

## GULF WAR ILLNESS

No Updates this Week for Gulf War Illness or Chronic Multisymptom Illness.

## CHRONIC FATIGUE SYNDROME

No Updates this Week for Chronic Fatigue Syndrome.

## HEADACHE and MIGRAINE

### [Female sex hormones in men with migraine.](#)

[van Oosterhout WPJ](#)<sup>1</sup>, [Schoonman GG](#)<sup>2</sup>, [van Zwet EW](#)<sup>2</sup>, [Dekkers OM](#)<sup>2</sup>, [Terwindt GM](#)<sup>2</sup>, [MaassenVanDenBrink A](#)<sup>2</sup>, [Ferrari MD](#)<sup>2</sup>.

Neurology. **2018 Jun 27**. pii: 10.1212/WNL.0000000000005855. doi: 10.1212/WNL.0000000000005855. PMID: 29950439.  
[Epub ahead of print]

**OBJECTIVE:** To assess the role of estradiol and testosterone in men with migraine.

**METHODS:** We measured 17 $\beta$ -estradiol (E2) and calculated free testosterone (T<sub>f</sub>) in serum of 17 medication-free men with migraine and 22 men without migraine group-matched for age and body mass index (BMI), targeted at 20 to 28 kg/m<sup>2</sup>. Blood was sampled on a single, for migraineurs interictal, day at 9 am, 12 pm, 3 pm, and 6 pm. Migraineurs were subsequently measured 3 to 4 times daily until an attack occurred. Clinical androgen deficiency was assessed with the Androgen Deficiency of Ageing Men questionnaire and the Aging Males' Symptoms (AMS) scale. We analyzed interictal data (mean  $\pm$  standard error) with repeated-measures analysis of covariance and longitudinal data by generalized estimated equations models.

**RESULTS:** Compared to controls, men with migraine had a lower interictal T<sub>f</sub>/E2 ratio (3.9  $\pm$  0.4 vs 5.0  $\pm$  0.3,  $p = 0.03$ ) due to higher E2 (96.8  $\pm$  6.1 vs 69.1  $\pm$  5.6 pmol/L,  $p = 0.001$ ) and similar T<sub>f</sub> (357.5  $\pm$  21.4 vs 332.6  $\pm$  18.7 pmol/L,  $p = 0.35$ ) levels. Preictal T<sub>f</sub> levels were increased in men with migraine reporting premonitory symptoms ( $p = 0.03$ ). Men with migraine more frequently reported symptoms of androgen deficiency (11 of 18 [61.1%] vs 6 of 22 [27.3%],  $p = 0.031$ ), which were also more frequently severe ( $p = 0.006$ ); their age- and BMI-adjusted AMS scores were higher (27.0  $\pm$  1.2 vs 21.0  $\pm$  1.0,  $p = 0.002$ ).

**CONCLUSIONS:** In this study, nonobese men with migraine exhibited increased levels of the sex hormone estradiol and showed clinical evidence of relative androgen deficiency. The role of estradiol in modulating migraine susceptibility and activity in men deserves further investigations.

## HEADACHE and MIGRAINE (Continued)

### [Musculoskeletal Pain and Headache in the Active Duty Military Population: An Integrative Review.](#)

[Bader CE](#)<sup>1</sup>, [Giordano NA](#)<sup>2</sup>, [McDonald CC](#)<sup>3</sup>, [Meghani SH](#)<sup>4</sup>, [Polomano RC](#)<sup>5</sup>.

Worldviews Evid Based Nurs. 2018 Jun 29. doi: 10.1111/wvn.12301. PMID: 29957866. [Epub ahead of print]

**BACKGROUND:** Since 2001, the U.S. Armed Forces' training and deployment have greatly increased, escalating the risk of injury and pain-related issues both at home station and deployment environments.

**AIMS:** This integrative review examines the incidence, prevalence, and risk factors for musculoskeletal pain (MSP) and headaches in active duty (AD) military populations.

**METHODS:** Peer-reviewed research published between 2001 and 2016 was identified relevant to MSP and headache in AD military personnel using MeSH terms in key biomedical databases. Inclusion criteria were: epidemiological studies examining MSP or headache as primary or secondary outcome; samples that included AD populations; and studies conducted in the theater of operations, at home station, and in military treatment or Veterans Health Administration facilities.

