

## GULF WAR ILLNESS

No Updates this Week.

## CHRONIC FATIGUE SYNDROME

[Poor sleep quality is associated with greater circulating pro-inflammatory cytokines and severity and frequency of chronic fatigue syndrome/myalgic encephalomyelitis \(CFS/ME\) symptoms in women.](#)

Milrad SF, Hall DL, Jutagir DR, Lattie EG, Ironson GH, Wohlgemuth W, Nunez MV, Garcia L, Czaja SJ, Perdomo DM, Fletcher MA, Klimas N, Antoni MH.

J Neuroimmunol. 2016 Dec 14. pii: S0165-5728(16)30449-0. doi: 10.1016/j.jneuroim.2016.12.008. [Epub ahead of print]

**OBJECTIVE:** Poor sleep quality has been linked to inflammatory processes and worse disease outcomes in the context of many chronic illnesses, but less is known in conditions such as chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). This study examines the relationships between sleep quality, pro-inflammatory cytokines, and CFS/ME symptoms.

**METHODS:** Sixty women diagnosed with CFS/ME were assessed using the Pittsburgh Sleep Quality Index (PSQI), Fatigue Symptom Inventory (FSI) and Center for Disease Control and Prevention (CDC)-based CFS/ME symptom questionnaires. Circulating plasma pro-inflammatory cytokine levels were measured by ELISA. Multiple regression analyses examined associations between sleep, cytokines and symptoms, controlling for age, education, and body mass index.

**RESULTS:** Poor sleep quality (PSQI global score) was associated with greater pro-inflammatory cytokine levels: interleukin-1 $\beta$  (IL-1 $\beta$ ) ( $\beta$ =0.258,  $p$ =0.043), IL-6 ( $\beta$ =0.281,  $p$ =0.033), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) ( $\beta$ =0.263,  $p$ =0.044). Worse sleep quality related to greater fatigue severity ( $\beta$ =0.395,  $p$ =0.003) and fatigue-related interference with daily activities ( $\beta$ =0.464,  $p$ <0.001), and more severe and frequent CDC-defined core CFS/ME symptoms ( $\beta$ =0.499,  $p$ <0.001, and  $\beta$ =0.556,  $p$ <0.001, respectively).

**CONCLUSIONS:** Results underscore the importance of managing sleep-related difficulties in this patient population. Further research is needed to identify the etiology of sleep disruptions in CFS/ME and mechanistic factors linking sleep quality to symptom severity and inflammatory processes.

[Herpesviruses dUTPases: A New Family of Pathogen-Associated Molecular Pattern \(PAMP\) Proteins with Implications for Human Disease.](#)

Williams MV, Cox B, Ariza ME.

Pathogens. 2016 Dec 28;6(1). pii: E2. doi: 10.3390/pathogens6010002. Review.

The human herpesviruses are ubiquitous viruses and have a prevalence of over 90% in the adult population. Following a primary infection they establish latency and can be reactivated over a person's lifetime. While it is well accepted that human herpesviruses are implicated in numerous diseases ranging from dermatological and autoimmune disease to cancer, the role of lytic proteins in the pathophysiology of herpesvirus-associated diseases remains largely understudied. Only recently have we begun to appreciate the importance of lytic proteins produced during reactivation of the virus, in particular the deoxyuridine triphosphate nucleotidohydrolases (dUTPase), as key modulators of the host innate and adaptive immune responses. In this review, we provide evidence from animal and human studies of the Epstein-Barr virus as a prototype, supporting the notion that herpesviruses dUTPases are a family of proteins with unique immunoregulatory functions that can alter the inflammatory microenvironment and thus exacerbate the immune pathology of herpesvirus-related diseases including myalgic encephalomyelitis/chronic fatigue syndrome, autoimmune diseases, and cancer.

## HEADACHE MIGRAINE

### [Structural Gray Matter Alterations in Chronic Migraine: Implications for a Progressive Disease?](#)

Neeb L, Bastian K, Villringer K, Israel H, Reuter U, Fiebach JB.

Headache. 2016 Dec 28. doi: 10.1111/head.13012. [Epub ahead of print]

**OBJECTIVE:** To identify possible gray matter alterations in patients with chronic migraine using voxel-based morphometry (VBM).

