

GULF WAR ILLNESS

[Gulf War Illness: Unifying Hypothesis for a Continuing Health Problem.](#)

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Int J Environ Res Public Health. **2019 Jan 3**;16(1). pii: E111. doi: 10.3390/ijerph16010111. PMID: 30609834.

An estimated 25%–32% of veterans of the 1991 Gulf War continue to experience multiple unexplained health problems known as Gulf War Illness (GWI). GWI encompasses chronic pain, musculoskeletal weakness, headache, fatigue, cognitive deficits, alterations in mood, and numerous multi-system complaints. Most potential exposures implicated in GWI were not well documented but included varying levels of several neurotoxicants as well as the anticholinergic drug pyridostigmine bromide (PB), which was routinely taken as prophylaxis against the nerve agent soman. While some veterans also took chloroquine as an antimalarial agent, the literature suggests an association between receipt of multiple vaccinations prior to or during the conflict (perhaps combined with other exposures), and GWI. In-theater exposures may account for any single individual veteran's ill health but many veterans of the same era who were not deployed overseas also suffer the same or similar symptoms. The features of GWI also overlap with those of fibromyalgia, chronic fatigue syndrome and multiple chemical sensitivity, in all of which liver dysfunction has been documented, suggesting a unifying hypothesis. It is proposed that multiple vaccinations, with concurrent or subsequent exposure to PB or additional chemical insults of a liver-damaging nature, plausibly explain the pathogenesis and the observed chronicity of GWI. The suggested mechanism for GWI is thus a chemically-induced impaired liver function, with the spillage of stored vitamin A compounds ("retinoids") into the circulation in toxic concentrations, resulting in an endogenous chronic form of hypervitaminosis A. Implications of the hypothesis are briefly reviewed.

CHRONIC FATIGUE SYNDROME

[Multidimensional Comparison of Cancer-Related Fatigue and Chronic Fatigue Syndrome: The Role of Psychophysiological Markers.](#)

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Psychiatry Investig. **2019 Jan 7**. doi: 10.30773/pi.2018.10.26. PMID: 30605994. [Epub ahead of print]

OBJECTIVE: The present study compared cancer-related fatigue (CRF) and chronic fatigue syndrome (CFS) using multidimensional measurements with the aim of better understanding characteristics and exploring markers of two similar fatigue syndromes.

METHODS: Twenty-five patients with CRF and twenty patients with CFS completed questionnaires, including the Fatigue Severity Scale (FSS), Hospital Anxiety Depression Scale (HADS), Perceived Stress Scale (PSS), and Pittsburgh Sleep Quality Index (PSQI). Additionally, levels of high sensitivity C-reactive protein (hs-CRP), heart rate variability (HRV), and electroencephalography (EEG) were obtained. Neurocognitive functioning was also evaluated.

RESULTS: Both groups showed comparable levels of psychological variables, including fatigue. Compared to CFS subjects, CRF patients had significantly higher hs-CRP levels and a reduced HRV-index. The within-group analyses revealed that the FSS score of the CRF group was significantly related to scores on the HADS-anxiety, HADS-depression, and PSQI scales. In the CFS group, FSS scores were significantly associated with scores on the PSS and the absolute delta, theta, and alpha powers in frontal EEG.

CONCLUSION: Findings indicate that different pathophysiological mechanisms underlie CFS and CRF. Inflammatory marker and HRV may be potential biomarkers for distinguishing two fatigue syndromes and frontal EEG parameters may be quantitative biomarkers for CFS.

HEADACHE and MIGRAINE

Cerebrovascular reactivity as a determinant of deep white matter hyperintensities in migraine.

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Neurology. **2019 Jan 4**. pii: 10.1212/WNL.0000000000006822. doi: 10.1212/WNL.0000000000006822. PMID: 30610094. [Epub ahead of print]

OBJECTIVE: To evaluate the association between the cerebrovascular reactivity to carbon dioxide (CO₂-CVR) and the deep white matter hyperintensity (WMH) burden in patients with migraine.

METHODS: A total of 86 nonelderly patients with episodic migraine without vascular risk factors and 35 headache-free controls underwent 3T MRI. Deep WMHs were quantified with a segmentation method developed for nonelderly migraineurs. The interictal CO₂-CVR was measured with transcranial Doppler with the breath-holding method. The mean breath-holding index of the bilateral middle cerebral arteries (MCA-BHI) was square root transformed and analyzed with univariate and multivariate logistic regression models to determine its association with the highest tertiles of deep WMH burden (number and volume).

