

## GULF WAR ILLNESS

### [The Association Between Toxic Exposures and Chronic Multisymptom Illness in Veterans of the Wars of Iraq and Afghanistan.](#)

DeBeer BB, Davidson D, Meyer EC, Kimbrel NA, Gulliver SB, Morissette SB.

J Occup Environ Med. 2017 Jan;59(1):54-60. doi: 10.1097/JOM.0000000000000922.

**OBJECTIVE:** The purpose of this study was to determine if post-9/11 veterans deployed to the Iraq and Afghanistan conflicts experienced toxic exposures and whether they are related to symptoms of chronic multisymptom illness (CMI).

**METHODS:** Data from 224 post-9/11 veterans who self-reported exposure to hazards in theater were analyzed using hierarchical regression.

**RESULTS:** Of the sample, 97.2% endorsed experiencing one or more potentially toxic exposure. In a regression model, toxic exposures and CMI symptoms were significantly associated above and beyond covariates. Follow-up analyses revealed that pesticide exposures, but not smoke inhalation was associated with CMI symptoms.

**CONCLUSIONS:** These findings suggest that toxic exposures were common among military personnel deployed to the most recent conflicts, and appear to be associated with CMI symptoms. Additional research on the impact of toxic exposures on returning Iraq and Afghanistan Veterans' health is needed.

## CHRONIC FATIGUE SYNDROME

### [Electric Stimulation for Pain Relief in Patients with Fibromyalgia: A Systematic Review and Meta-analysis of Randomized Controlled Trials.](#)

Salazar AP, Stein C, Marchese RR, Plentz RD, Pagnussat AS.

Pain Physician. 2017 Feb;20(2):15-25.

**BACKGROUND:** Fibromyalgia (FM) is a syndrome whose primary symptoms include chronic widespread muscle pain and fatigue. The treatment of patients with FM aims to provide symptomatic relief and improvement in physical capacities to perform daily tasks and quality of life. Invasive or non-invasive electric stimulation (ES) is used for pain relief in patients with FM.

**OBJECTIVE:** This systematic review aimed to assess the effects of treatment with ES, combined or not combined with other types of therapy, for pain relief in patients with FM.

**STUDY DESIGN:** Systematic review and meta-analysis.

**SETTING:** Electronic search was conducted on databases (from the inception to April 2016): MEDLINE (accessed by PubMed), EMBASE, Cochrane Central Register of Controlled Trials (Cochrane CENTRAL), and Physiotherapy Evidence Database (PEDro).

**METHODS:** Two independent reviewers assessed the eligibility of studies based on the inclusion criteria: randomized controlled trials (RCTs) examining the effects of ES combined or not with other types of treatment for pain relief in patients with FM (according to the American College of Rheumatology), regardless of the ES dosages. The primary outcome was pain, assessed by the visual analogue scale (VAS). The secondary outcomes extracted were quality of life, assessed by short form-36 health survey (SF-36), and fatigue, assessed by VAS.

**RESULTS:** Nine studies were included, with 301 patients. The meta-analysis for pain showed positive effect of ES treatment versus control [-1.24 (95% CI: -2.39 to -0.08; I<sup>2</sup>: 87%, P = 0.04) n = 8 RCTs]. The sensitivity analysis for pain showed significant results for invasive ES, combined or not with other types of therapy [-0.94 (95% CI, -1.50 to -0.38; I<sup>2</sup> 0%, P = 0.001) n = 3 RCTs]. No significant improvement was found regarding quality of life [-3.48 (95% CI: -12.58 to 5.62; I<sup>2</sup>: 0%, P = 0.45), n = 2 RCTs] or fatigue [-0.57 (95% CI, -1.25 to 0.11; I<sup>2</sup> 34%, P = 0.100; n = 4 RCTs].

**LIMITATIONS:** This systematic review included a small number of studies and reduced number of participants in each study. Furthermore, most of the studies showed some biases and lack of methodological quality.

**CONCLUSIONS:** This meta-analysis indicates that there is low-quality evidence for the effectiveness of ES for pain relief in patients with FM. However, moderate-quality evidence for the effectiveness of electroacupuncture (EA), combined or not combined with other types of treatment, was found for pain relief.

## HEADACHE and MIGRAINE

### [Medication Overuse Headache: Pathophysiological Insights from Structural and Functional Brain MRI Research.](#)

Schwedt TJ, Chong CD.

Headache. **2017 Feb 3**. doi: 10.1111/head.13037. [Epub ahead of print]

**BACKGROUND:** Research imaging of brain structure and function has helped to elucidate the pathophysiology of medication overuse headache (MOH).