**RESULTS:** Twenty-six articles met inclusion criteria. Low back pain (LBP) was the most prevalent MSP diagnosis. The incidence of LBP was 40.5 per 1,000 person-years and was comparable to nonmilitary populations. Inflammation and pain from overuse comprised the largest proportion of injury mechanism, accounting for about 82% of all injuries among nondeployed military personnel. The risk of MSP was greater for AD, female, Army, enlisted personnel, and those with greater time in a motor vehicle. Evidence suggests posttraumatic headache, occurring in up to 92% of military personnel who have sustained a mild traumatic brain injury, is associated with chronic daily headaches.

**IMPLICATIONS:** Nurses must recognize the consequences military service can have on the development of pain. Nurses have an opportunity to positively impact the health and well-being of military and veteran populations through early recognition and treatment of pain.

**LINKING EVIDENCE TO ACTION:** The findings from this review underscore considerable magnitude of MSP in military personnel and expose modifiable risk factors and potential targets for designing nurse-led interventions to improve pain and symptoms in military subpopulations.

### [Psychological, clinical, and therapeutic predictors of the outcome of detoxification in a large clinical population of medication-overuse headache: A six-month follow-up of the COMOESTAS Project.](#)

[Bottiroli S](#)<sup>1</sup>, [Allena M](#)<sup>1</sup>, [Sances G](#)<sup>1</sup>, [De Icco R](#)<sup>1,2</sup>, [Avenali M](#)<sup>1,2</sup>, [Fadic R](#)<sup>3</sup>, [Katsarava Z](#)<sup>4</sup>, [Lainez MJ](#)<sup>5</sup>, [Goicochea MT](#)<sup>6</sup>, [Bendtsen L](#)<sup>7</sup>, [Jensen RH](#)<sup>7</sup>, [Nappi G](#)<sup>1</sup>, [Tassorelli C](#)<sup>1,2</sup>; [COMOESTAS Consortium](#).

Cephalalgia. 2018 Jan 1;333102418783317. doi: 10.1177/0333102418783317. PMID: 29945464. [Epub ahead of print]

**Aim:** To identify factors that may be predictors of the outcome of a detoxification treatment in medication-overuse headache.

**Methods:** Consecutive patients entering a detoxification program in six centres in Europe and Latin America were evaluated and followed up for 6 months. We evaluated anxious and depressive symptomatology (though patients with severe psychiatric comorbidity were excluded), quality of life, headache-related disability, headache characteristics, and prophylaxis upon discharge.

**Results:** Of the 492 patients who completed the six-month follow up, 407 ceased overuse following the detoxification (non overusers), another 23 ceased overuse following detoxification but relapsed during the follow-up. In the 407 non-overusers, headache acquired an episodic pattern in 287 subjects (responders). At the multivariate analyses, lower depression scores (odds ratio = 0.891; p = 0.001) predicted ceasing overuse. The primary headache diagnosis - migraine with respect to tension-type headache (odds ratio = 0.224; p = 0.001) or migraine plus tension-type headache (odds ratio = 0.467; p = 0.002) - and the preventive treatment with flunarizine (compared to no such treatment) (odds ratio = 0.891; p = 0.001) predicted being a responder. A longer duration of chronic headache (odds ratio = 1.053; p = 0.032) predicted relapse into overuse. Quality of life and disability were not associated with any of the outcomes.

**Conclusions:** Though exploratory in nature, these findings point to specific factors that are associated with a positive outcome of medication-overuse headache management, while identifying others that may be associated with a negative outcome. Evaluation of the presence/absence of these factors may help to optimize the management of this challenging groups of chronic headache sufferers.

## CHRONIC PAIN

### [Longitudinal relationship between onset of physical symptoms and functional impairment.](#)

[McAndrew LM](#)<sup>1,2</sup>, [Helmer DA](#)<sup>3,4</sup>, [Lu SE](#)<sup>3,5</sup>, [Chandler HK](#)<sup>3</sup>, [Slotkin S](#)<sup>6</sup>, [Quigley KS](#)<sup>7,8</sup>.