RESULTS: A low MCA-BHI was independently associated with the highest tertile of deep WMH number in patients with migraine (adjusted odds ratio [OR] 0.02, 95% confidence interval [CI] 0.0007-0.63, $p = 0.026$). In controls, the MCA-BHI was not associated with deep WMH number. Interaction analysis revealed that migraine modified the effect of MCA-BHI on deep WMH number (p for interaction = 0.029). The MCA-BHI was not associated with increased deep WMH volume in both patients and controls. Age was independently associated with deep WMH volume in patients (adjusted OR 1.07, 95% CI 1.004-1.15, $p = 0.037$).

CONCLUSIONS: In this study, we found a migraine-specific association between a reduced CVR to apnea and increased number of deep WMHs in healthy, nonelderly patients with migraine. A dysfunctional vascular response to apnea may predispose migraineurs to an increased risk of WMHs.

The effects of concurrent Coenzyme Q10, L-carnitine supplementation in migraine prophylaxis: A randomized, placebo-controlled, double-blind trial.

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Cephalalgia. **2019 Jan 6**:333102418821661. doi: 10.1177/0333102418821661. PMID: 30612463. [Epub ahead of print]

PURPOSE: The present study aimed to determine the effects of combined supplementation of Coenzyme Q10 with L-carnitine on mitochondrial metabolic disorders marker and migraine symptoms among migraine patients.

METHODS: A total of 56 men and women, between 20-40 years of age with migraine headache, participated in this randomized, double-blind, placebo-controlled, parallel study. The subjects were randomly assigned to receive either 30 mg/day Coenzyme Q10 and 500 mg/day L-carnitine at the same time and/or placebo tablets for 8 weeks. The measurements were completed at the beginning and end of the study. The primary outcome was severity of headache attacks. The secondary outcomes included duration, frequency of headache attacks, the headache diary results (HDR), and serum levels of lactate.

RESULTS: A significant reduction was obtained in serum levels of lactate (-2.28 mg/dl, 95% CI: -3.65, -0.90; $p = 0.002$), severity (-3.03, 95% CI: -3.65, -2.40; $p \leq 0.001$), duration (-7.67, 95% CI: -11.47, -3.90; $p \leq 0.001$), frequency (-5.42, 95% CI: -7.31, -3.53; $p \leq 0.001$) and HDR (-103.03, 95% CI: -145.76, -60.29; $p \leq 0.001$) after 8 weeks.

CONCLUSION: This double-blind parallel study provides evidences supporting the beneficial effects of Coenzyme Q10 and L-carnitine supplements on serum levels of lactate and migraine symptoms.

TRIAL REGISTRATION: IRCT20121216011763N21.

HEADACHE and MIGRAINE (Continued)

[Greater occipital nerve block in migraine prophylaxis: Narrative review.](#)

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Cephalalgia. **2019 Jan 6**:333102418821669. doi: 10.1177/0333102418821669. PMID: 30612462. [Epub ahead of print]

OBJECTIVES: The importance and popularity of peripheral nerve block procedures have increased in the treatment of migraine. Greater occipital nerve (GON) block is a commonly used peripheral nerve block method, and there are numerous researches on its use in migraine treatment.

MATERIALS AND METHODS: A search of PubMed for English-language randomized controlled trials (RCT) and open studies on greater occipital nerve block between 1995 and 2018 was performed using greater occipital nerve, headache, and migraine as keywords.

RESULTS: In total, 242 potentially relevant PubMed studies were found. A sum of 228 of them which were non-English articles and reviews, case reports, letters and meta-analyses were excluded. The remaining articles were reviewed, and 14 clinical trials, seven of which were randomized-controlled on greater occipital nerve block in migraine patients, were identified and reviewed.

CONCLUSIONS: Although clinicians commonly use greater occipital nerve block in migraine patients, the procedure has yet to be standardized. The present study reviewed the techniques, drugs and dosages, the frequency of administration, side effects, and efficacy of greater occipital nerve block in migraine patients.

[Catechol-O-Methyltransferase \(COMT\) rs4680 Val158Met Polymorphism is Associated with Widespread Pressure Pain Sensitivity and Depression in Women with Chronic, but not Episodic, Tension Type Headache.](#)

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Clin J Pain. **2019 Jan 4**. doi: 10.1097/AJP.0000000000000684. PMID: 30614828. [Epub ahead of print]

OBJECTIVES: The aims of this study were: 1, to investigate the association between the rs4680 Val158Met polymorphism in frequent episodic (FETTH) and chronic (CTTH) tension-type headache; and 2, to analyse the association between the rs4680 Val158Met polymorphism with clinical, psychological, or psychophysical variables.