**METHODS:** This is a narrative review of imaging research studies that have investigated brain structural and functional alterations associated with MOH. Studies included in this review have investigated abnormal structure and function of pain processing regions in people with MOH, functional patterns that might predispose individuals to development of MOH, similarity of brain functional patterns in patients with MOH to those found in people with addiction, brain structure that could predict headache improvement following discontinuation of the overused medication, and changes in brain structure and function after discontinuation of medication overuse.

**RESULTS AND CONCLUSIONS:** MOH is associated with atypical structure and function of brain regions responsible for pain processing as well as brain regions that are commonly implicated in addiction. Several studies have shown "normalization" of structure and function in pain processing regions following discontinuation of the overused medication and resolution of MOH. However, some of the abnormalities in regions also implicated in addiction tend to persist following discontinuation of the overused medication, suggesting that they are a brain trait that predisposes certain individuals to medication overuse and MOH.

### [Potential Beneficial Effects of Probiotics on Human Migraine Headache: A Literature Review.](#)

Dai YJ, Wang HY, Wang XJ, Kaye AD, Sun YH.

Pain Physician. **2017 Feb**;20(2):E251-E255.

**BACKGROUND:** Recent studies have shown that migraine headache is often associated with concomitant gastrointestinal diseases. There is a higher prevalence of headaches in patients with gastrointestinal disorders. These associations between migraine and gastrointestinal disorders suggest a potential link to a bidirectional modulation of gut microbiota and brain function. The underlying working mechanistic links between migraine and gastrointestinal diseases may include increased intestinal epithelial permeability and inflammation.

**OBJECTIVE:** This review presents an overview of the relationship between gut microbiota and brain function, especially with regard to migraine headache.

**STUDY DESIGN:** Literature review.

**SETTING:** Anesthesia and Operation Center, Department of Anesthesiology, Chinese PLA General Hospital.

**METHODS:** The present investigation included a PubMed search using the following terms: migraine headache, gut microbiota, brain function, and probiotics.

**RESULTS:** In this literature review, we mainly discussed the relationship between gut microbiota and brain function, especially with regard to migraine headache. The potential effects of probiotics supplement on migraine headache were also included.

**LIMITATIONS:** There is limited evidence from clinical studies of the positive effects of probiotics in patients with migraine headache. Large-scale randomized, placebo-controlled clinical trials are warranted to evaluate the clinical efficacy and safety of probiotics in patients with migraine headache.

**CONCLUSIONS:** Similar to migraine headache, disorders of the brain involving depression and anxiety have been demonstrated to be associated with increased gut permeability. An improvement in gut microbiota and reduction of inflammation can have positive effects on strengthening gut and brain function. Moreover, it can be inferred that probiotics may have a beneficial effect on the frequency and severity of migraine headache attacks. Large-scale randomized, placebo-controlled studies are warranted in the future to evaluate the clinical efficacy and safety of probiotics in patients with migraine headache. **Key words:** Migraine headache, gut microbiota, brain function, probiotics.

## HEADACHE and MIGRAINE (Continued)

### [Association between lifetime headache and history of suicide attempts in the elderly.](#)

Calati R, Courtet P, Norton J, Ritchie K, Artero S.

Eur Psychiatry. 2017 Jan 30;41:132-139. doi: 10.1016/j.eurpsy.2016.10.009. [Epub ahead of print]

**BACKGROUND:** Pain-related conditions have been reported to play a key role among risk factors for suicide. Headache in particular has been repeatedly associated with suicidal thoughts and behaviors. The aims of this study were: 1) to assess the association between lifetime headache (both non-migrainous headache and migraine) and lifetime suicide attempts (SA); 2) to differentiate, within subjects with lifetime SA, patients with and without lifetime headache in terms of socio-demographic and clinical features.

**METHODS:** We studied 1965 subjects from a cohort of community-dwelling persons aged 65 years and over without dementia (the ESPRIT study), divided in two groups: those with (n=75), and those without a lifetime SA (n=1890). Logistic regression analyses were used to compare these groups according to lifetime headache status.

**RESULTS:** After adjusting for gender, living alone, tobacco and alcohol consumption, and depressive, manic/hypomanic and anxiety disorders, lifetime headache frequency was significantly higher in subjects with a lifetime SA compared with controls (OR=1.92 [1.17-3.15]). Additionally, different factors were identified as being associated with lifetime SA in participants with lifetime headache (female gender, a lower level of high-density lipoprotein cholesterol, insomnia, lifetime major depression) versus participants without headache (glycemia and lifetime major depression).

