GULF WAR ILLNESS

Gender Differences in Gulf War Illness: A Re-analysis of Data From the CDC Air Force Study Using CDC and Modified Kansas Case Definitions.

Heboyan V[1], Krengel MH, Sullivan K, Iobst S, Klimas N, Wilson C, Coughlin SS.

J Occup Environ Med. **2019 May 8**. doi: 10.1097/JOM.0000000000001620. PMID: 31090678. [Epub ahead of print]

OBJECTIVE: Estimate and compare the prevalence of Gulf War Illness (GWI) in male and female Gulf War veterans using CDC and modified Kansas case definitions.

METHODS: Data from the landmark CDC Air Force Study of GW Air Force veterans is used.

RESULTS: Nearly half of the deployed veterans met the GWI CDC case definition compared with 14% of non-deployed veterans. Only 29% met the definition using the modified Kansas criteria compared with 8% of non-deployed veterans. Deployed veterans and female veterans exhibited significantly higher GWI risk. Female GW veterans had higher rates of severe and mild-to-moderate cases of GWI.

CONCLUSION: Results suggest increased GWI rates based on CDC and modified Kansas criteria among deployed and female veterans. Further research is needed to examine the chronic health outcomes of female GW veterans independently.

CHRONIC FATIGUE SYNDROME

A nanoelectronics-blood-based diagnostic biomarker for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Esfandyarpour R[1], Kashi A[2], Nemat-Gorgani M[2,3], Wilhelmy J[3], Davis RW[4,3].

Proc Natl Acad Sci U S A. **2019 May 21**;116(21):10250-10257. doi: 10.1073/pnas.1901274116. PMCID: PMC6535016. PMID: 31036648. Epub 2019 Apr 29.

There is not currently a well-established, if any, biological test to diagnose myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). The molecular aberrations observed in numerous studies of ME/CFS blood cells offer the opportunity to develop a diagnostic assay from blood samples. Here we developed a nanoelectronics assay designed as an ultrasensitive assay capable of directly measuring biomolecular interactions in real time, at low cost, and in a multiplex format. To pursue the goal of developing a reliable biomarker for ME/CFS and to demonstrate the utility of our platform for point-of-care diagnostics, we validated the array by testing patients with moderate to severe ME/CFS patients and healthy controls. The ME/CFS samples' response to the hyperosmotic stressor observed as a unique characteristic of the impedance pattern and dramatically different from the response observed among the control samples. We believe the observed robust impedance modulation difference of the samples in response to hyperosmotic stress can potentially provide us with a unique indicator of ME/CFS. Moreover, using supervised machine learning algorithms, we developed a classifier for ME/CFS patients capable of identifying new patients, required for a robust diagnostic tool.

CHRONIC FATIGUE SYNDROME (Continued)

A possible role for mitochondrial-derived peptides humanin and MOTS-c in patients with Q fever fatigue syndrome and chronic fatigue syndrome.

Raijmakers RPH[1,2], Jansen AFM[3,4], Keijmel SP[3,4], Ter Horst R[4], Roerink ME[4], Novakovic B[5,6], Joosten LAB[3,4,7], van der Meer JWM[3,4], Netea MG[3,4,7], Bleeker-Rovers CP[3,4,7].

J Transl Med. **2019 May 14**;17(1):157. doi: 10.1186/s12967-019-1906-3. PMID: 31088495.

BACKGROUND: Q fever fatigue syndrome (QFS) is a well-documented state of prolonged fatigue following around 20% of acute Q fever infections. It has been hypothesized that low grade inflammation plays a role in its aetiology. In this study, we aimed to identify transcriptome profiles that could aid to better understand the pathophysiology of QFS.

METHODS: RNA of monocytes was collected from QFS patients (n = 10), chronic fatigue syndrome patients (CFS, n = 10), Q fever seropositive controls (n = 10), and healthy controls (n = 10) who were age- (± 5 years) and sex-matched. Transcriptome analysis was performed using RNA sequencing.

