GULF WAR ILLNESS

Neuroinflammation in Gulf War Illness is Linked with HMGB1 and Complement Activation, which can be Discerned from Brain-Derived Extracellular Vesicles in the Blood.

Madhu LN[1], Attaluri S[1], Kodali M[1], Shuai B[1], Upadhya R[1], Gitai D[1], Shetty AK[2].

Brain Behav Immun. **2019 Jun 27**. pii: S0889-1591(19)30476-3. doi: 10.1016/j.bbi.2019.06.040. PMID: 31255677. [Epub ahead of print]

Cognitive dysfunction and neuroinflammation are conspicuously observed in Gulf War Illness (GWI). We investigated whether brain inflammation in GWI is associated with activation of high mobility group box-1 (HMGB1) and complement-related proteins in neurons and astrocytes, and brain inflammation can be tracked through neuron-derived extracellular vesicles (NDEVs) and astrocyte-derived EVs (ADEVs) found in the circulating blood. We exposed animals to GWI-related chemicals pyridostigmine bromide, DEET and permethrin, and moderate stress for 28 days. We performed behavioral tests 10 months post-exposure and quantified activated microglia and reactive astrocytes in the cerebral cortex. Then, we measured the concentration of HMGB1, proinflammatory cytokines, and complement activation-related proteins in the cerebral cortex, and NDEVs and ADEVs in the circulating blood. Cognitive impairments persisted in GWI rats at 10 months post-exposure, which were associated with increased density of activated microglia and reactive astrocytes in the cerebral cortex. Moreover, the level of HMGB1 was elevated in the cerebral cortex with altered expression in the cytoplasm of neuronal soma and dendrites as well as the extracellular space. Also, higher levels of proinflammatory cytokines (TNFa, IL-1b, and IL-6), and complement activation-related proteins (C3 and TccC5b-9) were seen in the cerebral cortex. Remarkably, increased levels of HMGB1 and proinflammatory cytokines observed in the cerebral cortex of GWI rats could also be found in NDEVs isolated from the blood. Similarly, elevated levels of complement proteins seen in the cerebral cortex could be found in ADEVs. The results provide new evidence that persistent cognitive dysfunction and chronic neuroinflammation in a model of GWI are linked with elevated HMGB1 concentration and complement activation. Furthermore, the results demonstrated that multiple biomarkers of neuroinflammation could be tracked reliably via analyses of NDEVs and ADEVs in the circulating blood. Execution of such a liquid biopsy approach is especially useful in clinical trials for monitoring the remission, persistence or progression of brain inflammation in GWI patients with drug treatment.

Gender-based Differences among 1990-1991 Gulf War Era Veterans: Demographics, Lifestyle Behaviors, and Health Conditions.

Brown MC[1], Sims KJ[2], Gifford EJ[3], Goldstein KM[4], Johnson MR[5], Williams CD[6], Provenzale D[7].

Womens Health Issues. **2019 Jun 25**;29 Suppl 1:S47-S55. doi: 10.1016/j.whi.2019.04.004. PMCID: PMC6668031.

OBJECTIVE: The 1990-1991 Gulf War employed more women servicemembers than any prior conflict. Gender-based differences among veterans of this era have yet to be explored. This study is among the first and most recent to stratify Gulf War veteran demographics, lifestyle factors, and self-reported diagnoses by gender.

METHODS: Data from the cross-sectional Gulf War Era Cohort and Biorepository pilot study (n = 1,318; collected between 2014 and 2016), including users and nonusers of the Veterans Health Administration, were used to calculate demographics and adjusted odds ratios.