**BACKGROUND:** VBM studies demonstrate structural alterations of gray matter (GM) in episodic migraine (EM) patients. Some of these alterations correlate with disease duration and headache frequency. We assessed GM alterations in chronic migraine (CM) and EM to evaluate the concept of migraine as a progressive disorder of the brain.

**METHODS:** Individually age and sex-matched subjects with CM or EM (both without aura) and healthy controls (n = 21 per group) underwent magnetic resonance imaging-based VBM.

**RESULTS:** We found an increase of GM volume (GMV) in amygdala and putamen, in CM compared to controls. GMV of EM compared to controls did not differ statistically significantly. Headache frequency in all migraineurs (EM and CM) correlated positively with GMV in putamen, frontal and temporal gyrus and negatively in left cuneus.

**CONCLUSION:** CM is associated with structural changes in brain regions involved in pain processing but also in affective and cognitive aspects of pain. Some GM alterations are correlated with headache frequency assessed in EM and CM. The findings support the assumption that chronic pain alters brain plasticity. GMV increase may reflect a remodeling of the central nervous system due to repetitive headache attacks leading to chronic sensitization and a continuous ictal-like state of the brain in chronic migraineurs.

### [Transcranial Magnetic Stimulation: Basic Principles and Clinical Applications in Migraine.](#)

Barker AT, Shields K.

Headache. 2016 Dec 28. doi: 10.1111/head.13002. [Epub ahead of print]

**PURPOSE:** Transcranial magnetic stimulation (TMS) is a neurophysiological technique with a long established pedigree of safety, tolerability, and efficacy. Initially TMS was used to study the function of the cerebral cortex, but it has now become a treatment for migraine, one of the most common and debilitating neurological conditions. In this review we discuss the scientific background and development of the technique. We explore its application for the treatment of migraine and ponder the possible mechanisms of action in this most common neurological condition.

**OVERVIEW:** The generation of brief magnetic pulses by a suitable coil can induce electrical fields in the body. When applied to the cerebral cortex, currents are painlessly induced in cortical neurons. These currents can lead to neuronal depolarization and may influence cortical excitability by means that are as yet not fully understood. This ability to modulate cortical excitability has been exploited as a treatment for migraine with aura. Aura is implicated in the pathophysiology of migraine. Experimental studies have shown that transcranial magnetic pulses can block waves of cortical spreading depression - the experimental equivalent of migrainous aura.

**DISCUSSION:** Migraine is a debilitating condition characterized by headache, nausea, and sensory hypersensitivity. It may affect up to 15% of the population, yet current drug treatments are often poorly tolerated. Clinical studies have shown that TMS is an effective treatment for migraine. In addition, it has the added advantages of being safe and well tolerated by patients.

## HEADACHE MIGRAINE (Continued)

### [Intranasal Pathology in the Migraine Surgery Population: Incidence, Patterns, and Predictors of Surgical Success.](#)

Lee M, Erickson C, Guyuron B.

Plast Reconstr Surg. 2017 Jan;139(1):184-189. doi: 10.1097/PRS.0000000000002888.

**BACKGROUND:** The purpose of this study was to identify patterns of nasal pathology in patients with rhinogenic migraine headaches (site III).

**METHODS:** A retrospective review was performed on patients with rhinogenic migraine headaches. Demographics, pre- and post-migraine surgery symptoms, and pathology seen on preoperative computed tomographic scans were reviewed.

**RESULTS:** Twenty percent of 98 patients had preoperative sinus disease. The following abnormalities were seen on computed tomographic scan: septal deviation, 75 (77 percent); septal spur, 33 (34 percent); middle concha bullosa, 48 (49 percent); sinus pathology, 20 (20 percent); and intranasal contact points, 62 (62 percent). A higher incidence of clinical sinusitis (20 percent migraine versus 5 to 15 percent in the general population) was also seen. Septoplasty was performed in 89 percent of patients, and conservative turbinectomy was performed in 60 percent of patients. Patients who failed surgery (<50 percent reduction in migraine headache index) had a significantly higher incidence of contact points (80 percent versus 56 percent;  $p = 0.034$ ) than successful migraine patients. The surgery success group also had a higher incidence of preoperative middle concha bullosa compared with the failure group (71 percent versus 48 percent;  $p = 0.035$ ).