RESULTS: Mitochondrial-derived peptide (MDP)-coding genes MT-RNR2 (humanin) and MT-RNR1 (MOTS-c) were differentially expressed when comparing QFS (- 4.8 log2-fold-change $P = 2.19 \times 10^{-9}$ and - 4.9 log2-fold-change $P = 4.69 \times 10^{-8}$), CFS (- 5.2 log2-fold-change, $P = 3.49 \times 10^{-11}$ - 4.4 log2-fold-change, $P = 2.71 \times 10^{-9}$), and Q fever seropositive control (- 3.7 log2-fold-change $P = 1.78 \times 10^{-6}$ and - 3.2 log2-fold-change $P = 1.12 \times 10^{-5}$) groups with healthy controls, resulting in a decreased median production of humanin in QFS patients (371 pg/mL; Interquartile range, IQR, 325-384), CFS patients (364 pg/mL; IQR 316-387), and asymptomatic Q fever seropositive controls (354 pg/mL; 292-393).

CONCLUSIONS: Expression of MDP-coding genes MT-RNR1 (MOTS-c) and MT-RNR2 (humanin) is decreased in CFS, QFS, and, to a lesser extent, in Q fever seropositive controls, resulting in a decreased production of humanin. These novel peptides might indeed be important in the pathophysiology of both QFS and CFS.

HEADACHE and MIGRAINE

Long-Term Safety and Tolerability of OnabotulinumtoxinA Treatment in Patients with Chronic Migraine: Results of the COMPEL Study.

Winner PK[1], Blumenfeld AM[2], Eross EJ[3], Orejudos AC [4], Mirjah DL[4,5], Adams AM[4], Brin MF[4,6].

Drug Saf. **2019 May 17**. doi: 10.1007/s40264-019-00824-3. PMID: 31102144. [Epub ahead of print]

INTRODUCTION: OnabotulinumtoxinA is approved in the USA for the prevention of headache in adults with chronic migraine, a debilitating neurologic disease characterized by headaches occurring on ≥ 15 days per month for > 3 months and including migraine features on ≥ 8 days per month.

OBJECTIVE: The COMPEL Study (NCT01516892), a 108-week, multi-center, open-label study, evaluated the long-term efficacy and safety of onabotulinumtoxinA in adults with chronic migraine. The objective of this subanalysis was to examine the safety and tolerability of onabotulinumtoxinA after each of nine treatment cycles.

METHODS: OnabotulinumtoxinA 155 U was administered every 12 weeks. Safety and tolerability, overall and by treatment cycle, were assessed. Treatment-emergent adverse events reported between successive treatments were attributed to the preceding treatment. The safety population received one or more doses of onabotulinumtoxinA. The primary efficacy outcome was the reduction in headache days at week 108 compared with baseline.

RESULTS: Of 716 patients enrolled, 373 patients (52.1%) completed the study and 343 (47.9%) withdrew; 481 patients (67.2%) received 60 weeks of treatment and 402 (56.1%) received 108 weeks of treatment. In total, 436 (60.9%) patients reported treatment-emergent adverse events; most were mild/moderate in severity. Thirty-two patients (4.5%) discontinued the study after experiencing treatment-emergent adverse events. The incidence of treatment-emergent adverse events typically decreased with repeated onabotulinumtoxinA treatment: first cycle, 24.2%; fourth cycle, 18.4%; ninth cycle, 12.2%. Neck pain (2.7%), eyelid ptosis (1.8%), musculoskeletal stiffness (1.4%), injection-site pain (1.3%), and headache (1.3%) were the most common treatment-emergent adverse events after the first cycle. Seventy-five patients (10.5%) reported serious treatment-emergent adverse events, 13 (1.8%) withdrew. Treatment-related adverse events were reported by 131 patients (18.3%), one was considered serious. OnabotulinumtoxinA significantly reduced headache day frequency by 10.7 (6.4) days per 28-day period ($p < 0.0001$) at week 108.

CONCLUSIONS: OnabotulinumtoxinA treatment was well tolerated over 108 weeks; no new safety signals were identified. The overall incidence of treatment-emergent adverse events and the most common individual events decreased with repeated onabotulinumtoxinA administration.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov; NCT01516892.

HEADACHE and MIGRAINE (Continued)

Multiple cranial nerve blocks for the transitional treatment of chronic headaches.

Miller S[1], Lagrata S[1], Matharu M[1].

