GULF WAR ILLNESS

Curcumin Treatment Leads to Better Cognitive and Mood Function in a Model of Gulf War Illness with Enhanced Neurogenesis, and Alleviation of Inflammation and Mitochondrial Dysfunction in the Hippocampus.

Kodali M[1], Hattiangady B[1], Shetty GA[1], Bates A[1], Shuai B[1], Shetty AK[1].

Brain Behav Immun. **2018 Feb 15**. pii: S0889-1591(18)30009-6. doi: 10.1016/j.bbi.2018.01.009. PMID: 29454881. [Epub ahead of print]

Diminished cognitive and mood function are among the most conspicuous symptoms of Gulf WarIllness(GWI). Our previous studies in a rat model of GWI have demonstrated that persistent cognitive and mood impairments are associated with substantially declined neurogenesis, chronic low-grade inflammation, increased oxidative stress and mitochondrial dysfunction in the hippocampus. We tested the efficacy of curcumin (CUR) to maintain better cognitive and mood function in a rat model of GWI because of its neurogenic, antiinflammatory, antioxidant, and memory and mood enhancing properties. Male rats were exposed daily to low doses of GWI-related chemicals, pyridostigmine bromide, N, N-diethyl-m-toluamide (DEET) and permethrin, and 5-minutes of restraint stress for 28 days. Animals were next randomly assigned to two groups, which received daily CUR or vehicle treatment for 30 days. Animals also received 5'-bromodeoxyuridine during the last seven days of treatment for analysis of neurogenesis. Behavioral studies through object location, novel object recognition and novelty suppressed feeding tests performed sixty days after treatment revealed better cognitive and mood function in CUR treated GWI rats. These rats also displayed enhanced neurogenesis and diminished inflammation typified by reduced astrocyte hypertrophy and activated microglia in the hippocampus. Additional studies showed that CUR treatment to GWI rats enhanced the expression of antioxidant genes and normalized the expression of multiple genes related to mitochondrial respiration. Thus, CUR therapy is efficacious for maintaining better memory and mood function in a model of GWI. Enhanced neurogenesis, restrained inflammation and oxidative stress with normalized mitochondrial respiration may underlie better memory and mood function mediated by CUR treatment.

Meta-analysis of self-reported health symptoms in 1990-1991 Gulf War and Gulf War-era veterans.

Maule AL[1,2], Janulewicz PA[1], Sullivan KA[1], Krengel MH[1,3], Yee MK[3], McClean M[1], White RF[1,4].

BMJ Open. **2018 Feb 13**;8(2):e016086. doi: 10.1136/bmjopen-2017-016086. PMID: 29440208.

OBJECTIVES: Across diverse groups of Gulf War (GW) veterans, reports of musculoskeletal pain, cognitive dysfunction, unexplained fatigue, chronic diarrhoea, rashes and respiratory problems are common. GW illness is a condition resulting from GW service in veterans who report a combination of these symptoms. This study integrated the GW literature using meta-analytical methods to characterise the most frequently reported symptoms occurring among veterans who deployed to the 1990-1991 GW and to better understand the magnitude of ill health among GW-deployed veterans compared with non-deployed GW-era veterans.

DESIGN: Meta-analysis.

METHODS: Literature databases were searched for peer-reviewed studies published from January 1990 to May 2017 reporting health symptom frequencies in GW-deployed veterans and GW-era control veterans. Self-reported health symptom data were extracted from 21 published studies. A binomial-normal meta-analytical model was used to determine pooled prevalence of individual symptoms in GW-deployed veterans and GW-era control veterans and to calculate combined ORs of health symptoms comparing GW-deployed veterans and GW-era control veterans.

RESULTS: GW-deployed veterans had higher odds of reporting all 56 analysed symptoms compared with GW-era controls. Odds of reporting irritability (OR 3.21, 95% CI 2.28 to 4.52), feeling detached (OR 3.59, 95% CI 1.83 to 7.03), muscle weakness (OR 3.19, 95% CI 2.73 to 3.74), diarrhoea (OR 3.24, 95% CI 2.51 to 4.17) and rash (OR 3.18, 95% CI 2.47 to 4.09) were more than three times higher among GW-deployed veterans compared with GW-era controls.

CONCLUSIONS: The higher odds of reporting mood-cognition, fatigue, musculoskeletal, gastrointestinal and dermatological symptoms among GW-deployed veterans compared with GW-era controls indicates these symptoms are important when assessing GW veteran health status.