RESULTS: Women veterans were oversampled and comprised approximately 23% of the sample. Women reported similar rates of Veterans Health Administration use (44%) and deployment (67%) as men (46% and 72%, respectively). Women were less likely than men to report frequent alcohol use (adjusted odds ratio [aOR], 0.59; 95% confidence interval [CI], 0.43-0.81; p = .0009) or have a history of smoking (aOR, 0.65; 95% CI, 0.49-0.84; p = .0014). Among common health conditions, women were more likely than men to report a diagnosis of osteoporosis (aOR, 4.24; 95% CI, 2.39-7.51; p < .0001), bipolar disorder (aOR, 2.15; 95% CI, 1.15-4.04; p = .0167), depression (aOR, 2.39; 95% CI, 1.81-3.16; p < .0001), irritable bowel syndrome (aOR, 2.10; 95% CI, 1.43-3.09; p = .0002), migraines (aOR, 2.96; 95% CI, 2.18-4.01; p < .0001), asthma (aOR, 1.86; 95% CI, 1.29-2.67; p = .0008), and thyroid problems (aOR, 4.60; 95% CI, 3.14-6.73; p < .0001). Women were less likely than men to report hypertension (aOR, 0.55; 95% CI, 0.41-0.72; p < .0001), tinnitus (aOR, 0.46; 95% CI, 0.33-0.63; p < .0001), and diabetes (aOR, 0.44; 95% CI, 0.28-0.69; p = .0003).

CONCLUSIONS: Health differences exist between female and male veterans from the 1990-1991 Gulf War. Gender-specific analyses are needed to better understand the unique health care needs of Gulf War Era veterans and direct future research.

CHRONIC FATIGUE SYNDROME

The clinical value of cytokines in chronic fatigue syndrome.

Yang T[1], Yang Y[2], Wang D[2], Li C[2], Qu Y[2], Guo J[2], Shi T[2], Bo W[2], Sun Z[3], Asakawa T[4,5].

J Transl Med. **2019 Jun 28**;17(1):213. doi: 10.1186/s12967-019-1948-6. PMID: 31253154.

Chronic fatigue syndrome (CFS) is a heterogeneous disorder with uncertain pathogenesis. Without effective therapy, CFS is characterized by disabling fatigue, depression, memory loss, and somatic discomfort. This comprehensive and impartial review aimed to assess the available evidence and examined the potential clinical value of using cytokines for the monitoring of CFS and as targets for the treatment of CFS. Inflammatory reactions and immune modulation are considered to contribute to the pathophysiology of CFS, and it is well documented that cytokines present in both blood and cerebrospinal fluid (CSF) are closely associated with the progression and severity of CFS. However, pathophysiological and methodological limitations prevent using circulating cytokines as independent diagnostic indices. Moreover, there is no evidence to support the use of CSF cytokines as independent diagnostic indices. Nevertheless, a comprehensive evaluation of changes in circulating and CSF cytokines may improve clinical understanding of the pathophysiology of patients with CFS, aiding in the establishment of an appropriate diagnosis. Importantly, the available evidence does not support the value of cytokines as therapeutic targets. We believe that an improved understanding of cytokine-related mechanisms will be helpful to explore new cytokine-related therapeutic targets.

HEADACHE and MIGRAINE

Eptinezumab for prevention of chronic migraine: A randomized phase 2b clinical trial.

Dodick DW[1], Lipton RB[2], Silberstein S[3], Goadsby PJ[4,5], Biondi D[6], Hirman J[7], Cady R[6], Smith J[8].

Cephalalgia. **2019 Jun 24**:333102419858355. doi: 10.1177/0333102419858355. PMID: 31234642. [Epub ahead of print]

BACKGROUND: Calcitonin gene-related peptide plays an important role in migraine pathophysiology. We evaluated eptinezumab, an intravenous (IV) anti-calcitonin gene-related peptide monoclonal antibody, for the prevention of chronic migraine.

OBJECTIVE: To determine the safety, tolerability, and effectiveness of four dose levels of eptinezumab and to inform the phase 3 development program.

METHODS: This was a phase 2b, parallel-group, double-blind, randomized, placebo-controlled, dose-ranging clinical trial. Men and women (N = 616) aged 18-55 years were included if they had a diagnosis of chronic migraine, with onset at age ≤35 years and history of chronic migraine ≥1 year. During the 28-day screening period, patients must have had ≥15 headache days, including ≥8 migraine days, with ≥5 migraine attacks as recorded in the electronic diary. Patients were assigned in a 1:1:1:1:1 ratio to eptinezumab 300, 100, 30, 10 mg or placebo, administered as a single IV infusion. The primary endpoint was the percentage of patients with a ≥75% decrease in monthly migraine days over weeks 1-12 compared with the 28-day screening period.