Cephalalgia. **2019 May 13**:333102419848121. doi: 10.1177/0333102419848121. PMID: 31084198. [Epub ahead of print]

BACKGROUND: Multiple cranial nerve blocks of the greater and lesser occipital, supraorbital, supratrochlear and auriculotemporal nerves are widely used in the treatment of primary headaches. We present efficacy and safety data for these procedures.

METHODS: In an uncontrolled open-label prospective study, 119 patients with chronic cluster headache, chronic migraine, short lasting unilateral neuralgiform attack disorders, new daily persistent headaches, hemicrania continua and chronic paroxysmal hemicrania were examined. All had failed to respond to greater occipital nerve blocks. Response was defined as a 50% reduction in either daily attack frequency or moderate-to-severe headache days after 2 weeks.

RESULTS: The response rate of the whole cohort was 55.4%: Chronic cluster headache, 69.2%; chronic migraine, 49.0%; short lasting unilateral neuralgiform attack disorders, 56.3%; new daily persistent headache, 10.0%; hemicrania continua, 83.3%; and chronic paroxysmal hemicrania, 25.0%. Time to benefit was between 0.50 and 33.58 hours. Benefit was maintained for up to 4 weeks in over half of responders in all groups except chronic migraine and paroxysmal hemicrania. Only minor adverse events were recorded.

CONCLUSION: Multiple cranial nerve blocks may provide an efficacious, well tolerated and reproducible transitional treatment for chronic headache disorders when greater occipital nerve blocks have been unsuccessful.

Investigating macrophage-mediated inflammation in migraine using ultrasmall superparamagnetic iron oxide-enhanced 3T magnetic resonance imaging.

Khan S[1], Mohammad Amin F[1], Petrine Fliedner F[2], Emil Christensen C[1], Tolnai D[3], Younis S[1], Christine Rye Olinger A[1], Birgens H[4], Daldrup-Link H[5], Kjær A[2], Larsson HBW[6], Lindberg U[6], Ashina M[1].

Cephalalgia. **2019 May 19**:333102419848122. doi: 10.1177/0333102419848122. PMID: 31104505. [Epub ahead of print]

BACKGROUND: Initiating mechanisms of migraine headache remain poorly understood and a biomarker of migraine does not exist. Inflammation pertaining to the wall of cerebral arteries and brain parenchyma has been suggested to play a role in migraine pathophysiology.

OBJECTIVE: We conducted the first experimental human study to investigate macrophage-mediated inflammation as a possible biomarker of migraine.

METHODS: Using ultrasmall superparamagnetic iron oxide (USPIO)-enhanced 3T magnetic resonance imaging (MRI), we investigated the presence of macrophages in cerebral artery walls and in brain parenchyma of patients with migraine without aura. We used the phosphodiesterase-3-inhibitor cilostazol as an experimental migraine trigger, and investigated both patients who received sumatriptan treatment, and patients who did not. To validate our use of USPIO-enhanced MRI, we included a preclinical mouse model with subcutaneous capsaicin injection in the trigeminal V1 area. The study is registered at ClinicalTrials.gov with the identifier NCT02549898.

RESULTS: A total of 28 female patients with migraine without aura underwent a baseline MRI scan, ingested cilostazol, developed a migraine-like attack, and underwent an USPIO-enhanced MRI scan > 24 hours after intravenous administration of USPIO. Twelve patients treated their attack with 6 mg s.c. sumatriptan, while the remaining 16 patients received no migraine-specific rescue medication. The preclinical model confirmed that USPIO-enhanced MRI detects macrophage-mediated inflammation. In patients, however, migraine attacks were not associated with increased USPIO signal on the pain side of the head compared to the non-pain side.

CONCLUSION: Our findings suggest that migraine without aura is not associated with macrophage-mediated inflammation specific to the head pain side.

CHRONIC PAIN

Ketamine Infusions for Chronic Pain: A Systematic Review and Meta-analysis of Randomized Controlled Trials.

Orhurhu V[1], Orhurhu MS[2], Bhatia A[3], Cohen SP[4,5].