CHRONIC FATIGUE SYNDROME

Efficacy of web-based cognitive-behavioural therapy for chronic fatigue syndrome: randomised controlled trial.

Janse A[1], Worm-Smeitink M[1], Bleijenberg G[2], Donders R[3], Knoop H[1].

Br J Psychiatry. **2018 Feb**;212(2):112-118. doi: 10.1192/bjp.2017.22. PMID: 29436329

BACKGROUND: Face-to-face cognitive-behavioural therapy (CBT) leads to a reduction of fatigue in chronic fatigue syndrome (CFS). Aims To test the efficacy of internet-based CBT (iCBT) for adults with CFS.

METHOD: A total of 240 patients with CFS were randomised to either iCBT with protocol-driven therapist feedback or with therapist feedback on demand, or a waiting list. Primary outcome was fatigue severity assessed with the Checklist Individual Strength (Netherlands Trial Register: NTR4013).

RESULTS: Compared with a waiting list, intention-to-treat (ITT) analysis showed a significant reduction of fatigue for both iCBT conditions (protocol-driven feedback: B = -8.3, 97.5% CI -12.7 to -3.9, P < 0.0001; feedback on demand: B = -7.2, 97.5% CI -11.3 to -3.1, P < 0.0001). No significant differences were found between both iCBT conditions on all outcome measures (P = 0.3-0.9). An exploratory analysis revealed that feedback-on-demand iCBT required less therapist time (mean 4 h 37 min) than iCBT with protocol-driven feedback (mean 6 h 9 min, P < 0.001) and also less than face-to-face CBT as reported in the literature.

CONCLUSIONS: Both iCBT conditions are efficacious and time efficient. Declaration of interest None.

Perception of induced dyspnea in fibromyalgia and chronic fatigue syndrome.

Van Den Houte M[1], Bogaerts K[2], Van Diest I[3], De Bie J[4], Persoons P[5], Van Oudenhove L[6], Van den Bergh O[7].

J Psychosom Res. **2018 Mar**;106:49-55. doi: 10.1016/j.jpsychores.2018.01.007. PMID: 29455899. Epub 2018 Jan 11.

OBJECTIVE: Dyspnea perception is distorted in patients with medically unexplained dyspnea. The goals of this study were 1) to replicate these results in patients with fibromyalgia and/or chronic fatigue syndrome (CFS), and 2) to investigate predictors of distorted symptom perception within the patient group, with a focus on negative affectivity (NA), psychiatric comorbidity and somatic symptom severity.

METHODS: Seventy-three patients diagnosed with fibromyalgia and/or CFS and 38 healthy controls (HC) completed a rebreathing paradigm, consisting of a baseline (60s of room air), a rebreathing phase (150s, gradually increasing ventilation, partial pressure of CO_2 in the blood, and self-reported dyspnea), and a recovery phase (150s of room air). Dyspnea, respiratory flow and $FetCO_2$ levels were measured continuously.

RESULTS: Patients reported more dyspnea than HC in the recovery phase (p=0.039), but no differences between patients and HC were found in the baseline (p=0.07) or rebreathing phase (p=0.17). No significant differences between patients and HC were found in physiological reactivity. Within the patient group, the effect in the recovery phase was predicted by somatic symptom severity (p=0.046), but not by negative affectivity or by the number of psychiatric comorbidities.

CONCLUSION: This study extended earlier findings in patients with medically unexplained dyspnea to patients with fibromyalgia and CFS. This suggests that altered symptom perception is a non-symptom-specific mechanism underlying functional somatic syndromes in general, particularly in patients with high levels of somatic symptom severity. The results are discussed in a predictive coding framework of symptom perception.

HEADACHE and MIGRAINE

Direct and Indirect Healthcare Resource Utilization and Costs Among Migraine Patients in the United States.

Bonafede M[1], Sapra S[2], Shah N[2], Tepper S[3], Cappell K[1], Desai P[2].

Headache. **2018 Feb 15**. doi: 10.1111/head.13275. PMID: 29446063. [Epub ahead of print]

OBJECTIVE: The goal of this analysis was to provide a contemporary estimate of the burden of migraine, incorporating both direct and indirect costs, by comparing the costs of migraine patients to a matched group of patients without migraine in a large, nationally representative sample of commercially insured patients in the United States.