J Behav Med. 2018 Jun 9. doi: 10.1007/s10865-018-9937-4. PMID: 29948542. [Epub ahead of print]

Patients with chronic physical symptoms (e.g., chronic pain) often have significant functional impairment (i.e., disability). The fear avoidance model is the dominant theoretical model of how the relationship between chronic physical symptoms and functional impairment develops and proposes a cyclical/bidirectional relationship. There has never been a definitive test of the proposed bi-directional relationship. The current study followed 767 Operation Enduring Freedom/Operation Iraqi Freedom soldiers from pre-deployment, when they were relatively healthy, to 1 year after deployment, when it was anticipated that symptoms would increase or develop. Over the four assessment time points, physical symptom severity consistently predicted worse functional impairment at the subsequent time point. Functional impairment did not show a consistent relationship with worsening of physical symptom severity. These findings suggest that changes to functional impairment do not have a short-term impact on physical symptom severity.

### [Effect of vitamin D supplementation in chronic widespread pain: a systematic review and meta-analysis.](#)

[Yong WC](#)<sup>1</sup>, [Sanguankeeo A](#)<sup>2,3</sup>, [Upala S](#)<sup>2,3</sup>.

Clin Rheumatol. 2017 Dec;36(12):2825-2833. doi: 10.1007/s10067-017-3754-y. PMID: 28812209. Epub 2017 Aug 15.

Chronic non-specific widespread pain (CWP) including fibromyalgia (FMS) is characterized by widespread pain, reduced pain threshold, and multiple tender points on examination, causing disability and decreased quality of life. Vitamin D has been proposed as an associated factor in CWP. This meta-analysis aimed to explore the benefit of vitamin D supplementation in the management of CWP. A comprehensive search of the CENTRAL, MEDLINE, and Embase databases was performed from inception through January 2017. The inclusion criterion was the randomized clinical trials' evaluating the effects of vitamin D treatment in adult subjects with CWP or FMS. CWP was defined as chronic recurrent musculoskeletal pain without secondary causes; FMS patients met the American College of Rheumatology criteria for FMS. Study outcome was assessed using visual analog scale (VAS) of pain intensity. Pooled mean difference (MD) of VAS and 95% confidence interval (CI) were calculated using a random-effect meta-analysis. Meta-regression analysis using a random-effects model was performed to explore the effects of change in vitamin D in the treatment group on difference in the mean of VAS. Sensitivity analysis was performed to evaluate the robustness of results. The between-study heterogeneity of effect size was quantified using the Q statistic and  $I^2$ . Data were extracted from four randomized controlled trials involving 287 subjects. Pooled result demonstrated a significantly lower VAS in CWP patients who received vitamin D treatment compared with those who received placebo (MD = 0.46; 95% CI 0.09-0.89,  $I^2 = 48\%$ ). Meta-regression analysis revealed no significant relationship between the changes of vitamin D and VAS (coefficient = 0.04 (95% CI -0.01 to 0.08),  $p = 0.10$ ). In this meta-analysis, we conclude that vitamin D supplementation is able to decrease pain scores and improve pain despite no significant change in VAS after increasing serum vitamin D level. Further studies need to be conducted in order to explore the improvement of functional status, quality of life, and the pathophysiological change that improves chronic widespread pain.

## CHRONIC PAIN (Continued)

### Unexpectedly decreased plasma cytokines in patients with chronic back pain.

[Capossela S](#)<sup>1</sup>, [Pavlicek D](#)<sup>1</sup>, [Bertolo A](#)<sup>1</sup>, [Landmann G](#)<sup>2</sup>, [Stoyanov JV](#)<sup>1</sup>.

J Pain Res. 2018 Jun 21;11:1191-1198. doi: 10.2147/JPR.S153872. PMCID: PMC6016579. PMID: 29950891. eCollection 2018.

**Introduction:** Chronic back pain is one of the most important socioeconomic problems that affects the global population. Elevated levels of inflammatory mediators, such as cytokines, have been correlated with pain, but their role in chronic back pain remains unclear. The effectiveness of anti-inflammatory drugs seems to be limited for chronic back pain. The authors wanted to investigate the levels of inflammatory mediators in long-term medically treated patients with persistent chronic back pain.

