple organ systems and pathways in the etiology of this multisymptom illness.

Although the exact pathobiological mechanism(s) have yet to be fully understood, effects from single and combined GW-relevant exposures have implications for the lasting health problems experienced by a significant proportion of GW veterans.

Further characterization of adverse effects of these exposures on the multiple targets and systems already identified, as well as the identification of additional novel targets affected by GW exposures will provide a more global view of the etiology of this illness and lead to effective therapeutic interventions.

REPORT REVIEW: Research Section 2, Etiology (Exposure effects)

Human studies (White/Steele/Sullivan)

Summary of literature review, Human studies-1

Pesticides and PB, studies published since the 2008 report continue to support exposures to pesticides and pyridostigmine bromide as etiologically important in development of Gulf War illness and behavioral/cognitive dysfunction in Gulf War veterans.

Nerve gas agents: Exposure to nerve gas agents has been identified in two more studies to changes in structural MRI findings that have been linked to cognitive decrements, further supporting exposure to these agents as etiologically important to dysfunction in some subsets of Gulf war veterans.

Oil well fires: New evidence has emerged suggesting that oil well fire exposures may be important in the development of Gulf War illness and brain cancer.

Summary of literature review, human studies-2

Vaccines: Vaccine exposures may also be contributing, though these are not clearly understood.

DU: Although exposure to depleted uranium has been demonstrated, with continuing levels in body tissue, its contribution to ill health is unclear: studies on this chemical have focused on small groups of individuals.

Complex exposures: Most veterans experienced exposures to chemical mixtures in theater and effects of these complex exposures remain unknown. Improved modeling of contributions of individual and mixed exposures would inform the debate on mixed exposures, as would the development of biomarkers of exposures to specific chemicals in the past.

Research Findings and Recommendations – Animal

Research Findings

Animal studies. As noted in the RACGWI 2008 Report, animal studies have identified biological effects of Gulf War exposures and combinations of exposures that were previously unknown. The evidence concerning these effects has burgeoned since 2008. Animal models of Gulf War-relevant exposures to individual chemicals, chemical mixtures, and chemicals plus other stressors have demonstrated alterations in nervous system outcomes (behavior, cognition, neurotransmission, intracellular signaling, molecular and cellular disruptions of axonal transport), liver and cardiovascular function, genomic and proteomic profiles, and mitchondrial changes. These outcomes are important because they confirm hypotheses that exposures are important in Gulf war illness symptomatology but, more importantly, they identify systemic alterations and physiological changes that can be the target of treatment approaches. Furthermore, animal models can be used to pre-test promising treatment approaches.

Research Findings and Recommendations – Animal -2

Recommendations

Studies that utilize animal models to characterize persistent molecular, cellular, systemic, and behavioral effects of individual and combined exposure to pyridostigmine bromide, pesticides and insect repellants used in the Gulf War, as well as low-level sarin or sarin surrogate, have been key to date. Future animal model research should focus on:

--Studies that characterize persistent effects of Gulf War-related exposures, alone and in combination, on proinflammatory processes in the central nervous system and peripheral target organs.

--Studies that evaluate systemic immune parameters in animal models, with an emphasis on those parameters that sensitize ill veterans to Gulf War illness.

--Studies that identify biomarkers indicative of past exposure to Gulf War-related neurotoxic compounds that can be applied to Gulf War veterans. This includes studies that identify persistent or "downstream" changes in biochemical processes in relation to past neurotoxicant exposure(s), and studies that identify persistent changes in the central nervous system and in autonomic function associated with Gulf War-related exposures and conditions.

Research Findings and Recommendations – Human

Research Findings

Human exposure studies. Studies published since the 2008 report continue to support exposures to pesticides and pyridostigmine bromide as etiologically important in development of Gulf War illness and behavioral/cognitive dysfunction in Gulf War veterans. Findings in Gulf War veterans associated with organophosphate exposure are consistent with those seen in other occupational groups (see Appendix X). Exposure to nerve gas agents has been linked in two more studies to changes in structural MRI that have been linked to cognitive decrements, further supporting exposure to these agents as etiologically important to dysfunction in some subsets of Gulf War veterans. New evidence has emerged suggesting that oil well fire exposures may be important in the development of Gulf War illness and brain cancer.