BACKGROUND: Previous studies have shown that the economic burden of migraine in the United States is substantial for payers, patients, and employers. Despite the availability of multiple acute and preventive pharmacological treatment options and a relatively stable migraine prevalence in the United States, there has been a documented increase in migraine-related healthcare resource and pharmacy use. Given the frequently disabling nature of migraine and its high prevalence, especially during peak productive years, and the lack of recent estimates of the burden of migraine, there is a need to update the existing literature with more current data.

METHODS: This retrospective, observational cohort study identified migraine patients in the Truven Health Market Scan Research Databases between January 2008 and June 2013. Adult patients had 12 months of continuous enrollment before (baseline period) and after (follow-up period) the day they received migraine diagnoses and/or medications (index) and no diagnosis of HIV or malignancy during the study period. The patients with migraine were matched 1:1 to a group of patients without migraine on demographic variables and index date. Direct healthcare utilization and costs and indirect (absenteeism, short-term disability, and long-term disability) costs were assessed during the 12-month follow-up period and differences between patients with vs without migraine were assessed. Two additional multivariable logistic regression analyses were conducted. First, an analysis was conducted comparing the odds of having a short-term disability claim between patients with and without migraine after controlling for patient demographic and clinical characteristics. A second analysis, conducted among the migraine patients only, compared the odds of having a short-term disability claim between (1) patients treated with acute or preventive migraine medications only during the baseline period and patients with no migraine treatment during baseline and (2) patients treated with both acute and preventive migraine medications during the baseline period and patients with no migraine treatment during baseline, after controlling for patient demographic and clinical characteristics.

RESULTS: Migraine patients had total annual direct plus indirect costs that were $8924 (in 2014 United States dollars) higher than those of demographically similar individuals without evidence of migraine. Migraine patients' mean annual direct all-cause healthcare costs were $6575 higher than those of matched patients without migraine ($11,010 [standard deviation = $19,663] vs $4436 [standard deviation=$13,081]; P < .01). Total mean annual indirect costs were $2350 higher in the migraine cohort than in the matched no migraine patients ($11,294 vs $8945. Migraine patients were 2.0 times more likely as their nonmigraine counterparts to use opioids (45.5% vs 21.9%; P < .01) and among patients with opioid prescriptions, migraine patients had 1.8 times the number of opioid prescriptions per patient than did those without migraine (4.9 [standard deviation = 6.9] vs 2.7 [standard deviation = 4.0]; P < .01). After adjusting for baseline demographic and clinical characteristics, migraine patients treated with either acute or preventive migraine medications (odds ratio = 0.81 [95% confidence interval = 0.72-0.91]; P < .01) or both acute and preventive migraine medications during the baseline period (odds ratio = 0.93 [95% confidence interval = 0.89-0.98]; P < .01) were significantly less likely to have short-term disability claims than untreated patients during the follow-up period (Migraine patients with either acute or preventive medications only: 7290/45,632 [16.0%]; with both acute and preventive medications: 3085/14,941 [20.6%]; untreated patients: 1604/11,169 [14.4%] had a short-term disability claim.) However, overall, migraine patients had 1.94 times the odds of having a short-term disability claim than their matched counterparts (95% confidence interval = 1.83-2.05; P < .01; migraine patients: 11,979/71,742 [16.7%]; nonmigraine patients: 4801/71,742 [6.7%] had a short-term disability claim).

CONCLUSIONS: Results from this real-world assessment of the economic burden of migraine suggest that migraine imposes a substantial direct and indirect cost burden in the United States. Compared to matched nonmigraine patients, migraine patients were more likely to have work loss and longer periods of work loss, leading to significantly higher indirect costs. Migraine patients also had higher levels of healthcare utilization, despite the relatively stable prevalence of migraine and the available acute and preventive treatment options for migraine management.

HEADACHE and MIGRAINE (Continued)

Testing of diagnosis criteria of tension-type headache: A multicenter clinical study.

Kong X[1], Chen J[1], Jiang H[1], Li Q[2], Lv Y[3], Huang Y[4], Wu J[5], Zhang L[6], Tang M[3], Jiang X[7], Chen L[8], Chen M[9], Zhou Z[10], Xiong L[11], Liu J[12], Zhou H[12], Wang R[13], Xue W[14], Lu G[15], Zhou J[1].

Cephalalgia. **2018 Jan 1**:333102418759784. doi: 10.1177/0333102418759784. PMID: 29436849. [Epub ahead of print].

