GULF WAR ILLNESS

Alterations in DNA Methylation Status Associated with Gulf War Illness.

Trivedi MS[1], Abreu MM[2,3], Sarria L[3], Rose N[1], Ahmed N[1], Beljanski V[4], Fletcher MA[2,3], Klimas NG[2,3], Nathanson L[3].

DNA Cell Biol. **2019 Mar 28**. doi: 10.1089/dna.2018.4469. PMID: 30920300. [Epub ahead of print]

Gulf War Illness (GWI) affects about 25% of Persian Gulf veterans with a cluster of chronic symptoms, including immune dysfunction and neurological issues. Recent studies implicate gene expression changes in immune function to be associated with GWI. Since DNA methylation can regulate such changes in gene expression, and disruption of DNA methylation pattern is implicated in various immune and neurological diseases, we aimed to study the DNA methylation patterns in peripheral blood mononuclear cells from GWI patients. Global DNA methylation levels were similar in GWI patients and controls. However, the genome-wide microarray technology detected 10,767 differentially methylated CpG sites across gene regulatory elements and within coding regions. Approximately 88% of them were hypermethylated in GWI patients. The separate analysis found 776 differentially methylated gene promoters (DMP), which were predominantly hypermethylated. Pyrosequencing validation confirmed microarray results. Functional analysis revealed that majority of the DMPs belonged to genes responsible for metabolism and immune system. This is the first pilot human study characterizing genome-wide epigenetic changes associated with GWI. It suggests a significant contribution of epigenetic dysfunction in GWI. Moreover, it supports the dysregulation of immune function in GWI. Lastly, it suggests studies with the larger cohort to validate our findings.

Improvements in Gulf War Illness Symptoms After Near-Infrared Transcranial and Intranasal Photobiomodulation: Two Case Reports.

Chao LL[1,2,3].

Mil Med. **2019 Mar 22**. pii: usz037. doi: 10.1093/milmed/usz037. PMID: 30916762. [Epub ahead of print]

At least one-fourth of US veterans who served in the 1990-1991 Gulf War (GW) are affected by the chronic symptomatic illness known as Gulf War illness (GWI). This condition typically includes some combination of fatigue, headaches, cognitive dysfunction, musculoskeletal pain, and respiratory, gastrointestinal and dermatologic complaints. To date, effective treatments for GWI have been elusive. Photobiomodulation (PBM) describes the non-pharmacological, non-thermal use of light to stimulate, heal, and protect tissue that has either been injured, is degenerating, or else is at risk of dying. Significant benefits have been reported following application of transcranial PBM to humans with acute stoke, traumatic brain injury (TBI), and dementia. This report describes the first documentation of improved GWI symptoms in two GW veterans following 12 weeks of PBM treatments.

CHRONIC FATIGUE SYNDROME

B-Lymphocyte Depletion in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial.

Fluge Ø[1], Rekeland IG[1], Lien K[2], Thürmer H[3], Borchgrevink PC[4], Schäfer C[5], Sørland K[1], Aßmus J[1], Ktoridou-Valen I[1], Herder I[2], Gotaas ME[4], Kvammen Ø[4], Baranowska KA[4], Bohnen LMLJ[5], Martinsen SS[2], Lonar AE[3], Solvang AH[4], Gya AES[5], Bruland O[1], Risa K[1], Alme K[1], Dahl O[6], Mella O[6].

Ann Intern Med. **2019 Apr 2**. doi: 10.7326/M18-1451. PMID: 30934066. [Epub ahead of print]

Background: Previous phase 2 trials indicated benefit from B-lymphocyte depletion in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Objective: To evaluate the effect of the monoclonal anti-CD20 antibody rituximab versus placebo in patients with ME/CFS.

Design: Randomized, placebo-controlled, double-blind, multicenter trial. (ClinicalTrials.gov: NCT02229942).

Setting: 4 university hospitals and 1 general hospital in Norway.

Patients: 151 patients aged 18 to 65 years who had ME/CFS according to Canadian consensus criteria and had had the disease for 2 to 15 years.

Intervention: Treatment induction with 2 infusions of rituximab, 500 mg/m2 of body surface area, 2 weeks apart, followed by 4 maintenance infusions with a fixed dose of 500 mg at 3, 6, 9, and 12 months (n = 77), or placebo (n = 74).