Research Findings and Recommendations – Human-2

Research Findings - continued

Vaccines exposures may also be contributing, though these are not clearly understood. Although exposure to depleted uranium has been demonstrated, with continuing levels in body tissue, its contribution to ill health is unclear: studies on this chemical have focused on small groups of individuals. Most veterans experienced exposures to chemical mixtures in theater and effects of these complex exposures remain unknown.

Taken together, these studies and those summarized in the Section of this review on epidemiologic investigations of Gulf War veterans (see pp. xx-xx) continue to support the conclusion that chemical exposures, not psychological stressors or psychiatric disorders, are the cause of Gulf War illness and other health and functional issues in Gulf War veterans.

Research Findings and Recommendations – Human-3

Recommendations

Exposure studies in Gulf War veterans to identify the etiologic agents that may have been causative in Gulf War illness remain important because they may help to determine treatment targets for Gulf War illness and other health problems in Gulf War veterans.

--Objective markers of exposure should be utilized whenever possible. These include environmental sampling and modeling of conditions in theater.

--Development of biomarkers of exposure that are present years after an exposure has occurred would help enormously in understanding the issues of etiology and possibly physiological effects of exposures.

--Statistical methods that consider the mixed exposure scenario experienced by Gulf War veterans in theater are essential. These should focus on assessing effects of individual exposure (if possible) as well as various exposure combinations and mixtures. Mixed exposures include not only mixtures of chemicals but also chemicals combined with heat, dehydration, infection, and other environmental stressors.

REPORT REVIEW: Research Section 1, Epidemiology (Steele)

Discussion: Conclusions and Recommendations, Epidemiology Section-1

Research Findings

Prevalence of Gulf War illness. Overall, 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. Conservative estimates using relatively restricted case definition criteria are in the 25-30% range.

Discussion: Conclusions and Recommendations, Epidemiology Section-2

Research Findings

Prognosis for veterans with Gulf War illness. Little additional information on the long-term prognosis of Gulf War illness has become available since 2008. Prior data suggest that there is little to no improvement in the health of ill Gulf War veterans over time. The effect that aging will have on this vulnerable population remains unclear.

Discussion: Conclusions and Recommendations, Epidemiology Section-3

Research Findings

General health among Gulf War veterans. Studies published since 2008 have continued to document poorer general health status and greater disability among Gulf War veterans. Despite the extensive number of studies conducted with Gulf War veterans in the 23 years since Desert Storm, medical surveillance in this population remains woefully inadequate.

Discussion: Conclusions and Recommendations, Epidemiology Section-4

Research Findings
Medical conditions in Gulf War veterans. Very little research has yet been conducted to determine rates at which Gulf War veterans have been affected by medical conditions of possible concern. As a result, it is not currently known if Gulf War veterans have experienced excess rates of most medical conditions. Disorders of concern reviewed in this report include the following:
--Neurological disorders. Although ALS and other neurological conditions are a prominent concern for Gulf War veterans, very little research is available that identifies rates of most neurological disorders in this population. Rates of multiple sclerosis, Parkinson's disease, and other neurological diseases are currently unknown and can be expected to increase as the Gulf War veteran population ages.

Discussion: Conclusions and Recommendations, Epidemiology Section-5

Research Findings
Medical conditions in Gulf War veterans.
--Cancer. Since 2008, research has suggested that there may be increased risk of brain and lung cancers in Gulf War veterans with Khamisyah exposure. In general, cancer risk remains unknown and understudied.

--Sleep dysfunction. A single study published since 2008 has identified sleep abnormalities in a group of Gulf War veterans compared to obesity matched controls. Since fatigue is an extremely common symptom in veterans with Gulf War illness and C-PAP treatment has shown some promise in a small treatment trial (see Treatment Research section, Table x), this may be an important finding.

