GULF WAR ILLNESS

Anxiety, neuroinflammation, cholinergic and GABAergic abnormalities are early markers of Gulf War Illness in a mouse model of the disease.

Carreras I[1], Aytan N[2], Mellott T[3], Choi JK[4], Lehar M[5], Crabtree L[6], Leite-Morris K[7], Jenkins BG[8], Blusztajn JK[9], Dedeoglu A[10].

Brain Res. **2017 Dec 22**. pii: S0006-8993(17)30564-4. doi: 10.1016/j.brainres.2017.12.030. PMID: 29277710. [Epub ahead of print]

Gulf War Illness (GWI) is a chronic disease that affects the 1991 Gulf War (GW) veterans for which treatment is lacking. It has been hypothesized that drugs used to protect military personnel from chemical attacks and insects during the war: pyridostigmine bromide (PB),N, N-diethyl-m-toluamide (DEET), and permethrin (PER) together with stress may have contributed collectively and synergistically to generate GWI. There is a need to find markers of pathology to be used in pre-clinical trials. For this purpose we employed a previously validated mouse model of GWI evoked by daily exposure to PB (1.3 mg/kg), DEET (40 mg/kg), PER (0.13 mg/kg), and 5 minutes of restraint stress for 28 days to analyze behavior, brain pathology and neurochemical outcomes three months later. GWI-model mice were characterized by increased anxiety, decreased hippocampal levels of N-acetyl aspartate, GABA, the GABA-producing enzyme GAD-67 and microglial activation. We also observed that GWI model was sexually dimorphic on some measures: males had increased while females had decreased protein levels of the acetylcholine-synthesizing enzyme, choline acetyltransferase, in the septum and hippocampus and decreased levels of the receptor for brain-derived neurotrophic factor, TrkB140, in the hippocampus. Increased hippocampal levels of nerve growth factor were detected in males only. Together the data show behavioral and neuropathological abnormalities detected at 3 months post-exposure and that some of them are sexually dimorphic. Future preclinical studies for GWI may take advantage of this short latency model and should include both males and females as their response to treatment may differ.

CHRONIC FATIGUE SYNDROME

Cytokine signatures in chronic fatigue syndrome patients: a Case Control Study and the effect of anakinra treatment.

Roerink ME[1], Knoop H[2], Bronkhorst EM[3], Mouthaan HA[4], Hawinkels LJAC[5], Joosten LAB[6], van der Meer JWM[6].

J Transl Med. **2017 Dec 29**;15(1):267. doi: 10.1186/s12967-017-1371-9.

BACKGROUND: Cytokine disturbances have been suggested to be associated with the Chronic Fatigue Syndrome/Myalgic encephalomyelitis (CFS/ME) for decades.

METHODS: Fifty female CFS patients were included in a study on the effect of the interleukin-1-receptor antagonist anakinra or placebo during 4 weeks. EDTA plasma was collected from patients before and directly after treatment. At baseline, plasma samples were collected at the same time from 48 healthy, age-matched female neighborhood controls. A panel of 92 inflammatory markers was determined in parallel in 1 µL samples using a 'proximity extension assay' (PEA) based immunoassay. Since Transforming growth factor beta (TGF-β) and interleukin-1 receptor antagonist (IL-1Ra) were not included in this platform, these cytokines were measured with ELISA.

RESULTS: In CFS/ME patients, the 'normalized protein expression' value of IL-12p40 and CSF-1 was significantly higher (p value 0.0042 and 0.049, respectively). Furthermore, using LASSO regression, a combination of 47 markers yielded a prediction model with a corrected AUC of 0.73. After correction for multiple testing, anakinra had no effect on circulating cytokines. TGF-β did not differ between patients and controls.

CONCLUSIONS: In conclusion, this study demonstrated increased IL-12p40 and CSF-1 concentrations in CFS/ME patients in addition to a set of predictive biomarkers. There was no effect of anakinra on circulating cytokines other than IL-1Ra.

TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT02108210 , Registered April 2014.

CHRONIC FATIGUE SYNDROME (Continued)

A test of the adaptive network explanation of functional disorders using a machine learning analysis of symptoms.