Measurements: Primary outcomes were overall response rate (fatigue score ≥4.5 for ≥8 consecutive weeks) and repeated measurements of fatigue score over 24 months. Secondary outcomes included repeated measurements of self-reported function over 24 months, components of the Short Form-36 Health Survey and Fatigue Severity Scale over 24 months, and changes from baseline to 18 months in these measures and physical activity level. Between-group differences in outcome measures over time were assessed by general linear models for repeated measures.

Results: Overall response rates were 35.1% in the placebo group and 26.0% in the rituximab group (difference, 9.2 percentage points [95% CI, -5.5 to 23.3 percentage points]; P = 0.22). The treatment groups did not differ in fatigue score over 24 months (difference in average score, 0.02 [CI, -0.27 to 0.31]; P = 0.80) or any of the secondary end points. Twenty patients (26.0%) in the rituximab group and 14 (18.9%) in the placebo group had serious adverse events.

Limitation: Self-reported primary outcome measures and possible recall bias.

Conclusion: B-cell depletion using several infusions of rituximab over 12 months was not associated with clinical improvement in patients with ME/CFS.

Primary Funding Source: The Norwegian Research Council, Norwegian Regional Health Trusts, Kavli Trust, MEandYou Foundation, and Norwegian ME Association.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Trial Fails to Confirm Earlier Observations of Rituximab's Effectiveness.

Rowe PC[1].

Ann Intern Med. **2019 Apr 2**. doi: 10.7326/M19-0643. PMID: 30934063. [Epub ahead of print]

Excerpt from text of this Editorial in *Annals of Internal Medicine*:

…As the authors acknowledge, the study results weaken the case for an important role of rituximab in treating ME/CFS. However, other immunologic abnormalities in ME/CFS (7) deserve further investigation, including replication of the single 1997 study that showed an overall benefit of intravenous immunoglobulin in adolescents (8), investigation of the overlap of symptoms between ME/CFS and mast cell activation syndrome, and further work on removing potentially pathogenic autoantibodies directed at adrenergic and cholinergic receptors.

A substantial challenge in ME/CFS research remains the heterogeneity of the illness. In other serious disorders like acute respiratory distress syndrome and sepsis, a profusion of trials with negative results prompted a call for strategies to enrich the signal of the intervention and reduce the effect of background noise caused by disease heterogeneity (9). Similar strategies would be germane in ME/CFS, such as excluding subgroups that have more limited potential to respond to an intervention or greater risk for adverse effects. Patients with prolonged illness who have not responded to multiple pretrial treatments might be less likely to respond to a new intervention (10). At a minimum, this indicates a need to stratify by disease duration. Persons with ME/CFS often meet criteria for several comorbid conditions, each of which could flare during a trial, possibly obscuring a true beneficial effect of an intervention. An open treatment run-in period might allow better control of the nontargeted conditions. Other enrichment strategies could include providing the intervention to all participants, then randomizing the responders to continuing versus discontinuing therapy. Enrolling only those with a specific biomarker might help match the disease subgroup to the intervention.

The profound level of impaired function of affected individuals warrants a new commitment to hypothesis-driven clinical trials that incorporate and expand on the methodological sophistication of the rituximab trial….

CHRONIC FATIGUE SYNDROME (Continued)

Epigenetic Components of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Uncover Potential Transposable Element Activation.

Almenar-Pérez E[1], Ovejero T[2], Sánchez-Fito T[1], Espejo JA[3], Nathanson L[4], Oltra E[5].

Clin Ther. **2019 Mar 22**. pii: S0149-2918(19)30072-4. doi: 10.1016/j.clinthera.2019.02.012. PMID: 30910331. [Epub ahead of print]

PURPOSE: Studies to determine epigenetic changes associated with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) remain scarce; however, current evidence clearly shows that methylation patterns of genomic DNA and noncoding RNA profiles of immune cells differ between patients and healthy subjects, suggesting an active role of these epigenetic mechanisms in the disease. The present study compares and contrasts the available ME/CFS epigenetic data in an effort to evidence overlapping pathways capable of explaining at least some of the dysfunctional immune parameters linked to this disease.

METHODS: A systematic search of the literature evaluating the ME/CFS epigenome landscape was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria. Differential DNA methylation and noncoding RNA differential expression patterns associated with ME/CFS were used to screen for the presence of transposable elements using the Dfam browser, a search program nurtured with the Repbase repetitive sequence database and the RepeatMasker annotation tool.

FINDINGS: Unexpectedly, particular associations of transposable elements and ME/CFS epigenetic hallmarks were uncovered. A model for the disease emerged involving transcriptional induction of endogenous dormant transposons and structured cellular RNA interactions, triggering the activation of the innate immune system without a concomitant active infection.