Objective: Tension-type headache is usually manifested as head pain without associated symptoms, and the validation of diagnostic criteria presented are lacking and highly required in the International Classification of Headache Disorders. The aim of the present study was to explore the diagnosis criteria of tension-type headache in a multicenter-based sample from Chongqing, China.

Methods: Clinical characteristics and demographics were systematically and prospectively collected between March 2014 and December 2015 from 15 participating hospitals in Chongqing, using a semi-structured face-to-face interview. All patients were asked to complete a headache diary for at least 4 weeks.

Results: Out of 1832 patients with headache, 150 patients (97 female/53 male, 44.56 ± 11.9 years old) were diagnosed with tension-type headache based on the standard International Classification of Headache Disorders, 3rd edition beta version, and interestingly, 114 (76%) patients were diagnosed with tension-type headache based on the alternative criteria. One patient was excluded because only two of the four characteristics were fulfilled. Thirty-five (23.3%) patients did not meet the alternative criteria because of associated symptoms, including mild nausea (n = 6), photophobia (n = 1), and phonophobia (n = 28). All patients with TTH had mild or moderate headaches, 98.0% of patients suffered from non-pulsating headaches, 99.3% of patients said their headaches were not aggravated by routine physical activity, and 77.3% of patients had bilateral headache.

Conclusions: Non-pulsating headaches and headaches that are not aggravated by routine physical activity may represent core criteria for screening patients with tension-type headache. Nausea might not be an exclusion feature for diagnosis of TTH, but an important criterion for screening. Further studies are needed.

Evaluating the reporting of adverse events in controlled clinical trials conducted in 2010-2015 on migraine drug treatments.

Tfelt-Hansen P[1], Lindqvist JK[2], Do TP[1].

Cephalalgia. **2018 Jan 1**:333102418759785. doi: 10.1177/0333102418759785. PMID: 29448820. [Epub ahead of print]

Background: In 2008, the International Headache Society published guidelines on the "evaluation and registration of adverse events in clinical drug trials on migraine". They listed seven recommendations for reporting adverse events in randomized controlled trials on migraine. The present study aimed to evaluate adherence to these recommendations, and based on the results, to recommend improvements.

Methods: We searched the PubMed/MEDLINE database to identify controlled trials on migraine drugs published from 2010 to 2015. For each trial, we noted whether five of the recommended parameters were presented. In addition, we noted whether adverse events were reported in abstracts.

Results: We identified 73 trials; 51 studied acutely administered drugs and 22 studied prophylactic drugs for migraine. The number of patients with any adverse events were reported in 74% of acute-administration and 86% of prophylactic drug trials. Only 30 (41%) of the 73 studies reported adverse events with data in the abstracts, and 27 (37%) abstracts did not mention adverse events.

Conclusion: Adverse events, both frequency and symptoms, should be reported to allow a fair judgement of benefit/tolerability ratio when randomized controlled trials in migraine treatment are published. Clinically significant adverse events should be included in the abstract of every randomized controlled trial in migraine treatment.

CHRONIC PAIN

Identification of FAM173B as a protein methyltransferase promoting chronic pain.

Willemen HLDM[1], Kavelaars A[2], Prado J[3], Maas M[1], Versteeg S[1], Nellissen LJJ[1], Tromp J[1], Gonzalez Cano R[1,4], Zhou W[2], Jakobsson ME[5], Małecki J[5], Posthuma G[6], Habib AM[7,8], Heijnen CJ[2], Falnes PØ[5], Eijkelkamp N[1, 3].

PLoS Biol. **2018 Feb 14**;16(2):e2003452. doi: 10.1371/journal.pbio.2003452. PMID: 29444090. [Epub ahead of print]

Chronic pain is a debilitating problem, and insights in the neurobiology of chronic pain are needed for the development of novel pain therapies. A genome-wide association study implicated the 5p15.2 region in chronic widespread pain. This region includes the coding region for FAM173B, a functionally uncharacterized protein. We demonstrate here that FAM173B is a mitochondrial lysine methyltransferase that promotes chronic pain. Knockdown and sensory neuron overexpression strategies showed that FAM173B is involved in persistent inflammatory and neuropathic pain via a pathway dependent on its methyltransferase activity. FAM173B methyltransferase activity in sensory neurons hyperpolarized mitochondria and promoted macrophage/microglia activation through a reactive oxygen species-dependent pathway. In summary, we uncover a role for methyltransferase activity of FAM173B in the neurobiology of pain. These results also highlight FAM173B methyltransferase activity as a potential therapeutic target to treat debilitating chronic pain conditions.