**CONCLUSIONS:** This is the first cohort study to identify the incidence and pattern of nasal pathology in migraine III patients. It is likely that the failure to achieve more successful outcomes in this patient population was the consequence of conservative nasal management and residual contact points because of concern for the development of nasal dryness. More frequent middle turbinate surgery may result in better clinical outcomes in this group of patients.

## CHRONIC PAIN

### [Structural characterization of nonactive site, TrkA-selective kinase inhibitors.](#)

Su HP, Rickert K, Burlein C, Narayan K, Bukhtiyarova M, Hurzy DM, Stump CA, Zhang X, Reid J, Krasowska-Zoladek A, Tummala S, Shipman JM, Kornienko M, Lemaire PA, Krosky D, Heller A, Achab A, Chamberlin C, Saradjian P, Sauvagnat B, Yang X, Ziebell MR, Nickbarg E, Sanders JM, Bilodeau MT, Carroll SS, Lumb KJ, Soisson SM, Henze DA, Cooke AJ.

Proc Natl Acad Sci U S A. 2016 Dec 30. pii: 201611577. doi: 10.1073/pnas.1611577114. [Epub ahead of print]

Current therapies for **chronic pain** can have insufficient efficacy and lead to side effects, necessitating research of novel targets against **pain**. Although originally identified as an oncogene, Tropomyosin-related kinase A (TrkA) is linked to **pain** and elevated levels of NGF (the ligand for TrkA) are associated with **chronic pain**. Antibodies that block TrkA interaction with its ligand, NGF, are in clinical trials for **pain** relief. Here, we describe the identification of TrkA-specific inhibitors and the structural basis for their selectivity over other Trk family kinases. The X-ray structures reveal a binding site outside the kinase active site that uses residues from the kinase domain and the juxtamembrane region. Three modes of binding with the juxtamembrane region are characterized through a series of ligand-bound complexes. The structures indicate a critical pharmacophore on the compounds that leads to the distinct binding modes. The mode of interaction can allow TrkA selectivity over TrkB and TrkC or promiscuous, pan-Trk inhibition. This finding highlights the difficulty in characterizing the structure-activity relationship of a chemical series in the absence of structural information because of substantial differences in the interacting residues. These structures illustrate the flexibility of binding to sequences outside of-but adjacent to-the kinase domain of TrkA. This knowledge allows development of compounds with specificity for TrkA or the family of Trk proteins.

## CHRONIC PAIN (Continued)

### [Cathepsin S in the spinal microglia contributes to remifentanil-induced hyperalgesia in rats.](#)

Ye L, Xiao L, Yang SY, Duan JJ, Chen Y, Cui Y, Chen Y.

Neuroscience. 2016 Dec 27. pii: S0306-4522(16)30730-8. doi: 10.1016/j.neuroscience.2016.12.030. [Epub ahead of print]

Cysteine protease Cathepsin S (CatS) expressed by spinal microglia has been shown to play a critical role in nerve injury and inflammation-induced **chronic pain**. However, whether microglial CatS contributes to remifentanil-induced acute hyperalgesia remains unstudied. In the present study, intravenous remifentanil infusion induced significant increase in the expression of premature and mature form of CatS in the activated microglia in the spinal cord. Spinal delivery of irreversible CatS inhibitor LHVS reduced hyperalgesia, attenuated activation of spinal microglia and blocked phosphorylation of NMDA receptor NR1 subunit induced by remifentanil. Furthermore, inhibition of microglia by minocycline effectively suppressed remifentanil-induced hyperalgesia, as well as CatS upregulation. In addition, remifentanil infusion also induced an increase in reactive oxygen species (ROS) levels in spinal neurons. Systemic administration of ROS scavenger PBN was sufficient to suppress remifentanil-induced painful hypersensitivity. Removal of ROS by PBN prevented upregulation of mature CatS in spinal microglia. However, increased protein level of premature form of CatS was not affected by PBN. Altogether, our findings demonstrate that neuronal ROS promote maturation of microglial CatS which facilitates activation of NMDA in the spinal dorsal horn. Therefore, such mechanism is involved in neuron-microglia positive feedback and contributes to remifentanil-induced hyperalgesia.