IMPLICATIONS: Repetitive sequence filters (ie, RepeatMasker) should be avoided when analyzing transcriptomic data to assess the potential participation of repetitive sequences ("junk repetitive DNA"), representing >45% of the human genome, in the onset and evolution of ME/CFS. In addition, transposable element screenings aimed at designing cost-effective, focused empirical assays that can confirm or disprove the suspected involvement of transposon transcriptional activation in this disease, following the pilot strategy presented here, will require databases gathering large ME/CFS epigenetic datasets.

Leveraging Prior Knowledge of Endocrine Immune Regulation in the Therapeutically Relevant Phenotyping of Women With Chronic Fatigue Syndrome.

Morris MC[1], Cooney KE[1], Sedghamiz H[1], Abreu M[2], Collado F[2], Balbin EG[2], Craddock TJA[3], Klimas NG[2], Broderick G[4], Fletcher MA[2].

Clin Ther. **2019 Mar 28**. pii: S0149-2918(19)30112-2. doi: 10.1016/j.clinthera.2019.03.002. PMID: 30929860. [Epub ahead of print]

PURPOSE: The complex and varied presentation of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) has made it difficult to diagnose, study, and treat. Its symptoms and likely etiology involve multiple components of endocrine and immune regulation, including the hypothalamic-pituitary-adrenal axis, the hypothalamic-pituitary-gonadal axis, and their interactive oversight of immune function. We propose that the persistence of ME/CFS may involve changes in the regulatory interactions across these physiological axes. We also propose that the robustness of this new pathogenic equilibrium may at least in part explain the limited success of conventional single-target therapies.

METHODS: A comprehensive model was constructed of female endocrine-immune signaling consisting of 28 markers linked by 214 documented regulatory interactions. This detailed model was then constrained to adhere to experimental measurements in a subset of 17 candidate immune markers measured in peripheral blood of patients with ME/CFS and healthy control subjects before, during, and after a maximal exercise challenge. A set of 26 competing numerical models satisfied these data to within 5% error.

FINDINGS: Mechanistically informed predictions of endocrine and immune markers that were either unmeasured or exhibited high subject-to-subject variability pointed to possible context-specific overexpression in ME/CFS at rest of corticotropin-releasing hormone, chemokine (C-X-C motif) ligand 8, estrogen, follicle-stimulating hormone (FSH), gonadotropin-releasing hormone 1, interleukin (IL)-23, and luteinizing hormone, and underexpression of adrenocorticotropic hormone, cortisol, interferon-γ, IL-10, IL-17, and IL-1α. Simulations of rintatolimod and rituximab treatment predicted a shift in the repertoire of available endocrine-immune regulatory regimens. Rintatolimod was predicted to make available substantial remission in a significant subset of subjects, in particular those with low levels of IL-1α, IL-17, and cortisol; intermediate levels of progesterone and FSH; and high estrogen levels. Rituximab treatment was predicted to support partial remission in a smaller subset of patients with ME/CFS, specifically those with low norepinephrine, IL-1α, chemokine (C-X-C motif) ligand 8, and cortisol levels; intermediate FSH and gonadotropin-releasing hormone 1 levels; and elevated expression of tumor necrosis factor-α, luteinizing hormone, IL-12, and B-cell activation.

IMPLICATIONS: Applying a rigorous filter of known signaling mechanisms to experimentally measured immune marker expression in ME/CFS has highlighted potential new context-specific markers of illness. These novel endocrine and immune markers may offer useful candidates in delineating new subtypes of ME/CFS and may inform on refinements to the inclusion criteria and instrumentation of new and ongoing trials involving rintatolimod and rituximab treatment protocols.

CHRONIC FATIGUE SYNDROME (Continued)

Relationship between different experimental measures of distorted symptom perception in functional syndrome patients.

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

Psychosom Med. **2019 Mar 26**. doi: 10.1097/PSY.0000000000000692. PMID: 30920465. [Epub ahead of print]

OBJECTIVE: Patients with functional somatic syndromes (FSS) show reduced correspondence between induced physiological changes and self-reported symptoms in a rebreathing paradigm, as well as elevated symptoms unrelated to physiological changes after induction of negative affective states in an affective picture viewing paradigm. Detailed results of both paradigms separately were published elsewhere. The main goal of the current report is to describe the relationship between the responses to these two paradigms measuring distortions in symptom perception in a well-described sample of patients with fibromyalgia and/or chronic fatigue syndrome (CFS).