Melidis C[1], Denham SL[2], Hyland ME[3].

Biosystems. **2017 Dec 23**. pii: S0303-2647(17)30243-5. doi: 10.1016/j.biosystems.2017.12.010. [Epub ahead of print]

The classification and etiology of functional disorders is controversial. Evidence supports both psychological and biological (disease) models that show, respectively, that functional disorders should be classified as one (bodily distress syndrome) and many (e.g., irritable bowel syndrome (IBS), fibromyalgia syndrome (FMS), and chronic fatigue syndrome (CFS)). Two network models (symptom network and adaptive network) can explain the specificity and covariation of symptomatology, but only the adaptive network model can explain the covariation of the somatic symptoms of functional disorders. The adaptive network model is based on the premise that a network of biological mechanisms has emergent properties and can exhibit adaptation. The purpose of this study was to test the predictions that symptom similarity increases with pathology and that network connection strengths vary with pathology, as this would be consistent with the notion that functional disorder pathology arises from network adaptation. We conducted a symptom internet survey followed by machine learning analysis. Participants were 1751 people reporting IBS, FMS or CFS diagnosis who completed a 61-item symptom questionnaire. Eleven symptom clusters were identified. Differences in symptom clusters between IBS, FMS and CFS groups decreased as overall symptom frequency increased. The strength of outgoing connections between clusters varied as a function of symptom frequency and single versus multiple diagnoses. The findings suggest that the pathology of functional disorders involves an increase in the activity and causal connections between several symptom causing mechanisms. The data provide support for the proposal that the body is capable of complex adaptation and that functional disorders result when rules that normally improve adaptation create maladaptive change.

HEADACHE and MIGRAINE

Long-term follow-up of patients with migrainous infarction.

Serrano F[1], Arauz A[2], Uribe R[2], Becerra LC[2], Mantilla K[2], Zermeño F[3].

Clin Neurol Neurosurg. **2017 Dec 9**;165:7-9. doi: 10.1016/j.clineuro.2017.12.008. [Epub ahead of print]\

Among patients with migrainous infarction, the long-term prognosis is unclear. This study aims to estimate the long-term risk of stroke recurrence and functional outcome in patients with migrainous infarction. In our study, 15 patients with migrainous infarction were followed for up to 7.5 years (12-240 months). For each patient, clinical and imaging data were reviewed. Disability after migrainous Infarction was assessed with modified Rankin Score. Mean age was 34.8 (± 11.1) years. At the end of the follow-up 80% of the patients had favorable prognosis, 47% recovered completely and no patient died or had stroke recurrence. Our series also confirmed a low frequency of the traditional risk factors and the reduction of migraine frequency after migrainous infarction. This study has clinical implications and public health relevance, since our case series confirms a low frequency, low recurrence rate, and good functional outcome for patients with migrainous infarction.

HEADACHE and MIGRAINE (Continued)

The enigma of site of action of migraine preventives: no effect of metoprolol on trigeminal pain processing in patients and healthy controls.

Hebestreit JM[1], May A[2].

J Headache Pain. **2017 Dec 19**;18(1):116. doi: 10.1186/s10194-017-0827-x.

BACKGROUND: Beta-blockers are a first choice migraine preventive medication. So far it is unknown how they exert their therapeutic effect in migraine. To this end we examined the neural effect of metoprolol on trigeminal pain processing in 19 migraine patients and 26 healthy controls. All participants underwent functional magnetic resonance imaging (fMRI) during trigeminal pain twice: Healthy subjects took part in a placebo-controlled, randomized and double-blind study, receiving a single dose of metoprolol and placebo. Patients were examined with a baseline scan before starting the preventive medication and 3 months later whilst treated with metoprolol.

RESULTS: Mean pain intensity ratings were not significantly altered under metoprolol. Functional imaging revealed no significant differences in nociceptive processing in both groups. Contrary to earlier findings from animal studies, we did not find an effect of metoprolol on the thalamus in either group. However, using a more liberal and exploratory threshold, hypothalamic activity was slightly increased under metoprolol in patients and migraineurs.