Defective Endogenous Pain Modulation in Fibromyalgia: a Meta-Analysis of Temporal Summation and Conditioned Pain Modulation Paradigms.

O'Brien AT[1], Deitos A[2], Triñanes Pego Y[3], Fregni F[4], Carrillo-de-la-Peña MT[5].

J Pain. **2018 Feb 15**. pii: S1526-5900(18)30073-7. doi: 10.1016/j.jpain.2018.01.010. PMID: 29454976. [Epub ahead of print]

To study the characteristics of temporal summation (TS) and conditioned pain modulation (CPM) in fibromyalgia (FM) patients, we systematically searched Pubmed and EMBASE for studies using TS or CPM comparing FM patients to healthy controls. We computed Hedge's g, risk of bias, sensitivity analysis and meta-regression tests with 10000 Monte-Carlo permutations. Twenty-three studies (625 female/23 male FM patients and 591 female/81 male healthy controls) were included. The meta-analyses showed an effect size of 0.53 for TS ($p<0.001$; 95% CI 0.23 to 0.83), which is a 68% relative difference between patients and controls, and of 0.57 for CPM ($p<0.001$; 95% CI -0.88 to -0.26), representing a 65% relative difference between the groups. The qualitative analyses revealed large heterogeneity between study protocols. Although studies were of low risk of bias, lack of blinding was substantial. Sensitivity analysis and meta-regression identified type and site of stimulation, age, lab, sample size, and medication control as important sources of between study variability. We demonstrate a significant alteration of pain modulation mechanisms in FM patients.

PERSPECTIVE: This novel meta-analysis provides evidence for defective endogenous pain modulation in fibromyalgia patients. We explored the impact of covariates on between study variability in these paradigms. These biomarkers may aid in diagnosis, and treatment of patients. However, validation requires further investigation under strict methodological settings, and into individual patient covariates.

CHRONIC PAIN (Continued)

Racial differences in presentations and predictors of acute pain following motor vehicle collision.

Beaudoin FL[1,2], Gutman R[3], Zhai W[3], Merchant RC[1,4], Clark MA[4,5], Bollen KA[6], Hendry P[7,8], Kurz MC[9], Lewandowski C[10], Pearson C[11], O'Neil B[12], Datner E[13], Mitchell P[14], Domeier R[15], McLean SA[15,16].

Pain. **2018 Feb 9**. doi: 10.1097/j.pain.0000000000001186. PMID: 29438226. [Epub ahead of print]

African-Americans experience a greater burden of acute pain than non-Hispanic white individuals across of variety of acute medical conditions, but it is unknown if this is the case following trauma. We evaluated pain, pain-related characteristics (e.g. peri-traumatic distress), and analgesic treatment in two cohorts of individuals (African-American (n=931) and non-Hispanic white (n=948)) presenting to the emergency department after a motor-vehicle crash (MVC). We performed a propensity-matched analysis (n=796 in each group) to assess racial differences in acute pain in the ED. In multivariable models conducted within the matched sample, race was associated with moderate to severe axial pain (OR 3.2; 95% CI 2.1, 5.0, p<0.001) and higher average NRS scores (1.3; 95% CI: 1.1, 1.6; p=<0.001). After adjustment for pain and other covariates, Non-Hispanic white patients were: more likely to receive an opioid analgesic in the ED (OR 2.0; 95% CI 1.4, 3.0, p<0.001) or at discharge (OR 4.9; 95% CI 3.4, 7.1, p<0.001), and also less likely to receive an NSAID in the ED (OR 0.54; 95% CI 0.38, 0.78; p=0.001) or at discharge (0.31; 95% CI 0.43, 0.84). Racial differences in the severity of acute post-traumatic pain following a motor vehicle collision are not explained by factors such as socio-economic status or crash characteristics. Despite a higher burden of acute pain, African-Americans were less likely to receive opioid analgesics and more likely to receive NSAIDs. Further work is needed to understand the relationship between pain severity, disparities in analgesic treatment and longer-term outcomes, such as post-MVC chronic pain.

Small Fiber Polyneuropathy Is Prevalent in Patients Experiencing Complex Chronic Pelvic Pain.

Chen A[1], De E[2], Argoff C[3].

Pain Med. **2018 Feb 13**. doi: 10.1093/pm/pny001. PMID: 29447372. [Epub ahead of print]

Objective: To demonstrate the prevalence of small fiber polyneuropathy (SFPN) in patients with refractory chronic pelvic pain (CPP).