**Methods:** Cytokine plasma levels of patients with chronic back pain (n=23), compared to pain-free healthy controls (n=30), were investigated by immunoassay. Patients with chronic back pain were exposed to long-term conservative medical therapy with physiotherapy and anti-inflammatories, also combined with antidepressants and/or muscle-relaxants.

**Results:** The patients with chronic back pain expressed lower levels of the chemokines MCP1, CCL5, and CXCL6 compared to pain-free healthy controls. Significantly lower concentrations of the anti-inflammatory cytokines, interleukin (IL)-4 and granulocyte-colony stimulating factor were also found. Interestingly, levels of proinflammatory cytokines (IL-2, IL-6, IL-1 $\beta$ , tumor necrosis factor alpha), IL-10, granulocyte-macrophage colony-stimulating factor, and stromal cell-derived factor 1 alpha showed no significant differences between both groups.

**Conclusion:** This decrease of inflammatory mediators in medically treated patients with chronic back pain is of unclear origin and might be either a long-term side effect of medical therapy or related to chronic pain. Further longitudinal research is necessary to elucidate the underlying cause of these findings.

### Pain Neurophysiology Education and Therapeutic Exercise for Patients With Chronic Low Back Pain: A Single-Blind Randomized Controlled Trial.

[Bodes Pardo G](#)<sup>1</sup>, [Lluch Girbés E](#)<sup>2</sup>, [Roussel NA](#)<sup>3</sup>, [Gallego Izquierdo T](#)<sup>4</sup>, [Jiménez Penick V](#)<sup>1</sup>, [Pecos Martín D](#)<sup>4</sup>.

Arch Phys Med Rehabil. 2018 Feb;99(2):338-347. doi: 10.1016/j.apmr.2017.10.016. PMID: 29138049. Epub 2017 Nov 11.

**OBJECTIVE:** To assess the effect of a pain neurophysiology education (PNE) program plus therapeutic exercise (TE) for patients with chronic low back pain (CLBP).

**DESIGN:** Single-blind randomized controlled trial.

**SETTING:** Private clinic and university.

**PARTICIPANTS:** Patients with CLBP for  $\geq 6$  months (N=56).

**INTERVENTIONS:** Participants were randomized to receive either a TE program consisting of motor control, stretching, and aerobic exercises (n=28) or the same TE program in addition to a PNE program (n=28), conducted in two 30- to 50-minute sessions in groups of 4 to 6 participants.

**MAIN OUTCOMES MEASURES:** The primary outcome was pain intensity rated on the numerical pain rating scale which was completed immediately after treatment and at 1- and 3-month follow-up. Secondary outcome measures were pressure pain threshold, finger-to-floor distance, Roland-Morris Disability Questionnaire, Pain Catastrophizing Scale, Tampa Scale for Kinesiophobia, and Patient Global Impression of Change.

**RESULTS:** At 3-month follow-up, a large change in pain intensity (numerical pain rating scale: -2.2; -2.93 to -1.28;  $P < .001$ ;  $d = 1.37$ ) was observed for the PNE plus TE group, and a moderate effect size was observed for the secondary outcome measures.

**CONCLUSIONS:** Combining PNE with TE resulted in significantly better results for participants with CLBP, with a large effect size, compared with TE alone.

## OTHER RESEARCH OF INTEREST

### [Federal Rule Overrides State Telemedicine Restrictions.](#)

[Rubin R.](#)

JAMA. **2018 Jun 26**;319(24):2469. doi: 10.1001/jama.2018.8166. PMID: 29946711

A new federal rule will allow US Department of Veterans Affairs (VA) physicians, nurses, and other health care professionals to use telemedicine when caring for veterans across state lines or outside a VA facility. It had been unclear whether VA clinicians could use telemedicine to provide care to veterans in other states because of licensing restrictions or state-specific telemedicine laws, [according to the VA](#). The VA worked with the White House Office of American Innovation and the Department of Justice on implementing the new rule, which overrides state restrictions and laws.

Veterans can now use [VA Video Connect](#), a video-conferencing app, and other forms of telemedicine in their own homes to connect with VA clinicians throughout the country.