Discussion: Conclusions and Recommendations, Epidemiology Section-6

Research Findings
Medical conditions in Gulf War veterans.
--Birth defects. No definitive new information is available on risk of birth defects in offspring of Gulf War veterans. Given the relatively low occurrence of birth defects in the general population and in deployed groups, well-designed larger pooled studies may be necessary to determine true associations between wartime exposures and adverse birth and reproductive outcomes.

Discussion: Conclusions and Recommendations, Epidemiology Section-7

Research Findings
Medical conditions in Gulf War veterans.
--Birth defects. No definitive new information is available on risk of birth defects in offspring of Gulf War veterans. Given the relatively low occurrence of birth defects in the general population and in deployed groups, well-designed larger pooled studies may be necessary to determine true associations between wartime exposures and adverse birth and reproductive outcomes.

Discussion: Conclusions and Recommendations, Epidemiology Section-8

Research Findings
Multisymptom illnesses. Chronic Fatigue Syndrome, Fibromyalgia, Multiple Chemical Sensitivity. These disorders share similar symptoms with Gulf War illness and occur at higher rates in patients with Gulf War illness but few Gulf war illness patients meet criteria for them. Gulf War illness is a distinct syndrome and Gulf War veterans who meet criteria for these disorders often differ significantly from non-veteran populations. It may be necessary to consider Gulf War veterans who do and do not meet criteria for these disorders separately in research on the illness, including treatment research.

Discussion: Conclusions and Recommendations, Epidemiology Section-9

Research Findings
Psychiatric disorders. 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 but do no predict or explain diagnosis of Gulf War illness.

Discussion: Conclusions and Recommendations, Epidemiology Section-10

Research Findings

Mortality. The lack of current information on overall and disease-specific mortality among U.S. Gulf War veterans is an important issue. No comprehensive information has been published on the mortality experience of U.S. Gulf War era veterans after the year 2000. The 13 years for which no mortality figures are available represent more than half of the 22 years since Desert Storm. Mortality information from the last decade is particularly crucial for understanding the health consequences of the Gulf War, given the latency periods often associated with chronic diseases of interest. Despite specific recommendations, over many years, from both the current Committee and Institute of Medicine panels, federal research efforts to monitor the mortality experience of 1990-1991 Gulf War veterans remain seriously inadequate.

Discussion: Conclusions and Recommendations, Epidemiology Section--11

Methodological Issues

Collecting data on Gulf War illness has been hampered by a number of methodological issues relating to case definitions of the illness, concurrent disorders and conditions in ill veterans, multiple exposures, subject recruitment, subject follow-up and survey tools. For example, as raised in both the 2004 and 2008 Committee reports, it is expedient to assess health outcomes in identifiable Gulf War veteran subgroups, as opposed to grouping all veterans with heterogeneous exposures and experiences together. Whether these groupings are based on exposure, unit membership, symptom profiles, deployment location or a combination of factors, comparisons of subgroups with healthy controls will be more informative than using deployed veterans as a single group.

Discussion: Conclusions and Recommendations, Epidemiology Section-12

Methodological Issues

Case definitions. Case definitions currently include the Haley syndrome criteria, chronic multisymptom illness (CMI), the Kansas definition and other adaptations of these approaches to defining Gulf War illness. Each of these definitions has advantages and drawbacks. The Haley syndromes are quite narrow and under-predict the occurrence of the disorder, but may allow highly specific characterization of veterans who meet criteria for a syndrome; the mild form of CMI is very broad and over inclusive, resulting in high prevalence rates even in control populations but is inclusive in terms of a range of ill health in Gulf War veterans, and the Kansas criteria predict Gulf War illness at rates that appear to be consistent with those seen across multiple Gulf War populations but exclude veterans with some concurrent medical disorders who may also have Gulf War illness.