RESULTS: The ≥75% migraine responder rates over weeks 1-12 for eptinezumab 300, 100, 30, and 10 mg were 33.3%, 31.4%, 28.2%, and 26.8%, respectively, versus 20.7% for placebo (p = 0.033, 0.072, 0.201, 0.294 vs. placebo). Secondary efficacy endpoints (e.g. ≥50% responder rate, change from baseline in frequency of migraine/headache days, and percentage of severe migraines) had results favoring the three higher eptinezumab doses versus placebo. Eptinezumab was well tolerated and adverse event rates were similar to placebo.

CONCLUSIONS: The results of this trial demonstrate that eptinezumab appears effective and well-tolerated for the preventive treatment of chronic migraine and justifies the conduct of pivotal phase 3 trials for migraine prevention.

TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT02275117.

HEADACHE and MIGRAINE (Continued)

Differential efficacy of non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: A meta-analysis.

de Coo IF[1], Marin JC[2], Silberstein SD[3], Friedman DI[4], Gaul C[5], McClure CK[6], Tyagi A[7], Liebler E[8], Tepper SJ[9], Ferrari MD[1], Goadsby PJ[2].

Cephalalgia. **2019 Jul**;39(8):967-977. doi: 10.1177/0333102419856607. PMID: 31246132. Epub 2019 Jun 10.

BACKGROUND: Two randomized, double-blind, sham-controlled trials (ACT1, ACT2) evaluated non-invasive vagus nerve stimulation (nVNS) as acute treatment for cluster headache. We analyzed pooled ACT1/ACT2 data to increase statistical power and gain insight into the differential efficacy of nVNS in episodic and chronic cluster headache.

METHODS: Data extracted from ACT1 and ACT2 were pooled using a fixed-effects model. Main outcome measures were the primary endpoints of each study. This was the proportion of participants whose first treated attack improved from moderate (2), severe (3), or very severe (4) pain intensity to mild (1) or nil (0) for ACT1 and the proportion of treated attacks whose pain intensity improved from 2-4 to 0 for ACT2.

RESULTS: The pooled population included 225 participants (episodic: n = 112; chronic: n = 113) from ACT1 (n = 133) and ACT2 (n = 92) in the nVNS (n = 108) and sham (n = 117) groups. Interaction was shown between treatment group and cluster headache subtype ($p < 0.05$). nVNS was superior to sham in episodic but not chronic cluster headache (both endpoints $p < 0.01$). Only four patients discontinued the studies due to adverse events.

CONCLUSIONS: nVNS is a well-tolerated and effective acute treatment for episodic cluster headache.

TRIAL REGISTRATION: The studies were registered at clinicaltrials.gov (ACT1: NCT01792817; ACT2: NCT01958125).

The synergistic effects of nano-curcumin and coenzyme Q10 supplementation in migraine prophylaxis: a randomized, placebo-controlled, double-blind trial.

Parohan M[1,2], Sarraf P[3], Javanbakht MH[1], Foroushani AR[4], Ranji-Burachaloo S[3], Djalali M[1].

Nutr Neurosci. **2019 Jun 26**:1-10. doi: 10.1080/1028415X.2019.1627770. PMID: 31241007. [Epub ahead of print]

Introduction: Migraine is a disabling neurovascular disorder characterized by increasing levels of pro-inflammatory cytokines and oxidative stress biomarkers. Curcumin and coenzyme Q10 (CoQ10) can exert neuroprotective effects through modulation of inflammation and oxidative stress. The aim of the present study was to evaluate the combined effects of nano-curcumin and CoQ10 supplementation on migraine symptoms and quality of life in migraine patients.