METHODS: Fifty women with FETTH, 50 with CTTH, and 50 matched healthy women participated. After amplifying Val158Met polymorphism by polymerase chain reaction, the genotype frequencies and allele distributions based on restriction fragment length polymorphism were assessed. Participants were classified according to the Val158Met polymorphism rs4680 genotype (Val/Val, Val/Met, or Met/Met). A headache diary collected clinical features. Disability (Headache Disability Inventory), sleep quality (Pittsburgh Sleep Quality Index), and depression/anxiety levels (Hospital Anxiety and Depression Scale) were also assessed. Pressure pain thresholds (PPT) were assessed bilaterally over the temporalis, upper trapezius, second metacarpal, and tibialis anterior by a blinded assessor.

RESULTS: The distribution of rs4680 Val158Met genotype was not significantly different between women with/without headache ($P=0.796$). No differences in headache features, disability, anxiety, and sleep quality were observed depending on the rs4680 Val158Met genotype. Women with CTTH, but not FETTH, carrying the Met/Met genotype had lower widespread PPTs and higher depressive symptoms than those with Val/Val or Val/Met genotype ($P<0.05$).

CONCLUSION: The Val158Met polymorphism (rs4680) does not appear to be involved in predisposition to suffer from tension-type headache; however, this genetic factor may be involved in the pathogenesis expression of CTTH, as greater pressure pain sensitivity and higher depressive levels were found in CTTH carrying the Met/Met genotype.

CHRONIC PAIN

[Core Outcome Measures for Chronic Musculoskeletal Pain Research: Recommendations from a Veterans Health Administration Work Group.](#)

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Pain Med. 2019 Jan 5. doi: 10.1093/pm/pny279. PMID: 30615172. [Epub ahead of print]

Objective: Chronic musculoskeletal pain (CMSP) disorders are among the most prevalent and disabling conditions worldwide. It would be advantageous to have common outcome measures when comparing results across different CMSP research studies.

Methods: The Veterans Health Administration appointed a work group to recommend core outcome measures for assessing pain intensity and interference as well as important secondary domains in clinical research. The work group used three streams of data to inform their recommendations: 1) literature synthesis augmented by three recently completed trials; 2) review and comparison of measures recommended by other expert groups; 3) two Delphi surveys of work group members.

Results: The single-item numerical rating scale and seven-item Brief Pain Inventory interference scale emerged as the recommended measures for assessing pain intensity and interference, respectively. The secondary domains ranked most important included physical functioning and depression, followed by sleep, anxiety, and patient-reported global impression of change (PGIC). For these domains, the work group recommended the Patient-Reported Outcome Information System four-item physical function and sleep scales, the Patient Health Questionnaire two-item depression scale, the Generalized Anxiety Disorder two-item anxiety scale, and the single-item PGIC. Finally, a single-item National Health Interview Survey item was favored for defining chronic pain.

Conclusions: Two scales comprising eight items are recommended as core outcome measures for pain intensity and interference in all studies of chronic musculoskeletal pain, and brief scales comprising 13 additional items can be added when possible to assess important secondary domains.

[Differential item functioning of the PROMIS physical function, pain interference, and pain behavior item banks across patients with different musculoskeletal disorders and persons from the general population.](#)

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Qual Life Res. 2019 Jan 2. doi: 10.1007/s11136-018-2087-x. PMID: 30600494. [Epub ahead of print]

PURPOSE: To investigate the validity of comparisons across patients with different musculoskeletal disorders and persons from the general population by evaluating differential item functioning (DIF) for the PROMIS physical function (PROMIS-PF), pain interference (PROMIS-PI), and pain behavior (PROMIS-PB) item banks.

METHODS: Patients with chronic pain, rheumatoid arthritis (RA), or osteoarthritis (OA); patients receiving physiotherapy (PT); and persons from the Dutch general population completed the full Dutch-Flemish PROMIS-PF (121-items), PROMIS-PI (40-items), or PROMIS-PB (39-items) banks. DIF was assessed with ordinal logistic regression models and McFadden's pseudo R^2 -change of $\geq 2\%$ as critical value. The impact of DIF on item scores and the T-scores per bank was examined by inspecting item characteristic curves (ICCs) and test characteristic curves (TCCs).