Discussion: Conclusions and Recommendations, Epidemiology Section-13

Methodological Issues (case definitions continued)

Many research papers and proposals never clearly define the criteria used for identifying veterans with Gulf War illness at all, an even greater problem. A VA Strategic Planning Group identified a process for a consensus case definition using input from experts on Gulf War illness and case definition methodology (see Appendix X), but this process was never initiated. VA has authorized the Institute of Medicine to develop a case definition, but the charge to the IOM is seen by the Committee as being seriously flawed. In the absence of a consensus case definition 22 years after the appearance of this condition, it is quite difficult to compare research findings in epidemiological, pathobiological or treatment research approaches to Gulf war illness.

Discussion: Conclusions and Recommendations, Epidemiology Section-14

Methodological Issues

Surveillance. As noted above, very little is known about prognosis of veterans with Gulf War illness and other health issues such as poor general health, neurological disorders, cancer, other medical conditions, sleep dysfunction, multisymptom illnesses such as Chronic Fatigue Syndrome and Fibromyalgia, adverse reproductive outcomes, hospitalizations, and mortality. Some of these issues are addressed in the VA longitudinal survey that is currently underway, but the survey instrument does not allow identification of veterans with Gulf War illness and other outcomes of interest, despite urging from the RAC and despite recommendations in the 2010 IOM report for improved surveillance of this population. Information about Gulf War illness prevalence and prognosis as well as other medical disorders is key to treatment planning for this population.

Discussion: Conclusions and Recommendations, Epidemiology Section-15

Recommendations-1 (Case definition)

Case definition of Gulf War illness. Differences in prevalence rates reported among the studies reviewed in this Section provide a clear illustration of the importance of an accepted case definition in Gulf War illness research. The Committee suggests the following approaches to the development of such a definition.

1. VA should implement the steps outlined in the draft strategic plan (see Appendix X) for developing an evidence based, expert consensus-driven case definition for Gulf War illness. This effort should involve representatives from other federal agencies sponsoring research in Gulf War veterans, a broad spectrum of scientists conducting research in Gulf War veterans, clinicians knowledgeable about the problem, and Gulf War veterans.

Discussion: Conclusions and Recommendations, Epidemiology Section-16

Recommendations-2 (Case definition-2)
2. VA should cancel the current IOM assignment to develop a Gulf War illness case definition, since it will not be developed using an evidence–based process that includes analytic assessment of data available to evaluate and optimize the definition. The IOM panel charged to develop this case definition does not include adequate representation by scientists with expertise in Gulf War illness research and methods for developing case definitions based on symptom profiles.

3. VA should adopt the name Gulf War illness for the symptomatic condition associated with military service in the 1990-1991 Gulf War.

Discussion: Conclusions and Recommendations, Epidemiology Section-17

Recommendations-3 (Surveillance-1)
Ongoing monitoring and surveillance of the Gulf War veteran population is critical as this group of veterans ages. A plan for such monitoring was included in the plan proposed by a VA Strategic Planning group composed of representatives from RAC, VA and DoD (see Appendix X) but never adopted. In brief, such surveillance must include the following elements:

1. Ongoing assessment of Gulf War illness and its impact on the health and lives of Gulf War veterans.

2. Systematic assessment of overall and disease-specific mortality in Gulf War veterans. Reports on the results of these assessments should be published at a minimum of 5-year intervals.

Discussion: Conclusions and Recommendations, Epidemiology Section-18

Recommendations-4 (Survelliance-2)
3. Use of VA's longitudinal survey to assess rates physician-diagnosed medical conditions in Gulf War and era veterans. Survey data can be used to flag conditions of possible importance and followed up with more in-depth study.

4. Use of VA's longitudinal survey to assess rates of health problems and birth defects in children of Gulf War era veterans. Survey data can be used to flag condition of possible concern and followed up with more in-depth study. It is also important to publish results of VA study of children conducted over 10 years ago.

5. Evaluation of health outcomes in Gulf War veterans in subgroups of potential importance—defined by suspected or documented exposures in theater, geographical locations in the Gulf War theater or other predictors.