Methods: One-hundred men and women (mean age 32 years) with episodic migraine based on the International Headache Society (IHS) criteria participated in this study. The subjects were randomly divided into four groups as (1) combination of nano-curcumin (80 mg) plus CoQ10 (300 mg), (2) nano-curcumin (80 mg), (3) CoQ10 (300 mg) and (4) the control (nano-curcumin and CoQ10 placebo included oral paraffin oil) beside usual prophylactic drugs for 8 weeks. Frequency, severity, duration of headache attacks, the headache diary results (HDR) and headache disability based on migraine-specific questionnaires were assessed at the baseline and end of the study.

Results: Ninety-one of 100 patients completed the study. The results showed a significant effect of nano-curcumin and CoQ10 supplementation on frequency, severity, duration of migraine attacks and HDR compared to other groups (All $P < 0.001$). Nano-curcumin and CoQ10 group also had better scores in migraine-specific questionnaires at the end of the study compared to other groups (All $P < 0.001$). There were no side effects reported by the participants.

Conclusions: These findings suggest a possible synergistic effect of nano-curcumin and CoQ10 on clinical features of migraine.

Trial registration number: IRCT2017080135444N1.

HEADACHE and MIGRAINE (Continued)

Volume of Hypothalamus as a Diagnostic Biomarker of Chronic Migraine.

Chen Z[1,2,3], Chen X[2], Liu M[1,3], Ma L[1], Yu S[2].

Front Neurol. **2019 Jun 6**;10:606. doi: 10.3389/fneur.2019.00606. PMCID: PMC6563769. PMID: 31244765. eCollection 2019.

It is believed than hypothalamus (HTH) might be involved in generation of migraine, and evidence from high resolution fMRI reported that the more anterior part of HTH seemed to play an important role in migraine chronification. The current study was aimed to identify the alteration of morphology and resting-state functional connectivity (FC) of the hypothalamus (HTH) in interictal episodic migraine (EM) and chronic migraine (CM). High-resolution structural and resting-state functional magnetic resonance images were acquired in 18 EM patients, 16 CM patients, and 21 normal controls (NC). The volume of HTH was calculated and voxel-based morphometry (VBM) was performed over the whole HTH. Receiver operating characteristics (ROC) curve analysis was applied to evaluate the diagnostic efficacy of HTH volume. Correlation analyses with clinical variables were performed and FC maps were generated for positive HTH regions according to VBM comparison. The volume of the HTH significantly decreased in both EM and CM patients compared with NC. The cut-off volume of HTH as 1.429 ml had a good diagnostic accuracy for CM with sensitivity of 81.25% and specificity of 100%. VBM analyses identified volume reduction of posterior HTH in EM vs. NC which was negatively correlated with headache frequency. The posterior HTH presented decreased FC with the left inferior temporal gyrus (Brodmann area 20) in EM. Decreased volume of anterior HTH was identified in CM vs. NC and CM vs. EM which was positively correlated with headache frequency in CM. The anterior HTH presented increased FC with the right anterior orbital gyrus (AOrG) (Brodmann area 11) in CM compared with NC and increased FC with the right medial orbital gyrus (MOrG) (Brodmann area 11) in CM compared with EM. Our study provided evidence of structural plasticity and FC changes of HTH in the pathogensis of migraine generation and chronification, supporting potential therapeutic target toward the HTH and its peptide.

Structural and Functional Brain Alterations in Post-traumatic Headache Attributed to Mild Traumatic Brain Injury: A Narrative Review.

Schwedt TJ[1].

Front Neurol. **2019 Jun 14**;10:615. doi: 10.3389/fneur.2019.00615. PMCID: PMC6587675. PMID: 31258507. eCollection 2019.

Introduction: By definition, post-traumatic headache (PTH) attributed to mild traumatic brain injury (mTBI) is not associated with brain structural abnormalities that are seen on routine clinical inspection of brain images. However, subtle brain structural abnormalities, as well as functional abnormalities, detected via research imaging techniques yield insights into the pathophysiology of PTH. The objective of this manuscript is to summarize published findings regarding research imaging of the brain in PTH attributed to mTBI.

Methods: For this narrative review, PubMed was searched using the terms "post-traumatic headache" or "post-concussion headache" and "imaging" or "magnetic resonance imaging" or "research imaging" or "positron emission tomography". Articles were chosen for inclusion based on their relevance to the topic.