METHODS: Patients (N=81) with fibromyalgia and/or CFS participated in a test session comprising four well-validated paradigms, including the picture viewing and rebreathing paradigm. Using mixed model analyses, it was tested whether the amount of affective modulation of symptom reporting was related to distorted perception of induced dyspnea. In an exploratory way, we assessed the role of several individual difference variables as moderators.

RESULTS: There was no relationship between patients' amount of affective modulation of symptom reporting, as assessed with the picture paradigm, and level of distortion in dyspnea perception, as assessed with the rebreathing paradigm (effect of affective modulation in the subjective recovery from induced dyspnea: $F_{1,70} = 0.16$, $p = 0.70$; time*affective modulation interaction effect: $F_{4,70} = 0.14$, $p = 0.97$).

CONCLUSIONS: Biased symptom reporting in one paradigm is unrelated to biased symptom reporting in the other paradigm, indicating that distortions in symptom perception in FSS patients is not a trait-like, cross-situationally stable condition, but a versatile dysfunction that is context-dependent.

HEADACHE and MIGRAINE

Is Head Computerized Tomography Indicated for the Workup of Headache in Patients with Intact Neurological Examination.

Goldstein L[1], Laytman T[2], Steiner I[3].

Eur Neurol. **2019 Mar 29**;80(5-6):341-344. doi: 10.1159/000496805. PMID: 30928972. [Epub ahead of print]

INTRODUCTION: The use of neuroimaging as part of the initial workup in the emergency department (ED) for patients with atraumatic headache is increasing, whereas the proportion of cases in which clinically significant intracranial pathology is detected is decreasing. In the last few decades, the exposure to medical ionized radiation from utilization of computer tomography (CT) increased dramatically, raising concern about radiation-induced cancer. Different guidelines were suggested to address the role of neuroimaging in the investigation of adult patients presenting to the ED with nontraumatic headache.

MATERIALS AND METHODS: We retrospectively evaluated data from all consecutive patients who underwent a head CT in the ED for the evaluation of headache during 2015. Patients were included only if a normal neurologic examination was documented.

RESULTS: In total, 422 patients were included. About 43.4% of scans were normal. Most abnormal findings were sinusitis (148 patients, 35%) or ischemic changes. Seven CT scans (1.6%) showed clinically significant findings requiring an immediate change in management.

CONCLUSION: A normal neurologic examination, even when performed by a neurologist, does not rule out a significant secondary cause for headache. A CT scan in the ED is indicated for patients presenting with severe nonremitting headache who never had neuroimaging in the past.

HEADACHE and MIGRAINE (Continued)

Differences in fibertract profiles between patients with migraine and those with persistent post-traumatic headache.

Chong CD[1], Peplinski J[2], Berisha V[2], Ross K[3], Schwedt TJ[1].

Cephalalgia. **2019 Mar 26**:333102418815650. doi: 10.1177/0333102418815650. PMID: 30913910. [Epub ahead of print]

OBJECTIVES: Often, persistent post-traumatic headache and migraine are phenotypically similar. However, the similarities and differences in the neuropathological underpinnings of persistent post-traumatic headache and migraine require further understanding. We used diffusion tensor imaging (DTI) and a novel method for detecting subtle changes in fibertract integrity by measuring node-by-node parameters along each tract to compare fibertract profiles between those with migraine and those with persistent post-traumatic headache, and compared both cohorts to a group of controls.

METHODS: Eighteen fibertracts were reconstructed for 131 subjects, including 49 patients with persistent post-traumatic headache attributed to mild traumatic brain injury, 41 with migraine, and 41 controls. Node-by-node diffusion parameters of mean diffusivity and radial diffusivity were calculated along each tract. Mean diffusivity and radial diffusivity measurements were averaged along quartiles of each tract for statistical interpretation and group comparison. Using a post-hoc analysis, correlations between tract quartile measurements and headache frequency were calculated.

RESULTS: There were significant differences between migraine and persistent post-traumatic headache cohorts for quartile measurements of mean diffusivity or radial diffusivity in the bilateral anterior thalamic radiations, cingulum (angular bundles and cingulate gyri), inferior longitudinal fasciculi, and uncinate fasciculi, the left corticospinal tract, and the right superior longitudinal fasciculi-parietal portion. For migraine patients, there was a significant positive correlation between headache frequency and forceps major mean diffusivity, whereas for persistent post-traumatic headache there was a positive correlation between headache frequency and cingulum angular bundle mean diffusivity and radial diffusivity.