CONCLUSIONS: No significant effect of metoprolol on trigeminal pain processing was observed, suggesting a peripheral effect of metoprolol. Exploratory analyses revealed slightly enhanced hypothalamic activity under metoprolol in both groups. Given the emerging role of the hypothalamus in migraine attack generation, these data need further examination.

Migraine and subsequent chronic kidney disease risk: a nationwide population-based cohort study.

Weng SC[1,2], Wu CL[1,3,4,5], Kor CT[5], Chiu PF[3,4, 5], Wu MJ[1,2,4], Chang CC[3,4,5], Tarng DC[1,6,7].

BMJ Open. **2017 Dec 27**;7(12):e018483. doi: 10.1136/bmjopen-2017-018483.

OBJECTIVE: We compared the incidence and risk of chronic kidney disease (CKD) between subjects with new-onset migraine and matched controls without migraine in this large-scale retrospective cohort study.

DESIGN: Population-based cohort study.

SETTING: 8880 subjects with migraine and 503 070 subjects without migraine were enrolled between January 1, 2000 and December 31, 2013, all diagnosed to be without kidney disease. All the participants were registered in the National Health Insurance Research Database.

PARTICIPANTS: Finally, data from 7156 subjects with migraine and 7156 propensity-score-matched control subjects were analysed.

PRIMARY OUTCOME MEASURE: We used Cox proportional hazards regression to estimate adjusted HRs for incident CKD; subgroup analyses were performed to assess the interactive effects of migraine with demographics, comorbidities and long-term medications.

RESULTS: The incidence of CKD was higher in the migraine group than in the control group. The risk of developing CKD was significantly higher in subjects with migraine than without migraine (P=0.031). Subjects with migraine aged <65 years (age 40-64 (adjusted HR (aHR) 1.35; 95% CI 1.05 to 1.73); age <40 (aHR 1.55; 95% CI 1.02 to 2.36)), with ≥1 comorbid diseases (1-2 diseases (aHR 1.30; 95% CI 1.01 to 1.68); ≥3 diseases (aHR 1.45; 95% CI 1.01 to 2.07)), and not receiving anti-migraine agents (aHR 1.26; 95% CI 1.04 to 1.54) were at a higher risk of developing CKD compared with the control subjects. The interaction between migraine and comorbidities was not significant; age, male gender and long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) were independent risk factors for CKD in subjects with migraine.

CONCLUSION: Migraine may be an independent risk factor for CKD. Young subjects with migraine, and those with comorbid conditions or without medical control, are likely to be at higher risk for CKD. Ageing, male sex and NSAIDs tend to have an association with CKD in subjects with migraine.

CHRONIC PAIN

Classifying clinical notes with pain assessment using machine learning.

Fodeh SJ[1], Finch D[2], Bouayad L[2], Luther SL[2], Ling H[3], Kerns RD[4,5,6,7], Brandt C[7,8].

Med Biol Eng Comput. **2017 Dec 26**. doi: 10.1007/s11517-017-1772-1. [Epub ahead of print]

Pain is a significant public health problem, affecting millions of people in the USA. Evidence has highlighted that patients with chronic pain often suffer from deficits in pain care quality (PCQ) including pain assessment, treatment, and reassessment. Currently, there is no intelligent and reliable approach to identify PCQ indicators in electronic health records (EHR). Hereby, we used unstructured text narratives in the EHR to derive pain assessment in clinical notes for patients with chronic pain. Our dataset includes patients with documented pain intensity rating ratings > = 4 and initial musculoskeletal diagnoses (MSD) captured by (ICD-9-CM codes) in fiscal year 2011 and a minimal 1 year of follow-up (follow-up period is 3-yr maximum); with complete data on key demographic variables. A total of 92 patients with 1058 notes was used. First, we manually annotated qualifiers and descriptors of pain assessment using the annotation schema that we previously developed. Second, we developed a reliable classifier for indicators of pain assessment in clinical note. Based on our annotation schema, we found variations in documenting the subclasses of pain assessment. In positive notes, providers mostly documented assessment of pain site (67%) and intensity of pain (57%), followed by persistence (32%). In only 27% of positive notes, did providers document a presumed etiology for the pain complaint or diagnosis. Documentation of patients' reports of factors that aggravate pain was only present in 11% of positive notes. Random forest classifier achieved the best performance labeling clinical notes with pain assessment information, compared to other classifiers; 94, 95, 94, and 94% was observed in terms of accuracy, PPV, F1-score, and AUC, respectively. Despite the wide spectrum of research that utilizes machine learning in many clinical applications, none explored using these methods for pain assessment research. In addition, previous studies using large datasets to detect and analyze characteristics of patients with various types of pain have relied exclusively on billing and coded data as the main source of information. This study, in contrast, harnessed unstructured narrative text data from the EHR to detect pain assessment clinical notes. We developed a Random forest classifier to identify clinical notes with pain assessment information. Compared to other classifiers, ours achieved the best results in most of the reported metrics. Graphical abstract Framework for detecting pain assessment in clinical notes.