Results: Ten articles were ultimately included within this review. The studies investigated white matter tract integrity and functional connectivity in acute PTH, structural measures, white matter tract integrity, cerebral blood flow, and functional connectivity in persistent PTH (PPTH), and proton spectroscopy in both acute and persistent PTH. The articles demonstrate that acute and persistent PTH are associated with abnormalities in brain structure, that acute and persistent PTH are also associated with abnormalities in brain function, that it might be possible to predict the persistence of PTH using brain imaging findings, and that there are differences in imaging findings when comparing PTH to healthy controls and when comparing PTH to migraine. Although it is not entirely clear if the imaging findings are directly attributable to PTH as opposed to the underlying TBI or other post-TBI symptoms, correlations between the imaging findings with headache frequency and headache resolution suggest a true relationship between the imaging findings and PTH.

Conclusions: PTH attributed to mTBI is associated with abnormalities in brain structure and function that can be detected via research imaging. Additional studies are needed to determine the specificity of the findings for PTH, to differentiate findings attributed to PTH from those attributed to the underlying TBI and coexistent post-TBI symptoms, and to determine the accuracy of imaging findings for predicting the development of PPTH.

CHRONIC PAIN

Pain Intensity and Pain Interference in Male and Female Iraq/Afghanistan-era Veterans.

Naylor JC[1], Wagner HR[2], Johnston C[3], Elbogen EE[2], Brancu M[2], Marx CE[2]; VA Mid-Atlantic MIRECC Work Group[4]; VA Mid-Atlantic MIRECC Women Veterans Work Group[4], Strauss JL[5].

Womens Health Issues. **2019 Jun 25**;29 Suppl 1:S24-S31. doi: 10.1016/j.whi.2019.04.015. PMID: 31253239.

BACKGROUND: Chronic pain conditions are common among both male and female Iraq/Afghanistan-era veterans and can have substantial negative impacts on quality of life and function. Although in general women tend to report higher levels of pain intensity than men, findings remain mixed on whether gender differences in pain exist in Iraq/Afghanistan-era veterans. Additionally, the relationships between functional impairment, pain intensity, and gender remain unknown.

METHODS: This project examined gender differences in pain intensity and pain interference in 875 male and female Iraq/Afghanistan-era veterans. Nonparametric Wilcoxon rank-tests examined gender differences in pain scores. Multivariable generalized linear regression modeling was used to evaluate the magnitude of pain intensity and interference across levels of chronicity and gender, and to evaluate the role of chronicity in gender effects in measures of pain and function.

RESULTS: Pain intensity and interference scores were significantly greater among both male and female veterans reporting chronic pain relative to acute pain. Women veterans endorsed higher levels of pain intensity and pain interference compared with men. Results derived from multivariable analyses implicated pain intensity as a factor underlying gender differences in functional impairment among chronic pain sufferers, indicating that gender differences in functional measures were eliminated after controlling statistically for pain intensity.

CONCLUSIONS: Results demonstrate that the effects of functional impairment are impacted by pain intensity, and not by gender.

Functional and neurochemical disruptions of brain hub topology in chronic pain.

Kaplan CM[1], Schrepf A[1], Vatansever D[2,3], Larkin TE[4], Mawla I[4], Ichesco E[1], Kochlefl L[1], Harte SE[1], Clauw DJ[1], Mashour GA[4,5], Harris RE[1,4].

Pain. **2019 Apr**;160(4):973-983. doi: 10.1097/j.pain.0000000000001480. PMCID: PMC6424595.