Design: Retrospective study of prospective database.

Subjects: Participants were complex CPP patients recruited from subspecity referral clinics defined as those who were refractory to initial treatment and/or exhibited comorbid pain syndromes at initial presentation.

Methods: Comprehensive treatment history for CPP was obtained, and participants referred as above; 3-mm punch biopsies were obtained of the lower extremity and sent to diagnostic reference labs to evaluate for SFPN. The reported lab sensitivity and specificity for SFPN are 78-92% and 65-90%, respectively.

Results: Twenty-five of 39 patients (64%) were positive for SFPN. Comorbid conditions noted in our population included gastroesophageal reflux disease (46%), migraine (38%), irritable bowel syndrome (33%), lower back pain (33%), fibromyalgia (38%), endometriosis (15%), interstitial cystitis (18%), vulvodynia (5%), and other chronic pain syndromes (36%).

Conclusions: The prevalence of SFPN in our specialty referral patients with complex CPP is remarkably high vs published general population prevalence data (53/100,000). Identification of SFPN in this complex population shifts the focus from undefined syndromes to symptom complexes with linked potentially treatable mechanisms (e.g., SFPN, central sensitization). Most CPP patients with SFPN are undiagnosed. Considering the diagnosis may expand treatment options beyond conventional or so-called adjuvant analgesics. Treatment may expand to therapies such as IV lidocaine, IVIG, or other immunomodulatory options. In addition, the value to the patient of receiving a diagnosis for a multisystem or refractory pain syndrome, often attributed to negative psychologic factors, cannot be underestimated. Identifying SFPN should be contemplated in CPP patients who present with multisystem pain or who have not responded to initial evaluation and management.

OTHER RESEARCH OF INTEREST

FDA authorizes marketing of first blood test to aid in the evaluation of concussion in adults. New quick testing option to help reduce need for CT scans, radiation exposure for patients

FDA News Release. **February 14, 2018**.

The U.S. Food and Drug Administration today permitted marketing of the first blood test to evaluate mild traumatic brain injury (mTBI), commonly referred to as concussion, in adults. The FDA reviewed and authorized for marketing the Banyan Brain Trauma Indicator in fewer than 6 months as part of its Breakthrough Devices Program.

Most patients with a suspected head injury are examined using a neurological scale, called the 15-point Glasgow Coma Scale, followed by a computed tomography or CT scan of the head to detect brain tissue damage, or intracranial lesions, that may require treatment; however, a majority of patients evaluated for mTBI/concussion do not have detectable intracranial lesions after having a CT scan. Availability of a blood test for concussion will help health care professionals determine the need for a CT scan in patients suspected of having mTBI and help prevent unnecessary neuroimaging and associated radiation exposure to patients. [Full text of FDA News Release.]

Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies.

Ng SC[1], Shi HY[2], Hamidi N[3], Underwood FE[3], Tang W[4], Benchimol EI[5], Panaccione R[3], Ghosh S[6], Wu JCY[4], Chan FKL[4], Sung JJY[4], Kaplan GG[7].

Lancet. **2017 Dec 23**;390(10114):2769-2778. doi: 10.1016/S0140-6736(17)32448-0. PMID: 29050646. Epub 2017 Oct 16.

Comment in: **Rapid changes in epidemiology of inflammatory bowel disease.** [Lancet. 2018]

BACKGROUND: Inflammatory bowel disease is a global disease in the 21st century. We aimed to assess the changing incidence and prevalence of inflammatory bowel disease around the world.

METHODS: We searched MEDLINE and Embase up to and including Dec 31, 2016, to identify observational, population-based studies reporting the incidence or prevalence of Crohn's disease or ulcerative colitis from 1990 or later. A study was regarded as population-based if it involved all residents within a specific area and the patients were representative of that area. To be included in the systematic review, ulcerative colitis and Crohn's disease needed to be reported separately. Studies that did not report original data and studies that reported only the incidence or prevalence of paediatric-onset inflammatory bowel disease (diagnosis at age <16 years) were excluded. We created choropleth maps for the incidence (119 studies) and prevalence (69 studies) of Crohn's disease and ulcerative colitis. We used temporal trend analyses to report changes as an annual percentage change (APC) with 95% CI.