Anesth Analg. **2019 May 9**. doi: 10.1213/ANE.0000000000004185. PMID: 31082965. [Epub ahead of print]

BACKGROUND: IV ketamine is widely used to treat patients with chronic pain, yet the long-term impact remains uncertain. We synthesized evidence from randomized control trials to investigate the effectiveness of IV ketamine infusions for pain relief in chronic conditions and to determine whether any pain classifications or treatment regimens are associated with greater benefit.

METHODS: We searched Medline, Embase, and Google Scholar, as well as the clinicaltrials.gov website from inception through December 16, 2017 for randomized control trials comparing IV ketamine to placebo infusions for chronic pain that reported outcomes for ≥48 hours after the intervention. Three authors independently screened the studies, pooled the data, and appraised risk of bias. Random-effects model was used to calculate weighted mean differences for pain scores and secondary outcomes. Our primary outcome was the lowest recorded pain score ≥48 hours after cessation of treatment. Secondary outcomes included responder rate and adverse effects.

RESULTS: Among 696 studies assessed for eligibility, 7 met inclusion criteria. All studies except one were at high risk of bias. These studies randomly assigned 211 patients with neuropathic (n = 2), mixed (n = 2), and nonneuropathic (nociplastic or nociceptive) (n = 3) pain. Three studies reported significant analgesic benefit favoring ketamine, with the meta-analysis revealing a small effect up to 2 weeks after the infusion (mean difference in pain scores, -1.83 points on a 0-10 numerical rating scale; 95% CI, -2.35 to -1.31 points; P < .0001). In the 3 studies that reported responder rates, the proportion with a positive outcome was greater in the ketamine than in the placebo group (51.3% vs 19.4%; relative risk, 2.43; 95% CI, 1.10-5.40; P = .029; I = 0.0%). No differences were noted based on pain classification or condition. Compared to low-dose ketamine studies and investigations that evaluated non-complex regional pain syndrome conditions, a small but nonsignificant greater reduction in pain scores was found among studies that either utilized high-dose ketamine therapy (P = .213) or enrolled complex regional pain syndrome patients (P = .079).

CONCLUSIONS: Evidence suggests that IV ketamine provides significant short-term analgesic benefit in patients with refractory chronic pain, with some evidence of a dose-response relationship. Larger, multicenter studies with longer follow-ups are needed to better select patients and determine the optimal treatment protocol.

IRRITABLE BOWEL SYNDROME

Glutamatergic Signaling Along The Microbiota-Gut-Brain Axis.

Baj A[1], Moro E[2], Bistoletti M[3], Orlandi V[4], Crema F[5], Giaroni C[6].

Int J Mol Sci. **2019 Mar 25**;20(6). pii: E1482. doi: 10.3390/ijms20061482. PMID: 30934533.

A complex bidirectional communication system exists between the gastrointestinal tract and the brain. Initially termed the "gut-brain axis" it is now renamed the "microbiota-gut-brain axis" considering the pivotal role of gut microbiota in maintaining local and systemic homeostasis. Different cellular and molecular pathways act along this axis and strong attention is paid to neuroactive molecules (neurotransmitters, i.e., noradrenaline, dopamine, serotonin, gamma aminobutyric acid and glutamate and metabolites, i.e., tryptophan metabolites), sustaining a possible interkingdom communication system between eukaryota and prokaryota. This review provides a description of the most up-to-date evidence on glutamate as a neurotransmitter/neuromodulator in this bidirectional communication axis. Modulation of glutamatergic receptor activity along the microbiota-gut-brain axis may influence gut (i.e., taste, visceral sensitivity and motility) and brain functions (stress response, mood and behavior) and alterations of glutamatergic transmission may participate to the pathogenesis of local and brain disorders. In this latter context, we will focus on two major gut disorders, such as irritable bowel syndrome and inflammatory bowel disease, both characterized by psychiatric co-morbidity. Research in this area opens the possibility to target glutamatergic neurotransmission, either pharmacologically or by the use of probiotics producing neuroactive molecules, as a therapeutic approach for the treatment of gastrointestinal and related psychiatric disorders.

IRRITABLE BOWEL SYNDROME (Continued)

How can we develop better antispasmodics for irritable bowel syndrome?