A critical component of brain network architecture is a robust hub structure, wherein hub regions facilitate efficient information integration by occupying highly connected and functionally central roles in the network. Across a wide range of neurological disorders, hub brain regions seem to be disrupted, and the character of this disruption can yield insights into the pathophysiology of these disorders. We applied a brain network-based approach to examine hub topology in fibromyalgia, a chronic pain condition with prominent central nervous system involvement. Resting state functional magnetic resonance imaging data from 40 fibromyalgia patients and 46 healthy volunteers, and a small validation cohort of 11 fibromyalgia patients, were analyzed using graph theoretical techniques to model connections between 264 brain regions. In fibromyalgia, the anterior insulae functioned as hubs and were members of the rich club, a highly interconnected nexus of hubs. In fibromyalgia, rich-club membership varied with the intensity of clinical pain: the posterior insula, primary somatosensory, and motor cortices belonged to the rich club only in patients with the highest pain intensity. Furthermore, the eigenvector centrality (a measure of how connected a region is to other highly connected regions) of the posterior insula positively correlated with clinical pain and mediated the relationship between glutamate + glutamine (assessed by proton magnetic resonance spectroscopy) within this structure and the patient's clinical pain report. Together, these findings reveal altered hub topology in fibromyalgia and demonstrate, for the first time to our knowledge, a neurochemical basis for altered hub strength and its relationship to the perception of pain.

CHRONIC PAIN (Continued)

Feasibility of a Real-Time Clinical Augmented Reality and Artificial Intelligence Framework for Pain Detection and Localization From the Brain.

Hu XS[1,2], Nascimento TD[1], Bender MC[1], Hall T[3], Petty S[3], O'Malley S[3], Ellwood RP[4], Kaciroti N[1,2,5], Maslowski E[6], DaSilva AF[1,2].

J Med Internet Res. **2019 Jun 28**;21(6):e13594. doi: 10.2196/13594. PMID: 31254336.

BACKGROUND: For many years, clinicians have been seeking for objective pain assessment solutions via neuroimaging techniques, focusing on the brain to detect human pain. Unfortunately, most of those techniques are not applicable in the clinical environment or lack accuracy.

OBJECTIVE: This study aimed to test the feasibility of a mobile neuroimaging-based clinical augmented reality (AR) and artificial intelligence (AI) framework, CLARAi, for objective pain detection and also localization direct from the patient's brain in real time.

METHODS: Clinical dental pain was triggered in 21 patients by hypersensitive tooth stimulation with 20 consecutive descending cold stimulations (32°C-0°C). We used a portable optical neuroimaging technology, functional near-infrared spectroscopy, to gauge their cortical activity during evoked acute clinical pain. The data were decoded using a neural network (NN)-based AI algorithm to classify hemodynamic response data into pain and no-pain brain states in real time. We tested the performance of several networks (NN with 7 layers, 6 layers, 5 layers, 3 layers, recurrent NN, and long short-term memory network) upon reorganized data features on pain diction and localization in a simulated real-time environment. In addition, we also tested the feasibility of transmitting the neuroimaging data to an AR device, HoloLens, in the same simulated environment, allowing visualization of the ongoing cortical activity on a 3-dimensional brain template virtually plotted on the patients' head during clinical consult.

RESULTS: The artificial neutral network (3-layer NN) achieved an optimal classification accuracy at 80.37% (126,000/156,680) for pain and no pain discrimination, with positive likelihood ratio (PLR) at 2.35. We further explored a 3-class localization task of left/right side pain and no-pain states, and convolutional NN-6 (6-layer NN) achieved highest classification accuracy at 74.23% (1040/1401) with PLR at 2.02.

CONCLUSIONS: Additional studies are needed to optimize and validate our prototype CLARAi framework for other pains and neurologic disorders. However, we presented an innovative and feasible neuroimaging-based AR/AI concept that can potentially transform the human brain into an objective target to visualize and precisely measure and localize pain in real time where it is most needed: in the doctor's office.

INTERNATIONAL REGISTERED REPORT IDENTIFIER (IRRID): RR1-10.2196/13594.

IRRITABLE BOWEL SYNDROME

Symptom frequency and development of a generic functional disorder symptom scale suitable for use in studies of patients with irritable bowel syndrome, fibromyalgia syndrome or chronic fatigue syndrome.

Hyland ME[1], Bacon AM[1], Lanario JW[1], Davies AF[2].

Chronic Dis Transl Med. **2019 Jun 24**;5(2):129-138. doi: 10.1016/j.cdtm.2019.05.003. PMCID: PMC6656911. PMID: 31367702.