Diagnostic value of trunk flexion-extension testing in old chronic low back pain patients.

Kienbacher T[1], Fehrmann E[2], Habenicht R[2], Oeffel C[2], Kollmitzer J[2,3], Mair P[2,4], Ebenbichler G[2,5].

Eur Spine J. **2017 Feb**;26(2):510-517. doi: 10.1007/s00586-016-4758-z. Epub 2016 Sep 6.

PURPOSE: Dynamic trunk flexion-extension testing has been proven to objectively diagnose low back pain in persons under the age of 60 years but older persons have difficulty complying with standardized movement velocity.

METHODS: 190 patients and 71 matched healthy volunteers (18-90 years of age) performed modified testing by holding static positions at standing, half, and full trunk flexion.

RESULTS: Lumbar extensor muscle activity in isometric positions was significantly higher in patients with higher activity in the oldest (60-90 years) and the middle-aged (40-59 years) but not in the youngest (18-39 years) subgroups compared to normal. There were no differences in gross trunk range of motion, half flexion relaxation ratio, proprioception, muscle activity differences between positions, and fear-avoidance behavior. The diagnostic accuracy as expressed by the area under the curve was fair (0.74).

CONCLUSIONS: Lumbar extensor muscle activity demonstrated moderate to good diagnostic value in old patients.

OTHER RESEARCH OF INTEREST

Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial.

Daly EJ[1], Singh JB[2], Fedgchin M[1], Cooper K[3], Lim P[4], Shelton RC[5], Thase ME[6], Winokur A[7,8], Van Nueten L[9], Manji H[1], Drevets WC[1].

JAMA Psychiatry. **2017 Dec 27**. doi: 10.1001/jamapsychiatry.2017.3739. [Epub ahead of print]

Importance: Approximately one-third of patients with major depressive disorder (MDD) do not respond to available antidepressants.

Objective: To assess the efficacy, safety, and dose-response of intranasal esketamine hydrochloride in patients with treatment-resistant depression (TRD).

Design, Setting, and Participants: This phase 2, double-blind, doubly randomized, delayed-start, placebo-controlled study was conducted in multiple outpatient referral centers from January 28, 2014, to September 25, 2015. The study consisted of 4 phases: (1) screening, (2) double-blind treatment (days 1-15), composed of two 1-week periods, (3) optional open-label treatment (days 15-74), and (4) posttreatment follow-up (8 weeks). One hundred twenty-six adults with a DSM-IV-TR diagnosis of MDD and history of inadequate response to 2 or more antidepressants (ie, TRD) were screened, 67 were randomized, and 60 completed both double-blind periods. Intent-to-treat analysis was used in evaluation of the findings.

Interventions: In period 1, participants were randomized (3:1:1:1) to placebo (n = 33), esketamine 28 mg (n = 11), 56 mg (n = 11), or 84 mg (n = 12) twice weekly. In period 2, 28 placebo-treated participants with moderate-to-severe symptoms were rerandomized (1:1:1:1) to 1 of the 4 treatment arms; those with mild symptoms continued receiving placebo. Participants continued their existing antidepressant treatment during the study. During the open-label phase, dosing frequency was reduced from twice weekly to weekly, and then to every 2 weeks.