Ranjbar S[1], Seyednejad SA[1], Nikfar S[1,2], Rahimi R[1,3], Abdollahi M[4,5].

Expert Opin Drug Discov. **2019 Mar 28**:1-14. doi: 10.1080/17460441.2019.1593369. PMID: 30920313. [Epub ahead of print]

Irritable bowel syndrome (IBS) is a prevalent gastrointestinal (GI) disease. Antispasmodics are a heterogeneous group of drugs that tackle IBS-associated altered bowel habit and abdominal pain. However, some studies have shown their failure to exhibit benefit over placebo. Considering the place of antispasmodics in managing key symptoms of IBS, there is a growing need for developing more efficacious and safe antispasmodics. Areas covered: The authors discuss the role of rational drug design (RDD) in developing new antispasmodics with desired features. Furthermore, they review the potential pharmacological targets and herbal medicines with spasmolytic activity. In addition, the authors present the recent findings concerning novel mechanisms involved in GI motility modulation as well as the potential antispasmodic role of drugs used in other conditions. Expert opinion: To develop better antispasmodics, it will be essential to gain a deeper insight into the underlying mechanisms involved in IBS-induced dysmotility and to uncover GI-specific receptors that regulating motility. New antispasmodics with GI-restricted and the multi-targeting features can be developed via implementation of RDD. Furthermore, the modification of current antispasmodics by formulation technologies might expedite the development of better antispasmodics. To conclude, the complex nature of IBS means that future successful drug discovery will require a multi-disciplinary approach.

OTHER RESEARCH OF INTEREST

A Preliminary Examination of the Effect of Cognitive Processing Therapy on Sleep Disturbance Among Veterans with Military Sexual Trauma-Related Posttraumatic Stress Disorder.

Holder N[1,2], Holliday R[3,4], Wiblin J[1,2], Surís A[1,2].

Traumatology (Tallahass Fla). **2019 Apr 11**;1. doi: 10.1037/trm0000196. PMID: 31275080.

Veterans who have experienced military sexual trauma (MST) report numerous psychosocial difficulties including sleep disturbance and posttraumatic stress disorder (PTSD). Cognitive Processing Therapy (CPT) has been shown to effectively reduce total PTSD symptoms among veterans with MST-related PTSD; however, sleep disturbance may persist after successful treatment. Sleep disturbance is associated with suicidal self-directed violence, substance use, and poorer physical health. Identification of if and when CPT can sufficiently address sleep disturbance may help to determine when adjunctive interventions may be indicated. The current study described the rate of sleep disturbance in a sample of veterans with MST-related PTSD before and after CPT. In an exploratory analysis, potential baseline predictors (i.e., sociodemographic, PTSD symptoms, trauma-related cognitions, depression, physical health) of change in sleep disturbance following CPT were assessed. A secondary analysis of 72 male and female veterans enrolled in a randomized clinical trial examining the efficacy of CPT for MST-related PTSD was conducted. Most veterans reported clinically significant sleep disturbance at baseline (100%) and post-treatment (89%). A significant relationship between clinically significant change in PTSD symptoms and resolution of sleep disturbance was not identified. Using hierarchical multiple linear regression, potential predictors of change in sleep severity following CPT were assessed; however, no significant predictors were identified in this exploratory analysis. These results are consistent with previous research describing high residual rates of sleep disturbance in veterans with PTSD, despite reductions in overall PTSD symptoms. Future research should focus on identifying effective augmentation strategies for CPT to specifically address sleep disturbance.

OTHER RESEARCH OF INTEREST (Continued)

Risk of Serious Infection in Patients Receiving Systemic Medications for the Treatment of Psoriasis.

Dommasch ED[1,2,3], Kim SC[2,3], Lee MP[3,4], Gagne JJ[2,3].

JAMA Dermatol. **2019 May 10**. doi: 10.1001/jamadermatol.2019.1121. PMCID: PMC6512303. PMID: 31075163. [Epub ahead of print]

Importance: There is a need for better understanding of the comparative safety of systemic medications used in the treatment of psoriasis.

Objective: To compare the risk of serious infection associated with biologic and nonbiologic systemic medications in patients with psoriasis.