Objectives: To describe the extent to which irritable bowel syndrome (IBS), fibromyalgia syndrome (FMS), and chronic fatigue syndrome (CFS) exhibit symptom overlap, and to validate a patient-derived, generic symptom questionnaire.

Methods: A patient-derived 61-item symptom-frequency questionnaire was completed by participants recruited through IBS, FMS and CFS self-help websites. Principal axis factor analysis with oblimin rotation was performed separately for those reporting an IBS, FMS or CFS diagnosis.

Results: Questionnaires were completed by 1751 participants of whom 851 reported more than one of the three diagnoses. Stomach pain on at least a weekly basis was reported by 79% of IBS, 52% of FMS, and 43% of CFS single diagnosis participants. Pain increasing the day after activity was reported by 32% of IBS, 94% of FMS, and 85% of CFS single diagnosis participants. Waking still tired at least once weekly was reported by 75% of IBS, 97% of FMS, and 95% of CFS single diagnosis participants. Exploratory factor analysis produced consistent results across all three diagnostic groups, the 61 items loading on 12 correlated factors with a single higher order factor on which all items loaded. Frequency analysis led to the rejection of one item (cold sores on or near lips), and freeform reporting by participants of additional symptoms identified an additional five, namely, restless legs, hair loss/brittle hair/thinning, dizziness/balance problems, blurred vision and urination problems.

Conclusions: IBS, FMS and CFS are polysymptomatic spectrum disorders with a wide range of overlapping symptoms, many of which are unrelated to diagnostic criteria. Frequency analysis and factor analysis confirm the validity of using the same questionnaire across different diagnostic categories. The 65-item general symptom questionnaire (GSQ-65) is a valid generic symptom scale suitable for assessing the many different symptoms of people with IBS, FMS and CFS.

OTHER RESEARCH OF INTEREST

Health Status of Female and Male Gulf War and Gulf Era Veterans: A Population-Based Study.

Dursa EK[1], Barth SK[2], Porter BW[3], Schneiderman AI[4].

Womens Health Issues. **2019 Jun 25**;29 Suppl 1:S39-S46. doi: 10.1016/j.whi.2019.04.003. PMID: 31253241.

BACKGROUND: The health of women Gulf War (deployed) and Gulf Era (nondeployed) veterans is understudied; although most studies examining the health effects of deployment to the Gulf War adjust for gender in multivariate analyses, gender-specific prevalence and effect measures are not routinely reported. The National Academy of Medicine recommended that the Department of Veterans Affairs assess gender-specific health conditions in large cohort studies of Gulf War veterans.

METHODS: Data from this study come from the follow-up study of a national cohort of Gulf War and Gulf Era veterans. This study was conducted between 2012 and 2014, and was the second follow-up of a population-based cohort of Gulf War and Gulf Era veterans that began in 1995. Measures included self-reported medical conditions and frequency of doctor visits as well as validated screening instruments for mental health conditions.

RESULTS: Overall, female veterans (both Gulf War and Era) reported poorer health than their male counterparts as measured by the prevalence of self-reported disease. The top five prevalent conditions in both Gulf War and Gulf Era veterans were migraine, hypertension, major depressive disorder, arthritis, and dermatitis. Female Gulf War veterans were found to have a higher prevalence of disease than male Gulf Era veterans.

CONCLUSIONS: Women veterans, particularly deployed veterans, from this era have significant medical needs that may justify increased outreach from the Department of Veterans Affairs. Our findings highlight the importance of asking about military service, particularly for women veterans, in the clinical setting, both in the Department of Veterans Affairs and in the private sector.

OTHER RESEARCH OF INTEREST (Continued)

Gender Differences in Demographic and Health Characteristics of the Million Veteran Program Cohort.

Harrington KM[1], Nguyen XT[2], Song RJ[3], Hannagan K[4], Quaden R[4], Gagnon DR[5], Cho K[2], Deen JE[6], Muralidhar S[6], O'Leary TJ[7], Gaziano JM[2], Whitbourne SB[2]; VA Million Veteran Program.