Discussion: Conclusions and Recommendations, Epidemiology Section-19

Recommendations-5 (Methodology-1)
Improved methodology in Gulf War epidemiologic research. It is important that VA work with CDMRP to establish guidelines for improved methodology in Gulf War research that can be included in requests for proposals and subject to research application reviews. Such guidelines should include the following:

1. Systematic methods for assessing symptoms and other health outcomes in Gulf War veterans.

2. Evaluation of health outcomes in Gulf War veteran subgroups of importance—for example, subgroups defined by relevant exposure history or location in theater.

3. Consideration of subpopulations with multiple health outcomes.

Discussion: Conclusions and Recommendations, Epidemiology Section-20

Recommendations-6 (Methodology-2)

4. In evaluating risk factors for Gulf War illness and other health outcomes, use of analytic methods that adequately control for confounding effects of additional exposures and etiologic factors that may be associated both with the exposures and outcomes of interest as well as consideration of the effects of mixed exposures.

REPORT REVIEW: Research Section 3, Pathobiology (White/Sullivan)

Summary, Pathobiology-1

Imaging and EEG
Overall, studies of veterans with Gulf War illness define in various ways and of veterans with sarin/cyclosarin exposure that utilize varying imaging and EEG probes, consistently identify structural and electrical abnormalities in the central nervous system: 14 of the 15 papers summarized in Table 1 support this conclusion.

Summary, Pathobiology-2

Cognition
Overall, studies on cognitive function in Gulf War veterans continue to support the conclusion from the 2008 report that cognitive dysfunction is a central issue for Gulf War veterans with Gulf War illness and with specific exposures in theater. Four new studies support this conclusion. The Chao (2011) study, which found inconsistent results, is difficult to interpret given the fact that structural brain changes that would be expected to result in cognitive dysfunction Khamisyah exposure were clearly identified. The sixth study (Wallin et al, 2009) assessed a very small sample and was too underpowered to support any conclusions about cognitive dysfunction in Gulf War veterans.

Summary, Pathobiology-3

Neuroendocrine function
Studies from Golier et al. continue to support altered HPA-axis functioning in GWV that is not consistent with the typical pattern seen in PTSD. Recently, it was shown that ACTH response trends differed between Gulf War veterans, Vietnam veterans and OEF/OIF veterans, indicating a unique change in GWV (Golier et al., 2012). Further studies are warranted to determine the exact nature of the alteration, which may lead to potential treatment avenues.

Summary, Pathobiology

Immunological function-4
Six of eight studies conducted on immune system alterations in Gulf War veterans showed immune dysfunction. Research in this area appears to be narrowing in on changes occurring to the expression of certain cell lines. Additionally, changes occurring during exercise indicate that immunological manifestations of GWI may be state specific- i.e. evidence of underlying immune differences between symptomatic and asymptomatic veterans may only become apparent in specific experimental or clinical settings under 'challenge' conditions.

Discussion: Conclusions and Recommendations, Pathobiology Section-1

Research findings
Imaging and EEG parameters. Consistent with evidence presented in the 2008 Committee report, new research imaging and EEG research has assessed veterans with Gulf War illness defined in various ways and veterans with sarin/cyclosarin exposure. These studies consistently identify structural and electrical abnormalities in the central nervous system.

Cognitive abilities. Studies on cognitive function in Gulf War veterans continue to support the conclusion from the 2008 report that cognitive dysfunction is a central issue for Gulf War veterans with Gulf War illness and with specific exposures in theater, supporting the evidence from imaging and EEG probes that nervous system dysfunction is a key element in their ill health.

Discussion: Conclusions and Recommendations, Pathobiology Section-2

Research findings
Neuroendocrine function. Studies continue to support the conclusion from the 2008 report that altered HPA-axis functioning in Gulf War veterans is present and is not consistent with the typical pattern seen in PTSD.