**CONCLUSIONS:** Lifetime headache was associated with lifetime SA. Subjects who are women and report the co-occurrence of headache and insomnia as well as lifetime major depression require higher attention and a careful screening for suicidal thoughts and behaviors.

### [Diet-Induced Obesity Enhances TRPV1-Mediated Neurovascular Reactions in the Dura Mater.](#)

Marics B, Peitl B, Pázmándi K, Bácsi A, Németh J, Oszlács O, Jancsó G, Dux M.

Headache. 2017 Jan 30. doi: 10.1111/head.13033. [Epub ahead of print]

**OBJECTIVE:** Exploring the pathophysiological changes in transient receptor potential vanilloid 1 (TRPV1) receptor of the trigeminovascular system in high-fat, high-sucrose (HFHS) diet-induced obesity of experimental animals.  
**BACKGROUND:** Clinical and experimental observations suggest a link between obesity and migraine. Accumulating evidence indicates that metabolic and immunological alterations associated with obesity may potentially modulate trigeminovascular functions. A possible target for obesity-induced pathophysiological changes is the TRPV1/capsaicin receptor which is implicated in the pathomechanism of headaches in a complex way.  
**METHODS:** Male Sprague-Dawley rats were fed a regular (n = 25) or HFHS diet (n = 26) for 20 weeks. At the end of the dietary period, body weight of the animals was normally distributed in both groups and it was significantly higher in animals on HFHS diet. Therefore, experimental groups were regarded as control and HFHS diet-induced obese groups. Capsaicin-induced changes in meningeal blood flow and release of calcitonin gene-related peptide (CGRP) from dural trigeminal afferents were measured in control and obese rats. The distribution of TRPV1- and CGRP-immunoreactive meningeal sensory nerves was also compared in whole mount preparations of the dura mater. Metabolic parameters of the animals were assessed by examining glucose and insulin homeostasis as well as plasma cytokine concentrations.

**RESULTS:** HFHS diet was accompanied by reduced food consumption and greater fluid and energy intakes in addition to increased body weight of the animals. HFHS diet increased fasting blood glucose and insulin concentrations as well as levels of circulating proinflammatory cytokines interleukin-1 $\beta$  and interleukin-6. In obese animals, dural application of the archetypal TRPV1 agonist capsaicin resulted in significantly augmented vasodilatory and vasoconstrictor responses as compared to controls. Diet-induced obesity was also associated with enhanced basal and capsaicin-induced CGRP release from meningeal afferents ex vivo. Except for minor morphological changes, the distribution of dural TRPV1- and CGRP-immunoreactive afferents was similar in control and obese animals.

**CONCLUSIONS:** Our results suggest that obesity induced by long-term HFHS diet results in sensitization of the trigeminovascular system. Changes in TRPV1-mediated vascular reactions and CGRP release are pathophysiological alterations that may be of relevance to the enhanced headache susceptibility of obese individuals.

## HEADACHE and MIGRAINE (Continued)

### [Estrogen-dependent effects of 5-hydroxytryptophan on cortical spreading depression in rat: Modelling the serotonin-ovarian hormone interaction in migraine aura.](#)

Chauvel V, Multon S, Schoenen J.

Cephalalgia. **2017 Jan** 1:333102417690891. doi: 10.1177/0333102417690891. [Epub ahead of print]

**Background** Cortical spreading depression (CSD) is the likely culprit of the migraine aura. Migraine is sexually dimorphic and thought to be a "low 5-HT" condition. We sought to decipher the interrelation between serotonin, ovarian hormones and cortical excitability in a model of migraine aura. **Methods** Occipital KCl-induced CSDs were recorded for one hour at parieto-occipital and frontal levels in adult male (n = 16) and female rats (n = 64) one hour after intraperitoneal (i.p.) injection of 5-hydroxytryptophan (5-HTP) or NaCl. Sixty-five oophorectomized females were treated with estradiol- (E2) or cholesterol- (Chol) filled capsules. Two weeks later we recorded CSDs after 5-HTP/NaCl injections before or 20 hours after capsule removal. **Results** 5-HTP had no effect in males, but decreased CSD frequency in cycling females, significantly so during estrus, at parieto-occipital (-3.5CSD/h, p < 0.001) and frontal levels (-2.5CSD/h, p = 0.014). In oophorectomized rats, CSD susceptibility increased during E2 treatment at both recording sites (+5CSD/h, p = 0.001 and +3CSD/h, p < 0.01), but decreased promptly after E2 withdrawal (-4.7CSD/h, p < 0.001 and -1.7CSD/h, p = 0.094). The CSD inhibitory effect of 5-HTP was significant only in E2-treated rats (-3.4CSD/h, p = 0.006 and -1.8CSD/h, p = 0.029). Neither the estrous cycle phase, nor E2 or 5-HTP treatments significantly modified CSD propagation velocity. **Conclusion** 5-HTP decreases CSD occurrence in the presence of ovarian hormones, suggesting its potential efficacy in migraine with aura prophylaxis in females. Elevated E2 levels increase CSD susceptibility, while estrogen withdrawal decreases CSD. In a translational perspective, these findings may explain why migraine auras can appear during pregnancy and why menstrual-related migraine attacks are rarely associated with an aura.