RESULTS: 2762 patients with chronic pain, 2029 with RA, 1247 with OA, 805 receiving PT, and 1310 healthy persons participated. For the PROMIS-PF, 25 out of 121 items were flagged for DIF, of which 10 items were flagged in multiple comparisons. For the PROMIS-PI, only 2 out of 40 items were flagged for DIF and for the PROMIS-PB, only 3 out of 39 items. Most DIF items had R^2 values just above the critical value of 2% and all showed uniform DIF. The ICCs and TCCs showed that the magnitude and impact of DIF on the item and T-scores were negligible.

CONCLUSIONS: This study supports the universal applicability of PROMIS across (patient) populations. Comparisons across patients with different musculoskeletal disorders and persons from the general population are valid, when applying the PROMIS-PF, PROMIS-PI, and PROMIS-PB banks.

CHRONIC PAIN (Continued)

[Acceptance and Commitment Therapy for Chronic Pain: Does Post-traumatic Stress Disorder Influence Treatment Outcomes?](#)

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Pain Med. 2019 Jan 2. doi: 10.1093/pm/pny272. PMID: 30602034. [Epub ahead of print]

Objective: The aim of this study was to determine whether post-traumatic stress disorder (PTSD) moderates treatment outcomes in Acceptance and Commitment Therapy for chronic pain.

Design: Longitudinal.

Setting: Veterans Affairs San Diego Healthcare System.

Subjects: A total of 126 veterans with chronic pain participating in an Acceptance and Commitment Therapy intervention for chronic pain. A structured clinical interview was used at baseline to designate PTSD-positive (N = 43) and -negative groups (N = 83).

Methods: Linear mixed-effects models to determine whether PTSD moderated change in pain interference, pain severity, pain acceptance, depressive symptoms, or pain-related anxiety at post-treatment and six-month follow-up.

Results: Participants with co-occurring PTSD reported greater pain interference, pain severity, depressive symptoms, and pain-related anxiety at baseline. PTSD status did not moderate treatment effects post-treatment. Rather, there were significant improvements on all study measures across groups ($P < 0.001$). PTSD status moderated change in depressive

Conclusions: PTSD status did not significantly affect treatment outcomes, with the exception of depressive symptoms at six-month follow-up. Overall, Acceptance and Commitment Therapy for chronic pain appears helpful for improving outcomes among veterans with co-occurring PTSD; however, veterans with co-occurring PTSD may experience fewer long-term gains compared with those with chronic pain alone.

OTHER RESEARCH OF INTEREST

[Genetic data and cognitively defined late-onset Alzheimer's disease subgroups.](#)

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Mol Psychiatry. 2018 Dec 4. doi: 10.1038/s41380-018-0298-8. PMID: 30514930. [Epub ahead of print]

Categorizing people with late-onset Alzheimer's disease into biologically coherent subgroups is important for personalized medicine. We evaluated data from five studies (total $n = 4050$, of whom 2431 had genome-wide single-nucleotide polymorphism (SNP) data). We assigned people to cognitively defined subgroups on the basis of relative performance in memory, executive functioning, visuospatial functioning, and language at the time of Alzheimer's disease diagnosis. We compared genotype frequencies for each subgroup to those from cognitively normal elderly controls. We focused on APOE and on SNPs with $p < 10^{-5}$ and odds ratios more extreme than those previously reported for Alzheimer's disease (< 0.77 or > 1.30). There was substantial variation across studies in the proportions of people in each subgroup. In each study, higher proportions of people with isolated substantial relative memory impairment had ≥ 1 APOE $\epsilon 4$ allele than any other subgroup (overall $p = 1.5 \times 10^{-27}$). Across subgroups, there were 33 novel suggestive loci across the genome with $p < 10^{-5}$ and an extreme OR compared to controls, of which none had statistical evidence of heterogeneity and 30 had ORs in the same direction across all datasets. These data support the biological coherence of cognitively defined subgroups and nominate novel genetic loci.

OTHER RESEARCH OF INTEREST (Continued)

Association of Long-term Exercise Training With Risk of Falls, Fractures, Hospitalizations, and Mortality in Older Adults: A Systematic Review and Meta-analysis.de Souto Barreto P^{1,2}, Rolland Y^{1,2}, Vellas B^{1,2}, Maltais M¹.