Autonomic nervous system. The 2008 RAC report outlined a number of scientific publications documenting autonomic nervous system dysregulation in Gulf War veterans. Since 2008, the only published study that looked specifically at autonomic function in Gulf War veterans was by Haley et al. (2013). This study confirmed diminished night time heart rate variability in all three Haley Syndrome groups. It is not clear if the findings are generalizable to Gulf War veterans meeting other criteria for Gulf War illness.

Discussion: Conclusions and Recommendations, Pathobiology Section-3

Research findings

Immune system. The majority of studies conducted on immune system alterations in Gulf War veterans since 2008 showed immune dysfunction. Research in this area appears to be narrowing in on changes occurring to the expression of certain cell lines. Additionally, changes occurring during exercise indicate that immunological manifestations of GWI may be state specific: evidence of underlying immune differences between symptomatic and asymptomatic veterans may only become apparent in specific experimental or clinical settings under 'challenge' conditions.

Discussion: Conclusions and Recommendations, Pathobiology Section-4

Recommendations

Research on the pathobiological underpinnings of Gulf War illness and ill health in Gulf War veterans should continue to focus on nervous system and immunological outcomes in this population in order to identify targets for treatment interventions and outcomes that should be improved during such treatments.

--Clear case definitions are important for this work. Findings may differ in differing patient populations, either defined with different Gulf War illness criteria or experiencing different health problems. For example, veterans with multisymptom illnesses like Chronic Fatigue Syndrome or Fibromyalgia may show different patterns of immunological or neurological function than veterans without these disorders.

Discussion: Conclusions and Recommendations, Pathobiology Section-5

Recommendations

--Similarly, Gulf War theater exposures, gender and other variable likely mediate these effects and should be carefully addressed in research.

--Variables that should be considered in mechanistic studies should be identified to aid in development of consistent research that contributes new and useful knowledge.

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

REPORT REVIEW: Research Section 4, Treatment Research (Sullivan/White)

Treatment research summary-1

2008 Report
Three treatments:
Doxycycline antibiotic treatment: reduced mycoplasma infections in 11 of 14 veterans in 1 study (Nicolson et al., 1995; Nicolson and Nicolson, 1996), whereas a different study found no significant positive effects (Donta et al., 2004).
Exercise and cognitive behavioral therapy (CBT) some benefits from CBT when veterans participated in both exercise and CBT (Donta et al., 2003),
Nutritional changes, exercise, and education: little improvement was seen, although female veterans were more likely to show improvement than male participants (Engel et al., 2000).

Since 2008 Report: Completed treatment studies-1

Amino acid supplement containing L-carnosine (Baraniuk et al., 2013): reduced irritable bowel syndrome (IBS) associated diarrhea, significant improvement in the digit symbol substitution cognitive task; no improvements in fatigue, pain, hyperalgesia and activity levels when measured before and after treatment.

Prolonged exposure therapy (Yoder et al., 2012): significantly reduced PTSD symptoms in a population of veterans from the Gulf War, OIF, OEF and OND (Operation New Dawn; (Yoder et al., 2012); Gulf War veterans showed a statistically significant reduced treatment effect compared to other veteran groups, and symptom reduction occurred at a slower pace than the other veteran groups.

CPAP (Amin et al. (2011): significant improvements in fatigue scores, cognitive function, sleep quality and measures of physical and mental health.

Since 2008 Report: Ongoing treatment studies-2

***Intranasal insulin*:** J. Golier (Bronx), K. Sullivan, M. Krengel (Boston); veterans with Gulf War illness; outcomes: cognition, overall health, neuroendocrine function

Mifepristone steroid treatmenI: J. Golier (Bronx); Gulf War veterans with Chronic Multisymptom Illness; outcomes: cognitive function, HPA axis activity, fatigue, depression and PTSD

Low-dose naltrexone and dextromethorphan: W. Meggs (East Carolina University); ill Gulf War veterans; outcomes: neuroinflammation and reported symptom scores