### [Spinal activation of alpha7-nicotinic acetylcholine receptor attenuates posttraumatic stress disorder-related chronic pain via suppression of glial activation.](#)

Sun R, Zhang W, Bo J, Zhang Z, Lei Y, Huo W, Liu Y, Ma Z, Gu X.

Neuroscience. 2016 Dec 27. pii: S0306-4522(16)30729-1. doi: 10.1016/j.neuroscience.2016.12.029. [Epub ahead of print]

The high prevalence of **chronic pain** in posttraumatic stress disorder (PTSD) individuals has been widely reported by clinical studies, which emphasized an urgent need to uncover the underlying mechanisms and identify potential therapeutic targets. Recent studies suggested that targeting activated glia and their pro-inflammatory products may provide a novel and effective therapy for the stress-related **pain**. In this study, we investigated whether activation of alpha-7 nicotinic acetylcholine receptor ( $\alpha 7$  nAChR), a novel anti-inflammatory target, could attenuate PTSD-related **chronic pain**. The experiments were conducted in a rat model of single prolonged stress (SPS), an established model of PTSD-**pain** comorbidity. We found that SPS exposure produced persistent mechanical allodynia. Immunohistochemical and enzyme-linked immuno sorbent assay analysis showed that SPS also induced elevated activation of glia cells (including microglia and astrocytes) and accumulation of pro-inflammatory cytokines in spinal cord. In another experiment, we found that intrathecal injection of PHA-543613, a selective  $\alpha 7$  nAChR agonist, attenuated the SPS-evoked allodynia in a dose dependent manner. However, this anti-hyperalgesic effect was blocked by pretreatment with methyllycaconitine (MLA), a selective  $\alpha 7$  nAChR antagonist. Further analyses showed that PHA-543613 suppressed SPS-induced spinal glial activation and SPS-elevated spinal pro-inflammatory cytokines, and these were abolished by MLA. Taken together, the present study showed that spinal activation of  $\alpha 7$  nAChR by PHA-543613 attenuated mechanical allodynia induced by PTSD-like stress, and the suppression of spinal glial activation may underlie this anti-hyperalgesic effect. Our study demonstrated the therapeutic potential of targeting  $\alpha 7$  nAChR in the treatment of PTSD-related **chronic pain**.

## CHRONIC PAIN (Continued)

### [A single-blind, randomized control trial of adjunctive transcranial direct current stimulation \(tDCS\) for chronic pain among patients receiving specialized, inpatient multimodal pain management.](#)

Janice Jimenez-Torres G, Weinstein BL, Walker CR, Christopher Fowler J, Ashford P, Borckardt JJ, Madan A.

Contemp Clin Trials. 2016 Dec 27. pii: S1551-7144(16)30215-4. doi: 10.1016/j.cct.2016.12.024. [Epub ahead of print]

**BACKGROUND:** Available treatments for chronic pain (CP) are modestly effective or associated with iatrogenic harm. Transcranial direct current stimulation (tDCS) is a minimally-invasive brain stimulation technique that may be an effective, adjunctive treatment to non-opioid therapies. In this randomized control trial (RCT), we compare adjunctive active versus sham tDCS among patients in a multimodal inpatient pain management program. The primary objectives of the RCT are to improve pain tolerance and subjective pain experience.

**METHODS AND DESIGN:** Patients admitted to the Pain Management Program at The Menninger Clinic in Houston, Texas are eligible for this trial. Thirty-six participants will be randomized (1:1) into a single-blind, 2x4 (groupxtime) controlled trial. A battery-powered direct and constant current stimulator (Soterix Medical Inc., 2014) delivers anodal stimulation over the left dorsolateral prefrontal cortex (DLPFC) and cathodal stimulation over the right DLPFC. Active tDCS is applied by supplying a 2mA current for 20min/session over 10 sessions. Participants complete self-report and performance-based assessments on a weekly basis just prior to brain stimulation. Self-report assessments are collected via Chronic Pain Tracker version 3.6, an iPad interfaced application. The performance-based pain tolerance task is completed through the cold presser task.