JAMA Intern Med. 2018 Dec 28. doi: 10.1001/jamainternmed.2018.5406. PMID: 30592475. [Epub ahead of print]

Importance: Long-term exercise benefits on prevalent adverse events in older populations, such as falls, fractures, or hospitalizations, are not yet established or known.

Objective: To systematically review and investigate the association of long-term exercise interventions (≥ 1 year) with the risk of falls, injurious falls, multiple falls, fractures, hospitalization, and mortality in older adults.

Data Sources: PubMed, Cochrane Central Register of Controlled Trials, SportDiscus, PsychInfo, and Ageline were searched through March 2018.

Study Selection: Exercise randomized clinical trials (RCTs) with intervention length of 1 year or longer, performed among participants 60 years or older.

Data Extraction and Synthesis: Two raters independently screened articles, abstracted the data, and assessed the risk of bias. Data were combined with risk ratios (RRs) using DerSimonian and Laird's random-effects model (Mantel-Haenszel method).

Main Outcomes and Measures: Six binary outcomes for the risk of falls, injurious falls, multiple falls (≥ 2 falls), fractures, hospitalization, and mortality.

Results: Forty-six studies (22 709 participants) were included in the review and 40 (21 868 participants) in the meta-analyses (mean [SD] age, 73.1 [7.1] years; 15 054 [66.3%] of participants were women). The most used exercise was a multicomponent training (eg, aerobic plus strength plus balance); mean frequency was 3 times per week, about 50 minutes per session, at a moderate intensity. Comparator groups were often active controls. Exercise significantly decreased the risk of falls ($n = 20$ RCTs; 4420 participants; RR, 0.88; 95% CI, 0.79-0.98) and injurious falls (9 RCTs; 4481 participants; RR, 0.74; 95% CI, 0.62-0.88), and tended to reduce the risk of fractures (19 RCTs; 8410 participants; RR, 0.84; 95% CI, 0.71-1.00; $P = .05$). Exercise did not significantly diminish the risk of multiple falls (13 RCTs; 3060 participants), hospitalization (12 RCTs; 5639 participants), and mortality (29 RCTs; 11 441 participants). Sensitivity analyses provided similar findings, except the fixed-effect meta-analysis for the risk of fracture, which showed a significant effect favoring exercisers (RR, 0.84; 95% CI, 0.70-1.00; $P = .047$). Meta-regressions on mortality and falls suggest that 2 to 3 times per week would be the optimal exercise frequency.

Conclusions and Relevance: Long-term exercise is associated with a reduction in falls, injurious falls, and probably fractures in older adults, including people with cardiometabolic and neurological diseases.

Depression as a Mediator of Chronic Fatigue and Post-Traumatic Stress Symptoms in Middle East Respiratory Syndrome Survivors.Lee SH¹, Shin HS², Park HY³, Kim JL⁴, Lee JJ⁵, Lee H⁶, Won SD⁷, Han W¹.

Psychiatry Investig. 2019 Jan 7. doi: 10.30773/pi.2018.10.22.3. PMID: 30605995. [Epub ahead of print]

OBJECTIVE: The relationship among chronic fatigue, depressive symptoms, and post-traumatic stress symptoms (PTSSs) among Middle East respiratory syndrome (MERS) survivors is poorly understood.

METHODS: Of 148 survivors who consented to be registered and underwent assessments at 12 months (T1) and 18 months (T2) after the MERS outbreak, 72 (48.65%) were evaluated for chronic fatigue, depressive symptoms, and PTSSs based on the Impact of Event Scale Revised (IES-R), the Patient Health Questionnaire-9 (PHQ-9), and the Fatigue Severity Scale (FSS). Data from 52 subjects, who completed both assessments, were analyzed using a regression-based serial multiple mediation model (PROCESS Model 6).

RESULTS: Bootstrap analyses indicated no direct effects of T1 FSS on T2 IES-R but significant positive indirect effects of T1 FSS on T2 IESR through T1 PHQ-9 and T2 PHQ-9 ($B=2.1601$, $SE=1.3268$, 95% confidence interval= $0.4250-6.1307$). In other words, both T1 PHQ-9 and T2 PHQ-9 fully mediated the relationship between T1 FSS and T2 IES.

CONCLUSION: Chronic fatigue 12 months after MERS had indirect effects on prolonged PTSSs 18 months after MERS via persisting depression in MERS survivors. This finding supports the need to promote interventional programs for emerging infectious disease survivors with chronic fatigue to reduce depression and prevent prolonged PTSSs.