Coenzyme Q10 (CoQ10): B. Golomb (UCSD); ill Gulf War veterans; outcomes: preliminary analysis showed that 100mg of CoQ10 significantly reduced symptoms such as fatigue, mood, pain and improved physical functioning

Since 2008 Report: Ongoing treatment studies-3

Probiotics: (Tuteja, Salt Lake City VA); Gulf War veterans with irritable bowel syndrome (IBS); outcomes: IBS and non-intestinal symptoms, blood markers of inflammation

Light emitting diodes (LED): M. Naeser (Boston VA); GWVs who reported musculoskeletal pain, fatigue, mood or cognitive symptoms; outcomes: attention, memory, executive function, psychomotor function, pain, fatigue, mood and inflammatory markers in blood

Repetitive transcranial magnetic stimulation (rTMS) (W. Ashford, Palo Alto VA); Gulf war veterans; outcome: chronic pain

Resistance exercise training (D. Cook, Middleton VA, Wisconsin); Gulf War veterans; outcomes: pain sensitivity and regulation, total physical activity level and changes in white matter as evaluated using magnetic resonance imaging (MRI).

Since 2008 Report: Ongoing treatment studies-4

Acupuncture (L. Conboy, New England School of Acupuncture); veterans with Gulf War illness; outcomes: sleep, fatigue, pain, psychosocial variables and inflammatory markers; preliminary data from the acupuncture treatment study show that veterans reported significant reductions in pain, and both primary and secondary health complaints, with results being more positive in the bi-weekly versus weekly treatment group.

Acupuncture in combination with restorative sleep and yoga practice (M. Reinhard, WRIISC); Gulf War veterans with CMI; outcomes: physical and cognitive function, pain and sleep.

Acupressure (V. Lin, Cleveland Clinic); symptomatic Gulf War veterans; outcomes: symptoms.

Since 2008 Report: Ongoing treatment studies-5

Nasal irrigation (saline, Xylitol)(D. Rabago, University of Wisconsin); Gulf War veterans; outcomes: sinus symptoms, quality of life measures and cytokine quantification

Detoxification protocol (exercise, vitamin and mineral supplementation, low-heat sauna) (D. Carpenter, SUNY Albany); outcomes: fatigue, pain, mental health, cognitive function

Mindfulness-Based Stress Reduction (MBSR) S. Hunt, D. Kearney, Puget Sound VA); veterans with Gulf War illness; outcomes: symptom severity and measures of neurocognitive function will be assessed before and after treatment.

Since 2008 Report: Ongoing treatment studies-6

Mind-body bridging (MBB) (Y. Nakamura, University of Utah); Gulf war veterans; outcomes: questionnaire data.

Problem Solving Cognitive Therapy (L. McAndrew at the New Jersey WRIISC); Gulf War illness; outcome: disability

Since 2008 Report: Animal treatment models-1

Minocycline: J. O'Callaghan from Centers for Disease Control is currently studying minocycline as a potential treatment to reduce neuroinflammation in an animal model of Gulf War illness.

Flupirtine: M. Abou-Donia from the Duke University Medical Center has been testing flupirtine in animal exposed to pesticides. Rats exposed to the pesticides and to subsequent daily doses of flupirtine will undergo sensorimotor and cognitive function tests, as well as be evaluated for signs of oxidative stress in the brain, apoptosis and abnormal neuronal morphology.

Since 2008 Report: Animal treatment models-2

Anti-depressant, anti-oxidants, exercise: A. Shetty and colleagues at the Texas A&M Health Science Center College of Medicine and the Central Texas Veterans Health Care System are exploring treatment of central nervous symptom impairments in mice exposed to stress, pyridostigmine bromide and two pesticides, using various combinations of anti-depressants, antoxidants and exercise. The efficacy of each treatment arm will be assessed using cognitive behavioral tests, neural stem cell proliferation, and measures of oxidative stress.