### [Mindfulness and pharmacological prophylaxis after withdrawal from medication overuse in patients with Chronic Migraine: an effectiveness trial with a one-year follow-up.](#)

Grazzi L, Sansone E, Raggi A, D'Amico D, De Giorgio A, Leonardi M, De Torres L, Salgado-García F, Andrasik F.

J Headache Pain. **2017 Dec**;18(1):15. doi: 10.1186/s10194-017-0728-z.

**BACKGROUND:** Chronic Migraine (CM) is a disabling condition, worsened when associated with Medication Overuse (MO). Mindfulness is an emerging technique, effective in different pain conditions, but it has yet to be explored for CM-MO. We report the results of a study assessing a one-year course of patients' status, with the hypothesis that the effectiveness of a mindfulness-based approach would be similar to that of conventional prophylactic treatments.

**METHODS:** Patients with CM-MO (code 1.3 and 8.2 of the International Classification of Headache Disorders-3Beta) completed a withdrawal program in a day hospital setting. After withdrawal, patients were either treated with Prophylactic Medications (Med-Group), or participated in a Mindfulness-based Training (MT-Group). MT consisted of 6 weekly sessions of guided mindfulness, with patients invited to practice 7-10 min per day. Headache diaries, the headache impact test (HIT-6), the migraine disability assessment (MIDAS), state and trait anxiety (STAI Y1-Y2), and the Beck Depression Inventory (BDI) were administered before withdrawal and at each follow-up (3, 6, 12 after withdrawal) to patients from both groups. Outcome variables were analyzed in separate two-way mixed ANOVAs (Group: Mindfulness vs. Pharmacology x Time: Baseline, 3-, 6-, vs. 12-month follow-up).

**RESULTS:** A total of 44 patients participated in the study, with the average age being 44.5, average headache frequency/month was 20.5, and average monthly medication intake was 18.4 pills. Data revealed a similar improvement over time in both groups for Headache Frequency (approximately 6-8 days reduction), use of Medication (approximately 7 intakes reduction), MIDAS, HIT-6 (but only for the MED-Group), and BDI; no changes on state and trait anxiety were found. Both groups revealed significant and equivalent improvement with respect to what has become a classical endpoint in this area of research, i.e. 50% or more reduction of headaches compared to baseline, and the majority of patients in each condition no longer satisfied current criteria for CM.

**CONCLUSIONS:** Taken as a whole, our results suggest that the longitudinal course of patients in the MT-Group, that were not prescribed medical prophylaxis, was substantially similar to that of patients who were administered medical prophylaxis.

## CHRONIC PAIN

### [Implementation of a pharmacy consult to reduce co-prescribing of opioids and benzodiazepines in a Veteran population.](#)

Pardo D, Miller L, Chiulli D.

Subst Abuse. **2017 Feb** 6:0. doi: 10.1080/08897077.2017.1290011. [Epub ahead of print]

**BACKGROUND:** The dangers of co-administration of opioid pain relievers (OPRs) and benzodiazepines (BZDs) are well documented. The combination of OPRs and BZDs make up the majority of medications involved in prescription drug-related overdose and are often used concomitantly. This pattern is consistent among the Veteran population where mental health illness and substance abuse are prominent. The Veterans Health Administration implemented the Opioid Safety Initiative (OSI) aimed at improving patient safety surrounding OPRs. In alignment with OSI, the study facility implemented a prior authorization pharmacy consult in an effort to reduce OPR and BZD co-prescribing and optimize patient safety. The purpose of this article is to report the frequency of co-prescribing before and after implementation of the consult. Secondary aims include reporting the emergency room visits and hospitalizations, prescriber's actions in the setting of disapproved consults, patient characteristics associated with co-prescribing and frequency of co-prescribing without a consult.