The rule may be especially beneficial for veterans in rural areas who otherwise would need to travel a considerable distance or across state lines to receive care, the VA said. It also will enable quicker access to mental health care and suicide prevention via telemedicine, according to the agency.

### [Usual Care for Rural Veterans With Posttraumatic Stress Disorder.](#)

[Grubbs KM](#)<sup>1,2,3</sup>, [Fortney JC](#)<sup>4,5</sup>, [Kimbrell T](#)<sup>1,2,3</sup>, [Pyne JM](#)<sup>1,2,3</sup>, [Hudson T](#)<sup>1,2,3</sup>, [Robinson D](#)<sup>6</sup>, [Moore WM](#)<sup>1,2</sup>, [Custer P](#)<sup>7</sup>, [Schneider R](#)<sup>6,8</sup>, [Schnurr PP](#)<sup>9,10</sup>.

J Rural Health. **2017 Jun**;33(3):290-296. doi: 10.1111/jrh.12230. PMID: 28112433. Epub 2017 Jan 23.

**PURPOSE:** Community-Based Outpatient Clinics (CBOCs) provide primary-care-based mental health services to rural veterans who live long distances from Veterans Affairs (VA) hospitals. Characterizing the composition of usual care will highlight the need and potential strategies to improve access to and engagement in evidence-based psychotherapy for posttraumatic stress disorder (PTSD).

**METHOD:** Veterans (N = 132) with PTSD recruited from 5 large- (5,000-10,000 patients) and 6 medium-sized (1,500-4,999) CBOCs were enrolled in the usual care arm of a randomized control trial for a PTSD collaborative care study. Chart review procedures classified all mental health encounters during the 1-year study period into 10 mutually exclusive categories (7 psychotherapy and 3 medication management).

**FINDINGS:** Seventy-two percent of participants received at least 1 medication management encounter with 30% of encounters being delivered via interactive video. More than half of veterans (58.3%) received at least 1 session of psychotherapy. Only 12.1% received a session of therapy classified as an evidence-based psychotherapy for PTSD. The vast majority of psychotherapy encounters were delivered in group format and only a small proportion were delivered via interactive video.

**CONCLUSIONS:** Findings suggest that veterans diagnosed with PTSD who receive their mental health treatment in large and medium CBOCs are likely to receive medication management, and very few veterans received evidence-based psychotherapy. There may be ways to increase access to evidence-based psychotherapy by expanding the use of interactive video to connect specialty mental health providers with patients, hosted either in CBOCs or in home-based care, and to offer more group-based therapies.

### [Analysis of shared heritability in common disorders of the brain.](#)

[Brainstorm Consortium, et al.](#)

Science. **2018 Jun 22**;360(6395). pii: eaap8757. doi: 10.1126/science.aap8757. PMID: 29930110.

Disorders of the brain can exhibit considerable epidemiological comorbidity and often share symptoms, provoking debate about their etiologic overlap. We quantified the genetic sharing of 25 brain disorders from genome-wide association studies of 265,218 patients and 784,643 control participants and assessed their relationship to 17 phenotypes from 1,191,588 individuals. Psychiatric disorders share common variant risk, whereas neurological disorders appear more distinct from one another and from the psychiatric disorders. We also identified significant sharing between disorders and a number of brain phenotypes, including cognitive measures. Further, we conducted simulations to explore how statistical power, diagnostic misclassification, and phenotypic heterogeneity affect genetic correlations. These results highlight the importance of common genetic variation as a risk factor for brain disorders and the value of heritability-based methods in understanding their etiology.

## OTHER RESEARCH OF INTEREST (Continued)

**Effect of Repetitive Transcranial Magnetic Stimulation on Treatment-Resistant Major Depression in US Veterans: A Randomized Clinical Trial.**

[Yesavage JA](#)<sup>1,2</sup>, [Fairchild JK](#)<sup>1,2</sup>, [Mi Z](#)<sup>3</sup>, [Biswas K](#)<sup>3</sup>, [Davis-Karim A](#)<sup>4</sup>, [Phibbs CS](#)<sup>5,6</sup>, [Forman SD](#)<sup>7,8</sup>, [Thase M](#)<sup>9</sup>, [Williams LM](#)<sup>1,2</sup>, [Etkin A](#)<sup>1,2,10</sup>, [O'Hara R](#)<sup>1,2</sup>, [Georgette G](#)<sup>1</sup>, [Beale T](#)<sup>1</sup>, [Huang GD](#)<sup>11</sup>, [Noda A](#)<sup>2</sup>, [George MS](#)<sup>12,13</sup>; VA Cooperative Studies Program Study Team.