Main Outcomes and Measures: The primary efficacy end point was change from baseline to day 8 (each period) in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score.

Results: Sixty-seven participants (38 women, mean [SD] age, 44.7 [10.0] years) were included in the efficacy and safety analyses. Change (least squares mean [SE] difference vs placebo) in MADRS total score (both periods combined) in all 3 esketamine groups was superior to placebo (esketamine 28 mg: -4.2 [2.09], P = .02; 56 mg: -6.3 [2.07], P = .001; 84 mg: -9.0 [2.13], P < .001), with a significant ascending dose-response relationship (P < .001). Improvement in depressive symptoms appeared to be sustained (-7.2 [1.84]) despite reduced dosing frequency in the open-label phase. Three of 56 (5%) esketamine-treated participants during the double-blind phase vs none receiving placebo and 1 of 57 participants (2%) during the open-label phase had adverse events that led to study discontinuation (1 event each of syncope, headache, dissociative syndrome, and ectopic pregnancy).

Conclusions and Relevance: In this first clinical study to date of intranasal esketamine for TRD, antidepressant effect was rapid in onset and dose related. Response appeared to persist for more than 2 months with a lower dosing frequency. Results support further investigation in larger trials.

Trial Registration: clinicaltrials.gov identifier: NCT01998958.

OTHER RESEARCH OF INTEREST (Continued)

Cognitive-behavioural therapy for adult attention-deficit hyperactivity disorder: a proof of concept randomised controlled trial.

Dittner AJ[1], Hodsoll J[2], Rimes KA[3], Russell AJ[4, 5], Chalder T[6].

Acta Psychiatr Scand. **2017 Dec 27**. doi: 10.1111/acps.12836. [Epub ahead of print]

OBJECTIVE: To investigate efficacy, patient acceptability and feasibility of formulation-based cognitive-behavioural therapy (CBT) for adults with attention-deficit hyperactivity disorder (ADHD). NICE guidelines for adult ADHD recommend further research into psychological treatments.

METHOD: Sixty participants with adult ADHD were randomly allocated to treatment as usual (TAU) vs. TAU plus up to 16 sessions of individual formulation-based CBT for ADHD.

RESULTS: Adding formulation-based CBT to TAU for ADHD significantly improved ADHD symptoms on the Barkley Current Symptoms Scale and scores on the Work and Social Adjustment Scale. Adjusted effect sizes (ES) were 1.31 and 0.82 respectively. There were also significant improvements on secondary outcomes including independently evaluated clinical global improvement, self-rated anxiety, depression, global distress and patient satisfaction (adjusted effect sizes 0.52-1.01).

CONCLUSIONS: This is the first randomised controlled trial to provide preliminary evidence of efficacy and acceptability of individual formulation-based CBT for ADHD when added to TAU over TAU alone. This approach now needs to be tested in a larger multicentred randomised controlled trial.

Voelker R.

JAMA. **2018 Jan 2**;319(1):14. doi: 10.1001/jama.2017.19313. PMID: 29297062.

Link to article in JAMA.

An electrical device approved for use in acupuncture has received an expanded indication to help reduce opioid withdrawal symptoms.

The NSS-2 Bridge is the first device authorized to help patients cope with acute withdrawal symptoms. It consists of a small electrical nerve stimulator placed behind the ear. The device sends electrical impulses to branches of cranial nerves V, VII, IX, and X and the occipital nerves through electrodes percutaneously implanted near nerve endings in and around the ear.

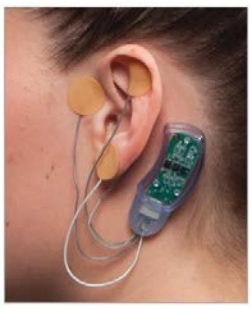
In a single-group study, researchers evaluated 73 patients' clinical opiate withdrawal scale (COWS) scores before and after using the NSS-2 Bridge. The COWS scores measure symptoms such as resting pulse rate, sweating, pupil size, gastrointestinal upset, bone and joint aches, tremors, and anxiety. Scores range from 0 to 36, with higher scores indicating more severe symptoms.