FINDINGS: We identified 147 studies that were eligible for final inclusion in the systematic review, including 119 studies of incidence and 69 studies of prevalence. The highest reported prevalence values were in Europe (ulcerative colitis 505 per 100 000 in Norway; Crohn's disease 322 per 100 000 in Germany) and North America (ulcerative colitis 286 per 100 000 in the USA; Crohn's disease 319 per 100 000 in Canada). The prevalence of inflammatory bowel disease exceeded 0·3% in North America, Oceania, and many countries in Europe. Overall, 16 (72·7%) of 22 studies on Crohn's disease and 15 (83·3%) of 18 studies on ulcerative colitis reported stable or decreasing incidence of inflammatory bowel disease in North America and Europe. Since 1990, incidence has been rising in newly industrialised countries in Africa, Asia, and South America, including Brazil (APC for Crohn's disease +11·1% [95% CI 4·8-17·8] and APC for ulcerative colitis +14·9% [10·4-19·6]) and Taiwan (APC for Crohn's disease +4·0% [1·0-7·1] and APC for ulcerative colitis +4·8% [1·8-8·0]).

INTERPRETATION: At the turn of the 21st century, inflammatory bowel disease has become a global disease with accelerating incidence in newly industrialised countries whose societies have become more westernised. Although incidence is stabilising in western countries, burden remains high as prevalence surpasses 0·3%. These data highlight the need for research into prevention of inflammatory bowel disease and innovations in health-care systems to manage this complex and costly disease.

OTHER RESEARCH OF INTEREST (Continued)

A Brief Exposure-Based Treatment vs Cognitive Processing Therapy for Posttraumatic Stress Disorder: A Randomized Noninferiority Clinical Trial.

Sloan DM[1,2], Marx BP[1,2], Lee DJ[1], Resick PA[3].

JAMA Psychiatry. **2018 Jan 17**. doi: 10.1001/jamapsychiatry.2017.4249. PMID: 29344631 [Epub ahead of print]

Importance: Written exposure therapy (WET), a 5-session intervention, has been shown to efficaciously treat posttraumatic stress disorder (PTSD). However, this treatment has not yet been directly compared with a first-line PTSD treatment such as cognitive processing therapy (CPT).

Objective: To determine if WET is noninferior to CPT in patients with PTSD.

Design, Setting, and Participants: In this randomized clinical trial conducted at a Veterans Affairs medical facility between February 28, 2013, and November 6, 2016, 126 veteran and nonveteran adults were randomized to either WET or CPT. Inclusion criteria were a primary diagnosis of PTSD and stable medication therapy. Exclusion criteria included current psychotherapy for PTSD, high risk of suicide, diagnosis of psychosis, and unstable bipolar illness. Analysis was performed on an intent-to-treat basis.

Interventions: Participants assigned to CPT (n = 63) received 12 sessions and participants assigned to WET (n = 63) received 5 sessions. The CPT protocol that includes written accounts was delivered individually in 60-minute weekly sessions. The first WET session requires 60 minutes while the remaining 4 sessions require 40 minutes.

Main Outcomes and Measures: The primary outcome was the total score on the Clinician-Administered PTSD Scale for DSM-5; noninferiority was defined by a score of 10 points. Blinded evaluations were conducted at baseline and 6, 12, 24, and 36 weeks after the first treatment session. Treatment dropout was also examined.

Results: For the 126 participants (66 men and 60 women; mean [SD] age, 43.9 [14.6] years), improvements in PTSD symptoms in the WET condition were noninferior to improvements in the CPT condition at each of the assessment periods. The largest difference between treatments was observed at the 24-week assessment (mean difference, 4.31 points; 95% CI, -1.37 to 9.99). There were significantly fewer dropouts in the WET vs CPT condition (4 [6.4%] vs 25 [39.7%]; $\chi 21 = 12.84$, Cramer V = 0.40).

Conclusions and Relevance: Although WET involves fewer sessions, it was noninferior to CPT in reducing symptoms of PTSD. The findings suggest that WET is an efficacious and efficient PTSD treatment that may reduce attrition and transcend previously observed barriers to PTSD treatment for both patients and providers.

Trial Registration: clinicaltrials.gov Identifier: NCT01800773.

Neurobiological features of fibromyalgia are also present among rheumatoid arthritis patients.

Basu N[1], Kaplan CM[2], Ichesco E[2], Larkin T[2], Harris RE[2], Murray A[1], Waiter G[1], Clauw DJ[2].