Design, Setting, and Participants: An observational cohort study was conducted using medical and outpatient pharmacy claims from 2 large US health insurance claims databases from January 1, 2003, through September 30, 2015. We included patients with a diagnosis of psoriasis who were new users of systemic medications for psoriasis.

Exposures: Prescription claims for acitretin, adalimumab, apremilast, etanercept, infliximab, methotrexate, or ustekinumab.

Main Outcomes and Measures: The primary outcome was serious infection, defined by inpatient discharge diagnosis International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Cox proportional hazards regression was used to compare rates of serious infection for each exposure (acitretin, adalimumab, apremilast, etanercept, infliximab, and ustekinumab) with the referent group (methotrexate). We used pairwise 1:1 propensity score (PS) matching to adjust for potential confounders, which were assessed during a 180-day baseline period prior to study drug initiation. Results from the 2 databases were pooled via fixed-effects analysis.

Results: The databases included 31 595 patients in the Optum Clinformatics Data Mart and 76 112 patients in Truven MarketScan who were new users of acitretin, adalimumab, apremilast, etanercept, infliximab, methotrexate, and ustekinumab. Users of acitretin, apremilast, infliximab, and methotrexate were older and had higher baseline comorbidity scores than subcutaneous biologic users (adalimumab, etanercept, and ustekinumab). The pooled PS-matched analysis yielded a decreased rate of overall serious infection in users of apremilast (hazard ratio [HR], 0.50; 95% CI, 0.26-0.94), etanercept (HR, 0.75; 95% CI, 0.61-0.93), and ustekinumab (HR, 0.65; 95% CI, 0.47-0.89) compared with methotrexate. We did not find a different rate of overall serious infection among users of acitretin, adalimumab, and infliximab compared with methotrexate. Subanalysis by type of serious infection showed a significantly increased risk of cellulitis among users of acitretin compared with methotrexate (PS-adjusted HR, 1.76; 95% CI, 1.11-2.80).

Conclusions and Relevance: Among patients with psoriasis treated with systemic medications in 2 large US claims databases, new users of apremilast, etanercept, and ustekinumab had a decreased rate of serious infection compared with methotrexate.

Interleukin-1-related activity and hypocretin-1 in cerebrospinal fluid contribute to fatigue in primary Sjögren's syndrome.

Bårdsen K[1,2], Brede C[2,3], Kvivik I[1], Kvaløy JT[1,4], Jonsdottir K[1], Tjensvoll AB[5], Ruoff P[6], Omdal R[7,8].

J Neuroinflammation. **2019 May 17**;16(1):102. doi: 10.1186/s12974-019-1502-8. PMID: 31101054.

BACKGROUND: Fatigue is a common and sometimes debilitating phenomenon in primary Sjögren's syndrome (pSS) and other chronic inflammatory diseases. We aimed to investigate how IL-1 β-related molecules and the neuropeptide hypocretin-1 (Hcrt1), a regulator of wakefulness, influence fatigue.

METHODS: Hcrt1 was measured by radioimmunoassay (RIA) in cerebrospinal fluid (CSF) from 49 patients with pSS. Interleukin-1 receptor antagonist (IL-1Ra), IL-1 receptor type 2 (IL-1RII), IL-6, and S100B protein were measured by enzyme-linked immunosorbent assay (ELISA). Fatigue was rated by the fatigue visual analog scale (fVAS).

RESULTS: Simple univariate regression and multiple regression analyses with fatigue as a dependent variable revealed that depression, pain, and the biochemical variable IL-1Ra had a significant association with fatigue. In PCA, two significant components were revealed. The first component (PC1) was dominated by variables related to IL-1β activity (IL-1Ra, IL-1RII, and S100B). PC2 showed a negative association between IL-6 and Hcrt1. fVAS was then introduced as an additional variable. This new model demonstrated that fatigue had a higher association with the IL-1β-related PC1 than to PC2. Additionally, a third component (PC3) became significant between low Hcrt1 concentrations and fVAS scores.

CONCLUSIONS: The main findings of this study indicate a functional network in which several IL-1β-related molecules in CSF influence fatigue in addition to the classical clinical factors of depression and pain. The neuropeptide Hcrt1 seems to participate in fatigue generation, but likely not through the IL-1 pathway.

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