Discussion: Conclusions and Recommendations, Treatment-1

Research findings

Treatment research has increased significantly since 2008, but most of these studies are underway, with results pending. Promising approaches that have gone through limited trials to date include dietary supplements and C-PAP. It will continue to be important to explore both conventional medical approaches (such as medications or devices) as well as alternative therapies such as meditation, mindfulness training and acupressure. Treatments based on proposed mechanisms of illness presentation and on specific symptoms are under development.

Discussion: Conclusions and Recommendations, Treatment-2

Recommendations-1

Treatment research is the top agenda item in scientific approaches to Gulf War illness and poor health in Gulf War veterans. This research should include the following elements:

--Clear case definitions and clinical targets for treatment.

--Objective outcomes demonstrating relevant functional improvement.

--Improvement in underlying expressions of pathology (abnormal laboratory and functional assays).

Discussion: Conclusions and Recommendations, Treatment Sections

Recommendations-2

Treatment approaches based on known mechanistic pathways of Gulf War illness, biomarker based treatments and gene-based therapy approaches should all be considered and could lead to significant breakthroughs in the treatment of Gulf War illness and other exposure-related occupational health problems. These will be expensive and may require support of intervention development at the proof-of-concept level as well as eventual large-scale clinical trials. It may be possible to leverage support from other federal health agencies interested in exposure-related diseases and disorders for this effort.

The CDMRP treatment consortia are an important step in developing integrated treatments for ill Gulf War veterans

Federal programs

Jim Binns

Discussion: Recommendations, Federal Programs-1

The Committee commends the effective Gulf War illness research program that has been created at the Department of Defense Congressionally Directed Medical Research Program and recommends that Congress authorize and appropriate $20 million annually for five years to support openly-competed, peer-reviewed studies focused on identifying:
1) Effective treatments for Gulf War illness,
2) Objective measures that distinguish ill from healthy veterans, and
3) Underlying biological mechanisms potentially amenable to treatment.

The Committee reiterates the findings and recommendations previously expressed regarding the Department of Veterans Affairs Gulf War research program in June 2012, February 2013, and June 2013.

Discussion: Recommendations, Federal Programs-2

The Committee recommends that the relationship between the Department of Veterans Affairs and the Institute of Medicine regarding Gulf War health research be investigated and reformed, including:

1) Reviewing the informal and formal input of VA and DoD staff into IOM report processes and content;

2) Reviewing the process for selecting IOM committee members and background speakers;

Discussion: Recommendations, Federal Programs-3

3) Re-conducting those IOM Gulf War and Health reports not conducted in accordance with the statutes mandating the reports, including:

a) The report on the best treatments for chronic multisymptom illness in Gulf War veterans required by Public Law 111-275, Section 805, which was not conducted in accordance with the provision of the statute requiring that the committee preparing the report be comprised of "medical professionals who are experienced in treating [Gulf War veterans] who have beem diagnosed with chronic multisymptom illlness or another health condition related to chemical and environmental exposures that may have occurred during such service." (Gulf War and Health, Treatment for Chronic Multisymptom Illness, 2013);

Discussion: Recommendations, Federal Programs-4

b) The report on the prevalence of "multiple sclerosis, Parkinson's disease, and brain cancers, as well as central nervous system abnormalities that are difficult to precisely diagnose" in Gulf War and recent Iraq/Afghanistan war veterans, required by Public Law 110-389, Section 804, which has never been conducted; and

c) The reports on the health effects of thirty-three "toxic agents, environmental or wartime hazards, or preventive medicines or vaccines associated with Gulf War service" required by Public Law 105-277 and Public Law 105-368, which were not conducted in accordance with the provisions of the statutes requiring that studies in animals, as well as humans, be considered in determining whether a statistical association exists between exposure to a substance and illness (Gulf War and Health Vol. 1 (2000), Vol. 2 (2003), Vol. 3 (2005), Updated Literature Review of Sarin (2004); Updated Literature Review of Depleted Uranium (2008)).

Other Review Topics

--Executive summary emphases and contents

--Findings in brief: which to highlight?

--Research priorities and recommendations: what goes here?

--Appendices?

--Other sections, issues?