CONCLUSIONS: Quartile measurements of radial diffusivity and mean diffusivity indicate unique differences in fibertract profiles between those with migraine vs. persistent post-traumatic headache. Although for both migraine and persistent post-traumatic headache there was a positive relationship between fibertract alterations and headache frequency, there were disease-specific differences between headache frequency and fibertract injury patterns. These findings might suggest potential differences in the neuropathological mechanisms underlying migraine and persistent post-traumatic headache.

Altered neural activity to monetary reward/loss processing in episodic migraine.

Kocsel N[1,2,3,4], Galambos A[1,2,5], Szabó E[1,2,5], Édes AE[3,4], Magyar M[6], Zsombók T[6], Pap D[4], Kozák LR[7], Bagdy G[4,5], Kökönyei G[8,9,10], Juhász G[3,4,11].

Sci Rep. **2019 Apr 1**;9(1):5420. doi: 10.1038/s41598-019-41867-x. PMID: 30931979.

The dysfunctions of the mesolimbic cortical reward circuit have been proposed to contribute to migraine pain. Although supporting empirical evidence was mainly found in connection with primary rewards or in chronic migraine where the pain experience is (almost) constant. Our goal however was to investigate the neural correlates of secondary reward/loss anticipation and consumption using the monetary incentive delay task in 29 episodic migraine patients and 41 headache-free controls. Migraine patients showed decreased activation in one cluster covering the right inferior frontal gyrus during reward consumption compared to controls. We also found significant negative correlation between the time of the last migraine attack before the scan and activation of the parahippocampal gyrus and the right hippocampus yielded to loss anticipation. During reward/loss consumption, a relative increase in the activity of the visual areas was observed the more time passed between the last attack and the scan session. Our results suggest intact reward/loss anticipation but altered reward consumption in migraine, indicating a decreased reactivity to monetary rewards. The findings also raise the possibility that neural responses to loss anticipation and reward/loss consumption could be altered by the proximity of the last migraine attack not just during pre-ictal periods, but interictally as well.

HEADACHE and MIGRAINE (Continued)

Increased connectivity of pain matrix in chronic migraine: a resting-state functional MRI study.

Lee MJ[1,2], Park BY[3,4], Cho S[1], Kim ST[5], Park H[4,6], Chung CS[7,8].

J Headache Pain. **2019 Mar 25**;20(1):29. doi: 10.1186/s10194-019-0986-z. PMID: 30909865.

OBJECTIVE: To investigate the whole-brain resting-state functional connectivity in patients with chronic migraine (CM) using a data-driven method.

METHODS: We prospectively recruited patients with either episodic migraine (EM) or CM aged 18-60 years who visited the headache clinic of the Samsung Medical Center from July 2016 to December 2017. All patients underwent 3 T MRI using an identical scanner. Patients were considered interictal if they did not have a migraine headache at the day and ± 1 days of functional MRI acquisition. Using the group-independent component analysis (ICA), connectivity analysis with a weighted and undirected network model was performed. The between-group differences in degree centrality (DC) values were assessed using 5000 permutation tests corrected with false discovery rate (FDR).

RESULTS: A total of 62 patients (44 EM and 18 CM) were enrolled in this study. Among the seven functionally interpretable spatially independent components (ICs) identified, only one IC, interpreted as the pain matrix, showed a significant between-group difference in DC (CM > EM, p = 0.046). This association remained significant after adjustment for age, sex, migraine with aura (MWA), allodynia, depression, and anxiety (p = 0.038). The pain matrix was functionally correlated with the hypothalamus (p = 0.040, EM > CM) and dorsal raphe nucleus (p = 0.039, CM > EM) with different levels of strength in EM and CM.

CONCLUSION: CM patients have a stronger connectivity in the pain matrix than do EM patients. Functional alteration of the pain network might play a role in migraine chronification.

Imaging of neuroinflammation in migraine with aura: A [^{11}C]PBR28 PET/MRI study.

Albrecht DS[1], Mainero C[1], Ichijo E[1], Ward N[1], Granziera C[1], Zürcher NR[1], Akeju O[1], Bonnier G[1], Price J[1], Hooker JM[1], Napadow V[1], Loggia ML[1], Hadjikhani N[2].

Neurology. **2019 Mar 27**. pii: 10.1212/WNL.0000000000007371. doi: 10.1212/WNL.0000000000007371. PMID: 30918090. [Epub ahead of print]

OBJECTIVE: To determine if migraine with aura is associated with neuroinflammation, which has been suggested by preclinical models of cortical spreading depression (CSD) as well as imaging of human pain conditions.