JAMA Psychiatry. **2018 Jun 27**. doi: 10.1001/jamapsychiatry.2018.1483. PMID: 29955803. [Epub ahead of print]

**Importance:** Treatment-resistant major depression (TRMD) in veterans is a major clinical challenge given the high risk for suicidality in these patients. Repetitive transcranial magnetic stimulation (rTMS) offers the potential for a novel treatment modality for these veterans.

**Objective:** To determine the efficacy of rTMS in the treatment of TRMD in veterans.

**Design, Setting, and Participants:** A double-blind, sham-controlled randomized clinical trial was conducted from September 1, 2012, to December 31, 2016, in 9 Veterans Affairs medical centers. A total of 164 veterans with TRD participated.

**Interventions:** Participants were randomized to either left prefrontal rTMS treatment (10 Hz, 120% motor threshold, 4000 pulses/session) or to sham (control) rTMS treatment for up to 30 treatment sessions.

**Main Outcomes and Measures:** The primary dependent measure of the intention-to-treat analysis was remission rate (Hamilton Rating Scale for Depression score  $\leq 10$ , indicating that depression is in remission and not a clinically significant burden), and secondary analyses were conducted on other indices of posttraumatic stress disorder, depression, hopelessness, suicidality, and quality of life.

**Results:** The 164 participants had a mean (SD) age of 55.2 (12.4) years, 132 (80.5%) were men, and 126 (76.8%) were of white race. Of these, 81 were randomized to receive active rTMS and 83 to receive sham. For the primary analysis of remission, there was no significant effect of treatment (odds ratio, 1.16; 95% CI, 0.59-2.26;  $P = .67$ ). At the end of the acute treatment phase, 33 of 81 (40.7%) of those in the active treatment group achieved remission of depressive symptoms compared with 31 of 83 (37.4%) of those in the sham treatment group. Overall, 64 of 164 (39.0%) of the participants achieved remission.

**Conclusions and Relevance:** A total of 39.0% of the veterans who participated in this trial experienced clinically significant improvement resulting in remission of depressive symptoms; however, there was no evidence of difference in remission rates between the active and sham treatments. These findings may reflect the importance of close clinical surveillance, rigorous monitoring of concomitant medication, and regular interaction with clinic staff in bringing about significant improvement in this treatment-resistant population.

**Trial Registration:** ClinicalTrials.gov Identifier: [NCT01191333](#).

**Lack of group-to-individual generalizability is a threat to human subjects research.**

[Fisher AJ](#)<sup>1</sup>, [Medaglia JD](#)<sup>2,3</sup>, [Jeronimus BF](#)<sup>4</sup>.

Proc Natl Acad Sci U S A. **2018 Jul 3**;115(27):E6106-E6115. doi: 10.1073/pnas.1711978115. PMID: 29915059 Epub 2018 Jun 18.

Only for ergodic processes will inferences based on group-level data generalize to individual experience or behavior. Because human social and psychological processes typically have an individually variable and time-varying nature, they are unlikely to be ergodic. In this paper, six studies with a repeated-measure design were used for symmetric comparisons of interindividual and intraindividual variation. Our results delineate the potential scope and impact of nonergodic data in human subjects research. Analyses across six samples (with 87-94 participants and an equal number of assessments per participant) showed some degree of agreement in central tendency estimates (mean) between groups and individuals across constructs and data collection paradigms. However, the variance around the expected value was two to four times larger within individuals than within groups. This suggests that literatures in social and medical sciences may overestimate the accuracy of aggregated statistical estimates. This observation could have serious consequences for how we understand the consistency between group and individual correlations, and the generalizability of conclusions between domains. Researchers should explicitly test for equivalence of processes at the individual and group level across the social and medical sciences.