Womens Health Issues. **2019 Jun 25**;29 Suppl 1:S56-S66. doi: 10.1016/j.whi.2019.04.012.

BACKGROUND: The Department of Veterans Affairs Million Veteran Program (MVP) is the largest ongoing cohort program of its kind, with 654,903 enrollees as of June 2018. The objectives of this study were to examine gender differences in the MVP cohort with respect to response and enrollment rates; demographic, health, and health care characteristics; and prevalence of self-reported health conditions.

METHODS: The MVP Baseline Survey was completed by 415,694 veterans (8% women), providing self-report measures of demographic characteristics, health status, and medical history.

RESULTS: Relative to men, women demonstrated a higher positive responder rate (23.0% vs. 16.0%), slightly higher enrollment rate (13.5% vs. 12.9%), and, among enrollees, a lower survey completion rate (59.7% vs. 63.8%). Women were younger, more racially diverse, had higher educational attainment, and were less likely to be married or cohabitating with a partner than men. Women were more likely to report good to excellent health status but poorer physical fitness, and less likely to report lifetime smoking and drinking than men. Compared with men, women veterans showed an increased prevalence of musculoskeletal conditions, thyroid problems, gastrointestinal conditions, migraine headaches, and mental health disorders, as well as a decreased prevalence of gout, cardiovascular diseases, high cholesterol, diabetes, and hearing problems.

CONCLUSIONS: These results revealed some substantial gender differences in the research participation rates, demographic profile, health characteristics, and prevalence of health conditions for veterans in the MVP cohort. Findings highlight the need for tailoring recruitment efforts to ensure representation of the increasing women veteran population receiving care through the Veterans Health Administration.

"Lumping" and "splitting" medically unexplained symptoms: is there a role for a transdiagnostic approach?

Chalder T[1], Willis C[2].

J Ment Health. **2017 Jun**;26(3):187-191. doi: 10.1080/09638237.2017.1322187. PMID: 28485682. Epub 2017 May 9.

[Note: Delayed posting in PubMed—Not previously listed in RAC Research Alerts.]

Medically unexplained syndromes (MUS) are defined as persistent bodily symptoms with functional disability but no explanatory pathology. They are highly prevalent in both primary and secondary care. In a meta-analysis of medically unexplained symptoms (not syndromes) in primary care, the percentage of patients complaining of at least one medically unexplained symptom ranged from 40.2 (95% CI 0.9–79.4%; I2¼98%) to 49% (95% CI 18–79.8%, I2¼98%) (Haller et al., 2015). MUS are associated with high levels of distress and do not respond easily to reassurance and simple explanation (Barsky & Borus, 1999). They are seen in all medical specialties. Fibromyalgia (FM) is frequently seen in rheumatology, irritable bowel syndrome (IBS) in gastroenterology, non-cardiac chest pain in cardiology, chronic fatigue syndrome (CFS) in infectious diseases, non-cardiac chest pain and functional palpitations in cardiology, hyperventilation syndrome in respiratory medicine, tension headache in neurology and multiple chemical sensitivity in allergy. These syndromes have mostly been studied in isolation. However, research has observed extensive symptom overlap with more than half of patients with one MUS condition fulfilling diagnostic criteria for at least one other MUS condition (Nimnuan et al., 2001). For this reason, Wessely et al. (1999) suggested advantages to redefining MUS as one syndrome. Fink & Schroder (2010) advocated a new overarching term, ‘‘bodily distress syndrome’’, to encompass all the different MUS. They submit that there is now substantial evidence that MUS conditions are not clearly distinct disease entities but rather a common phenomenon with different subtypes. They describe similarities in diagnostic criteria, aetiology, pathophysiological, neurobiology, psychological mechanisms, patient characteristics and treatment response. Some years earlier Yunus (2007) had suggested the generic term ‘‘central sensitivity syndrome’’ which suggests that the common mechanism underlying various MUS is central sensitisation which is the hyper-excitement of neurons in the central nervous system.

[Full text of this Editorial continues in Journal of Mental Health.]

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