METHODS: Thirteen migraineurs with aura and 16 healthy controls received integrated PET/MRI brain scans with [^{11}C]PBR28, a radioligand that binds to the 18 kDa translocator protein, a marker of glial activation. Standardized uptake value ratio (SUVR) was compared between groups, and regressed against clinical variables, using region of interest and whole-brain voxelwise analyses.

RESULTS: Compared to healthy controls, migraineurs demonstrated SUVR elevations in nociceptive processing areas (e.g., thalamus and primary/secondary somatosensory and insular cortices) as well as in areas previously shown to be involved in CSD generation (visual cortex). SUVR levels in frontoinsular cortex, primary/secondary somatosensory cortices, and basal ganglia were correlated with frequency of migraine attacks.

CONCLUSIONS: These findings demonstrate that migraine with aura is associated with neuroimmune activation/neuroinflammation, and support a possible link between CSD and glial activation, previously observed in animals.

HEADACHE and MIGRAINE (Continued)

The spectrum of cluster headache: A case report of 4600 attacks.

Hagedorn A[1], Snoer A[1], Jensen R[1], Haddock B[2], Barloese M[1,3].

Cephalalgia. **2019 Mar 26**:333102419833081. doi: 10.1177/0333102419833081. PMID: 30913909. [Epub ahead of print]

INTRODUCTION: Knowledge of the clinical features of cluster headache is mainly based on retrospective and cross-sectional studies. Here, we present a case of a chronic cluster headache patient who prospectively recorded timing and clinical features of all attacks for 6 years, aiming to describe the clinical spectrum and timing of cluster headache symptoms experienced and to identify daily and/or seasonal rhythmicity.

METHODS: Registration of attack timing, duration, associated symptoms and severity was done prospectively on a smartphone application. Pain severity was recorded on a 0-10 scale. Attacks were divided into mild, moderate, severe, and very severe. We analysed diurnal rhythmicity by multimodal Gaussian analysis and spectral analysis.

RESULTS: In total, 4600 attacks were registered (mean duration 39.3 (SD 18.5) min. Mean severity 3.6 (SD 1.28)). Mild attacks accounted for 14.2%, moderate 65.7%, severe 16.9% and very severe 3.2% of all attacks. Nocturnal attacks were more severe than daytime attacks. The number of autonomic symptoms and duration of attacks increased with pain severity. Peak chronorisk (risk of attacks occurring according to hour of day) was at 12.48 in the registration period. Over time, circadian rhythmicity and attack frequency varied.

CONCLUSION: Clinical characteristics of cluster headache attacks can vary greatly within the individual patient. Clinicians attempting to personalise the administration of preventive treatment should pay notice to the variation over time in diurnal rhythmicity. The recorded self-limiting mild attacks that do not fulfill the ICHD-3 criteria for a cluster headache attack warrant further investigation, as they could hold important information about disease activity.

CHRONIC PAIN

Factors Associated with Opioid Initiation in OEF/OIF/OND Veterans with Traumatic Brain Injury.

Hudson TJ[1,2], Painter JT[1,3], Gressler LE[1,3], Lu L[2], Williams JS[1], Booth BM[2], Martin BC[3], Sullivan MD[4], Edlund MJ[5,6].

Pain Med. **2018 Apr 1**;19(4):774-787. doi: 10.1093/pm/pnx208. PMID: 29036680.

[Note: Delayed posting in PubMed—Not previously listed in RAC Research Alerts.]

Objective: These analyses examined opioid initiation and chronic use among Iraq (OIF) and Afghanistan (OEF/OND) veterans with a new diagnosis of traumatic brain injury (TBI) in the Veterans Health Administration (VHA).

Methods: Data were obtained from national VHA data repositories. Analyses included OEF/OIF/OND veterans with a new TBI diagnosis in 2010-2012 who used the VHA at least twice, had not received a VHA opioid prescription in the 365 days before diagnosis, and had at least 365 days of data available after TBI diagnosis.

Results: Analyses included 35,621 veterans. Twenty-one percent initiated opioids; among new initiators, 23% used chronically. The mean dose was 24.0 mg morphine equivalent dose (MED) daily (SD = 24.26); mean days supplied was 60.52 (SD = 74.69). Initiation was significantly associated with age 36-45 years (odds ratio [OR] = 1.09, 95% CI = 1.01-1.17, P = 0.04), female gender (OR = 1.22, P < 0.001), having back pain (OR = 1.38, P < 0.0001), arthritis/joint pain (OR = 1.24, P < 0.0001), or neuropathic pain (OR = 1.415, P < 0.02). In veterans age 36-45 years, those living in small rural areas had higher odds of chronic opioid use (OR = 1.31, P < 0.0001, and OR = 1.33, P = 0.006, respectively) and back pain (OR = 1.36, P = 0.003). Headache/migraine pain was associated with decreased odds of chronic opioid use (OR = 0.639, P = 0.003).