**DISCUSSION:** Interventions with cross-symptomatic therapeutic potential are absolutely essential in the context of CP, in which psychiatric comorbidity is the norm. Modalities that can be used in tandem with evidence-based, non-opioid therapies have the potential to have a synergistic effect, resulting in increased effectiveness of what have been modestly effective treatments to date.

### [Psychosocial Influences on Exercise-Induced Hypoalgesia.](#)

Brellenthin AG, Crombie KM, Cook DB, Sehgal N, Koltyn KF.

Pain Med. 2016 Dec 29. pii: pnw275. doi: 10.1093/pm/pnw275. [Epub ahead of print]

**OBJECTIVE:** The purpose of this study was to examine psychosocial influences on exercise-induced hypoalgesia (EIH).

**DESIGN:** Randomized controlled trial.

**SETTING:** Clinical research unit in a hospital.

**SUBJECTS:** Fifty-eight healthy men and women (mean age = 21 ± 3 years) participated in this study.

**METHODS:** Participants were first asked to complete a series of baseline demographic and psychological questionnaires including the **Pain** Catastrophizing Scale, the Fear of **Pain** Questionnaire, and the Family Environment Scale. Following this, they were familiarized with both temporal summation of heat **pain** and pressure **pain** testing protocols. During their next session, participants completed the Profile of Mood States, rated the intensity of heat pulses, and indicated their pressure **pain** thresholds and ratings before and after three minutes of submaximal, isometric exercise. Situational catastrophizing was assessed at the end of the experimental session.

**RESULTS:** Results indicated that experimental **pain** sensitivity was significantly reduced after exercise ( $P < 0.05$ ). Men and women did not differ on any of the measured psychosocial variables ( $P > 0.05$ ). Positive family environments predicted attenuated **pain** sensitivity and greater EIH, whereas negative and **chronic pain**-present family environments predicted worse **pain** and EIH outcomes. Situational catastrophizing and negative mood state also predicted worse **pain** and EIH outcomes and were additionally associated with increased ratings of perceived exertion and muscle **pain** during exercise.

**CONCLUSIONS:** This study provides preliminary evidence that psychosocial variables, such as the family environment and mood states, can affect both **pain** sensitivity and the ability to modulate **pain** through exercise-induced hypoalgesia.

**CHRONIC PAIN (Continued)**[Enhancing Risk Assessment in Patients Receiving Chronic Opioid Analgesic Therapy Using Natural Language Processing.](#)

Haller IV, Renier CM, Juusola M, Hitz P, Steffen W, Asmus MJ, Craig T, Mardekian J, Masters ET, Elliott TE.

Pain Med. 2016 Dec 29. pii: pnw283. doi: 10.1093/pm/pnw283. [Epub ahead of print]

**OBJECTIVES:** Clinical guidelines for the use of opioids in chronic noncancer pain recommend assessing risk for aberrant drug-related behaviors prior to initiating opioid therapy. Despite recent dramatic increases in prescription opioid misuse and abuse, use of screening tools by clinicians continues to be underutilized. This research evaluated natural language processing (NLP) together with other data extraction techniques for risk assessment of patients considered for opioid therapy as a means of predicting opioid abuse.

**DESIGN:** Using a retrospective cohort of 3,668 chronic noncancer pain patients with at least one opioid agreement between January 1, 2007, and December 31, 2012, we examined the availability of electronic health record structured and unstructured data to populate the Opioid Risk Tool (ORT) and other selected outcomes. Clinician-documented opioid agreement violations in the clinical notes were determined using NLP techniques followed by manual review of the notes.

**RESULTS:** Confirmed through manual review, the NLP algorithm had 96.1% sensitivity, 92.8% specificity, and 92.6% positive predictive value in identifying opioid agreement violation. At the time of most recent opioid agreement, automated ORT identified 42.8% of patients as at low risk, 28.2% as at moderate risk, and 29.0% as at high risk for opioid abuse. During a year following the agreement, 22.5% of patients had opioid agreement violations. Patients classified as high risk were three times more likely to violate opioid agreements compared with those with low/moderate risk.

**CONCLUSION:** Our findings suggest that NLP techniques have potential utility to support clinicians in screening chronic noncancer pain patients considered for long-term opioid therapy.

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