Arthritis Rheumatol. **2018 Feb 13**. doi: 10.1002/art.40451. PMID: 29439291. [Epub ahead of print]

OBJECTIVES: Many rheumatoid arthritis (RA) patients report pain despite excellent control of inflammation with immunotherapies. Variable degrees of co-existing fibromyalgia (FM) may explain this disparity. FM has been characterised by aberrant brain functional connectivity, especially between the Default Mode Network (DMN) and insula. We hypothesised that RA patients reporting the highest 2011 ACR FM survey criteria scores- a continuous measure of FM degree also known as fibromyalgianess (FMness)- would demonstrate functional connectivity abnormalities similar to FM.

METHODS: RA patients underwent an 11 min functional connectivity MRI brain scan (fcMRI) and a clinical evaluation which included a measure of FMness. Brain networks were isolated from FcMRI data. Individual patient network to whole brain connectivity analyses were then conducted followed by group level regression which correlated the connectivity of each network with FMness. Results were significant on the cluster level with a family wise error (FWE) rate p-value <0.05 derived from an uncorrected voxel level p-value <0.001.

RESULTS: 54 patients participated (mean age 54.9years; 75.9% female; mean FMness score 13.3 [range 1-29]). From the whole brain analyses, a single significant positive correlation between DMN connectivity to the left mid/posterior insula and FMness (r=0.58, p=0.001 FWE) was demonstrated.

CONCLUSIONS: RA patients who have increased levels of FMness appear to share neurobiological features consistently observed in FM patients. This study is the first to provide neuroimaging evidence that RA is a mixed pain state, with many patients' symptoms being related to CNS rather than classic inflammatory mechanisms.

OTHER RESEARCH OF INTEREST (Continued)

Neurological Manifestations Among US Government Personnel Reporting Directional Audible and Sensory Phenomena in Havana, Cuba.

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Importance: From late 2016 through August 2017, US government personnel serving on diplomatic assignment in Havana, Cuba, reported neurological symptoms associated with exposure to auditory and sensory phenomena.

Objective: To describe the neurological manifestations that followed exposure to an unknown energy source associated with auditory and sensory phenomena.

Design, Setting, and Participants: Preliminary results from a retrospective case series of US government personnel in Havana, Cuba. Following reported exposure to auditory and sensory phenomena in their homes or hotel rooms, the individuals reported a similar constellation of neurological symptoms resembling brain injury. These individuals were referred to an academic brain injury center for multidisciplinary evaluation and treatment.

Exposures: Report of experiencing audible and sensory phenomena emanating from a distinct direction (directional phenomena) associated with an undetermined source, while serving on US government assignments in Havana, Cuba, since 2016.

Main Outcomes and Measures: Descriptions of the exposures and symptoms were obtained from medical record review of multidisciplinary clinical interviews and examinations. Additional objective assessments included clinical tests of vestibular (dynamic and static balance, vestibulo-ocular reflex testing, caloric testing), oculomotor (measurement of convergence, saccadic, and smooth pursuit eye movements), cognitive (comprehensive neuropsychological battery), and audiometric (pure tone and speech audiometry) functioning. Neuroimaging was also obtained.

Results: Of 24 individuals with suspected exposure identified by the US Department of State, 21 completed multidisciplinary evaluation an average of 203 days after exposure. Persistent symptoms (>3 months after exposure) were reported by these individuals including cognitive (n = 17, 81%), balance (n = 15, 71%), visual (n = 18, 86%), and auditory (n = 15, 68%) dysfunction, sleep impairment (n = 18, 86%), and headaches (n = 16, 76%). Objective findings included cognitive (n = 16, 76%), vestibular (n = 17, 81%), and oculomotor (n = 15, 71%) abnormalities. Moderate to severe sensorineural hearing loss was identified in 3 individuals. Pharmacologic intervention was required for persistent sleep dysfunction (n = 15, 71%) and headache (n = 12, 57%). Fourteen individuals (67%) were held from work at the time of multidisciplinary evaluation. Of those, 7 began graduated return to work with restrictions in place, home exercise programs, and higher-level work-focused cognitive rehabilitation.

Conclusions and Relevance: In this preliminary report of a retrospective case series, persistent cognitive, vestibular, and oculomotor dysfunction, as well as sleep impairment and headaches, were observed among US government personnel in Havana, Cuba, associated with reports of directional audible and/or sensory phenomena of unclear origin. These individuals appeared to have sustained injury to widespread brain networks without an associated history of head trauma.

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