Conclusions: Prevalence of opioid use is relatively low among OEF/OIF/OND veterans with newly diagnosed TBI who are using VHA. Among those who initiated opioids, about 25% use them chronically. Prescribing was mostly limited to moderate doses, with most veterans using opioids for approximately two months of the 12-month study period.

CHRONIC PAIN (Continued)

The Association Between Negative Trauma-Related Cognitions and Pain-Related Functional Status Among Veterans With Posttraumatic Stress Disorder and Alcohol Use Disorder.

Curry I[1,2], Malaktaris AL[1,2,3], Lyons R[4], Herbert MS[1,2,3], Norman SB[1,2,3,4,5].

J Trauma Stress. **2019 Mar 26**. doi: 10.1002/jts.22394. PMID: 30913347. [Epub ahead of print]

Among veterans with posttraumatic stress disorder (PTSD), alcohol use disorders (AUDs) are highly prevalent. Furthermore, PTSD frequently co-occurs with chronic pain (CP), and CP is associated with an increased risk of AUD. Pain-related beliefs and appraisals are significantly associated with poorer pain-related functional status, yet few studies have examined negative trauma-related cognitions and their impact on pain-related functional disability in veterans with co-occurring PTSD and AUD. Accordingly, we examined the association between negative trauma-related cognitions and pain severity and pain disability in 137 veterans seeking treatment for PTSD and AUD. Using hierarchical multiple linear regression, we found that higher levels of negative trauma-related cognitions (e.g., "I am completely incompetent") were associated with a higher level of pain severity, after controlling for PTSD symptom severity and frequency of alcohol use, total R^2 = .07, ΔR^2 = .06. Additionally, as hypothesized, we found that higher levels of negative trauma-related cognitions were associated with higher levels of pain disability, after controlling for PTSD symptom severity, frequency of alcohol use, and pain severity, total R^2 = .46, ΔR^2 = .03. Given that negative trauma-related cognitions contributed to pain severity and pain disability, even when controlling for PTSD severity and frequency of alcohol use, future studies should explore the potential impact of interventions that address negative trauma-related cognitions (e.g., prolonged exposure or cognitive processing therapy) on pain severity and disability.

Whether chronic pain is medically explained or not does not moderate the response to cognitive-behavioural therapy.

McNaughton DT[1], Hush JM[2], Beath AP[3], Gandy M[4], Dear BF[4], Jones MP[3].

J Psychosom Res. **2019 Mar 26**. pii: S0022-3999(19)30055-8. doi: 10.1016/j.jpsychores.2019.03.182. PMID: 30928209. [Epub ahead of print]

OBJECTIVES: To determine whether pain-related treatment outcomes, following an online Cognitive Behavioural Therapy (CBT) intervention for chronic pain, were moderated by the pain etiology of a medically explained or unexplained origin.

METHODS: Data were available from 471 participants who completed the online pain management program between March 2013 and August 2014. Participants' pain symptoms were classified as being medically explained symptoms (MES: n = 292) or medically unexplained symptoms (MUS: n = 222) via analysis of clinical data. Outcome variables were pain-related disability, average pain intensity, depression and anxiety.

RESULTS: Moderation analyses were non-significant for all dependent variables. Between group differences (CBT and control) were larger for depression in those classified with MES, compared with MUS (MUS: mean change = -3.50 [95% CI = -4.98 to -2.22]; MES: mean change = -5.72 [95% CI = -7.49 to -4.09]). However, between group differences were small for pain intensity (MUS: mean change = -0.03 [95% CI = -0.83 to 0.81]; MES: mean difference = -1.12 [95% CI = -1.84 to 0.40]).

CONCLUSION: The therapeutic outcomes examined in this study associated with an online CBT program do not appear to be altered by whether the participants' pain symptoms are medically explained or unexplained.

CHRONIC PAIN (Continued)

BEEP-Bodily and Emotional Perception of Pain. A Questionnaire to Measure Reaction to Pain in Chronic Pain Disorders.