Prior to using the device, patients in the study had a mean COWS score of 20.1.

After 20 minutes of use the mean score fell to 7.5; 60 minutes later it was 3.1. The mean score was 0.6 after using the device for 5 days. The device helped quell acute symptoms effectively enough so that nearly 90% of the patients could shift to medication-assisted therapy after 5 days of use.

Three drugs currently are approved to treat opioid addiction, FDA Commissioner Scott Gottlieb, MD, noted. "While we continue to pursue better medicines for the treatment of opioid use disorder, we also need to look to devices that can assist in this therapy," Gottlieb said in a statement.

The NSS-2 Bridge is available only by prescription.



OTHER RESEARCH OF INTEREST (Continued)

Hamstringing the Army

JAMA Revisited. Section Editor: Jennifer Reiling, Assistant Editor.

JAMA. January 2, 2018;319(1):88. **Originally Published** January 5, 1918 | *JAMA*. 1918;701:29–30.

Editor's Note: JAMA Revisited is transcribed verbatim from articles published previously, unless otherwise noted.

The forces arrayed against scientific medicine are many and various. They range from the honest but deluded crank with an obsession through the various cults and 'pathies to the downright quacks and medical fakers. The American Medical Association as representative of scientific medicine in this country has, naturally enough, been the target for many of the verbal poison-gas attacks made by these different interests. In general, the Association and the profession have ignored such outbursts, for in many instances one of the obvious objects of the attackers has been to obtain, through a reply, a publicity they could never get through the avenues normally open to them. In this matter, as in many others, war brings about changed conditions. Vilifying scientific medicine in times of peace was a matter that affected chiefly only the physician, and he, knowing its source, ignored it. With the entry of our country into war, medicine, in common with other sciences, was called on to do its "bit" in successfully prosecuting the gigantic task the nation had undertaken. How well it has responded we will leave others to say. The facts are that the lives and health of the hundreds of thousands of young Americans who form the new National Army have been entrusted to the care of the representatives of scientific medicine.

During the past few months there has been an especially virulent effort on the part of the opponents of modern medical science to discredit that science in the eyes of the American public. Not only has it been openly charged that the physicians in the Army are incompetent to care for the health of the soldiers, but the villainous accusation has also been made that much of the sickness in the camps is the result of the prophylactic inoculations given the men at the time they entrain.… Such a campaign may be counted on not only to weaken the confidence of the American public in the medical department of the Army, but also to arouse unfounded suspicions in the very integrity of the military organization.

These thoughts are suggested by a recent article appearing in the Los Angeles *Times*…. One of the departments of the Sunday editions of the *Times* is entitled "Care of the Body," and is conducted by one Brook… It would probably be difficult to put in the same space more misinformation regarding the human body and its processes than Brook manages to condense into his "department."...

In the *Times* for December 16, Brook suggests, both directly and by inference, that the cases of measles and pneumonia that have occurred in the various Army camps are "in part at least … due to the fact that their [the soldiers'] blood has been poisoned with injections of diseased animal matter …" In the same article Brook denies that medicine has progressed since the days of Hippocrates; he declares that "all disease has one cause, the accumulation of waste matter in the blood, due to surplus by-products of food"; that epidemics "occur when atmospheric conditions are favorable to them"; that "tertiary syphilis is mainly due to mercurial poisoning"; that physicians "of the regular school do not understand disease"; that pathogenic bacteria are never the cause, but always the result, of disease; that "the percentage of deaths from diphtheria is as large as it ever was"; that the "increase in cancer is attributed by some medical men to the general use of serums"—and so on *ad nauseam*.

The article can have only a pernicious and disquieting effect, not alone on the soldiers themselves, but also on their families and friends. Had the *Times* falsely charged that our soldiers were being sent to fight Germany armed only with old-fashioned muskets or blunderbusses; or had it charged that the warships of the United States Navy are so obsolete and old-fashioned as to imperil the lives of our sailors, that paper would have played into the hands of our enemy no more effectively than it does when it spreads broadcast ignorant slanders regarding the efficiency of modern medical science and attempts to discredit the modern physician and challenge the value of the service rendered by the Army Medical Corps….

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