**METHODS:** This was a single-center, retrospective chart review study. Microsoft® Structured Query Language server database and Veterans Health Information Systems and Technology Architecture were used to extract data and identify study patients. The Computerized Patient Record System was used to collect patient data. Microsoft® Access and Excel were utilized to organize, query and analyze the extracted data.

**RESULTS:** There was a 34.6 percent reduction in patients on chronic OPR therapy co-prescribed a BZD, and the total number of overdose-related events decreased after implementation of the consult. In the event of disapproved consults, pharmacists' evidence-based recommendations were implemented 63 percent of the time. Patients for whom co-prescribing consults were placed were more likely to have mental health diagnoses.

**CONCLUSIONS:** Following implementation of a pharmacy consult, there was a reduction in co-prescribing and overdose-related events at the study facility.

### [Volatility and Change in Chronic Pain Severity Predict Outcomes of Treatment for Prescription Opioid Addiction.](#)

Worley MJ, Heinzerling KG, Shoptaw S, Ling W.

Addiction. **2017 Feb** 5. doi: 10.1111/add.13782. [Epub ahead of print]

**BACKGROUND AND AIMS:** Buprenorphine-naloxone (BUP-NLX) can be used to manage prescription opioid addiction among persons with chronic pain, but post-treatment relapse is common and difficult to predict. This study estimated whether changes in pain over time and pain volatility during BUP-NLX maintenance would predict opioid use during the taper BUP-NLX taper.

**DESIGN:** Secondary analysis of a multisite clinical trial for prescription opioid addiction, using data obtained during a 12-week BUP-NLX stabilization and 4-week BUP-NLX taper.

**SETTING:** Community clinics affiliated with a national clinical trials network in 10 U.S. cities.

**PARTICIPANTS:** Subjects with chronic pain who entered the BUP-NLX taper phase (N = 125) with enrollment occurring from June, 2006 to July 2009 (52% male, 88% Caucasian, 31% married).

**MEASUREMENTS:** Outcomes were weekly biologically-verified and self-reported opioid use from the 4-week taper phase. Predictors were estimates of baseline severity, rate of change, and volatility in pain from weekly self-reports during the 12-week maintenance phase.

**FINDINGS:** Controlling for baseline pain and treatment condition, increased pain (OR = 2.38, p = .02) and greater pain volatility (OR = 2.43, p = .04) predicted greater odds of positive opioid urine screen during BUP-NLX taper. Increased pain (IRR = 1.40, p = .04) and greater pain volatility (IRR = 1.66, p = .009) also predicted greater frequency of self-reported opioid use.

**CONCLUSIONS:** Adults with chronic pain receiving outpatient treatment with buprenorphine-naloxone (BUP-NLX) for prescription opioid addiction have elevated risk for opioid use when tapering off of maintenance treatment. Those with relative persistence in pain over time and greater volatility in pain during treatment are less likely to sustain abstinence during BUP-NLX taper.

**OTHER RESEARCH OF INTEREST**[Neurotoxic reactive astrocytes are induced by activated microglia.](#)

Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, Bennett ML, Münch AE, Chung WS, Peterson TC, Wilton DK, Frouin A, Napier BA, Panicker N, Kumar M, Buckwalter MS, Rowitch DH, Dawson VL, Dawson TM, Stevens B, Barres BA.

Nature. **2017 Jan** 26;541(7638):481-487. doi: 10.1038/nature21029.

Reactive astrocytes are strongly induced by central nervous system (CNS) injury and disease, but their role is poorly understood. Here we show that a subtype of reactive astrocytes, which we termed A1, is induced by classically activated neuroinflammatory microglia. We show that activated microglia induce A1 astrocytes by secreting  $Il-1\alpha$ , TNF and C1q, and that these cytokines together are necessary and sufficient to induce A1 astrocytes. A1 astrocytes lose the ability to promote neuronal survival, outgrowth, synaptogenesis and phagocytosis, and induce the death of neurons and oligodendrocytes. Death of axotomized CNS neurons *in vivo* is prevented when the formation of A1 astrocytes is blocked. Finally, we show that A1 astrocytes are abundant in various human neurodegenerative diseases including Alzheimer's, Huntington's and Parkinson's disease, amyotrophic lateral sclerosis and multiple sclerosis. Taken together these findings help to explain why CNS neurons die after axotomy, strongly suggest that A1 astrocytes contribute to the death of neurons and oligodendrocytes in neurodegenerative disorders, and provide opportunities for the development of new treatments for these diseases.