Preti A[1], Stocchino S[1], Pinna F[1], Deidda MC[1], Musu M[1], Sancassiani F[1], Romano F[2], Machado S[3], Finco G[1], Carta MG[1].

Front Psychol. **2019 Mar 12**;10:480. doi: 10.3389/fpsyg.2019.00480. PMCID: PMC6422924. PMID: 30914997. eCollection 2019.

Background: The assessment of pain and its impact on quality of life is central to the evaluation of chronic pain syndromes. However, most available tools focus on the nociceptive experience of pain, and at best only consider the occurrence of anxious, depressive, or cognitive problems. Here is a new questionnaire aimed at measuring the multifaceted impact of pain in chronic pain syndromes, the Bodily and Emotional pErception of Pain (BEEP).

Methods: All consecutive patients who accessed a center for the treatment of pain were invited to take part in the study. The sample included 222 participants (51 with fibromyalgia, 84 with low back pain; 87 with other chronic pain syndromes). Women were 77% of the sample, the mean age was 61 ± 15. Participants completed the BEEP, the Patient Health Questionnaire-9 (PHQ-9), and the Mood Disorder Questionnaire (MDQ).

Results: Reliability was good for all questionnaires. The expected three dimensions of the BEEP were confirmed by confirmatory factor analysis, and a bifactor model with three orthogonal factors showed a good fit as well. Participants diagnosed with fibromyalgia showed higher scores on the BEEP than the participants who had been diagnosed with low back pain or other chronic pain syndromes. The prevalence of probable cases of major depression and bipolar disorder in the sample was higher than expected for non-clinical samples. Levels of depression, as measured by the PHQ-9, were associated with the three dimensions of the BEEP and with the intensity of pain.

Conclusions: The BEEP is a promising measure of the impact of pain in daily life and differentiates fibromyalgia from other chronic pain syndromes. The BEEP may be helpful to evaluate the patient's response to the treatment over time and may favor the identification of unmet needs in patients' personal, social, and daily functioning.

Patient-rated physician empathy and patient satisfaction during pain clinic consultations.

Walsh S[1], O'Neill A[1], Hannigan A[1], Harmon D[2,3].

Ir J Med Sci. **2019 Mar 27**. doi: 10.1007/s11845-019-01999-5. PMID: 30919198j. [Epub ahead of print]

BACKGROUND: Little is known about the influence of patient-perceived healthcare provider empathy on patient satisfaction in the setting of a hospital pain clinic consultation. The objective of this research was to examine the relationship between patient-rated physician empathy and patient satisfaction after a single new pain clinic consultation.

METHODS: After institutional ethics committee approval, a sample of 140 adult patients completed a two-page questionnaire, directly after a pain clinic consultation. This included a brief sociodemographic questionnaire, the Consultation and Relational Empathy (CARE) measure and an overall satisfaction rating.

RESULTS: The sample, N = 140 patients, was balanced for gender and 80% of participants ranged in age from 30 to 70. Of these patients, 80.7% had been living with chronic pain between 1 and 5 years. The data were deemed to be non-parametric and a Spearman's ranked order correlation analysis yielded a strong positive correlation between patient-rated physician empathy and patient consultation satisfaction.

CONCLUSION: Patient-rated physician empathy was strongly correlated with patient satisfaction in a pain clinic consultation. Patient satisfaction plays a significant role in adherence to treatment and contributes to a positive working patient-physician therapeutic relationship. This research supports the growing body of research citing the importance of investing in, promoting and developing educational programs for physicians and medical trainees to enhance empathic communication skills within the clinical setting.

CHRONIC PAIN (Continued)

Diffusion-Weighted Magnetic Resonance Imaging: A New Tool for the Diagnosis of Bladder Pain Syndrome/Interstitial Cystitis.

Charlanes A[1,2], Boudghene F[3], Chesnel C[4,5], Ciofu C[4,6], Le Breton F[4,5], Jousse M[4,5,7], Amarenco G[4,5], Manceau P[4,5].

Urol Int. **2019**;102(1):109-112. doi: 10.1159/000493507. PMID: 30428470. Epub 2018 Nov 14.

OBJECTIVES: To determine whether diffusion-weighted magnetic resonance imaging (DWMRI), a noninvasive procedure, can contribute to the diagnosis of bladder pain syndrome/interstitial cystitis (BPS/IC).

METHODS: The pelvic DWMRI of patients with chronic pelvic pain syndrome was selected between January 2012 and June 2017. A radiologist analyzed the bladder wall signal; he was blinded to the patients' clinical data. According to the 2008 European Society for the Study of Bladder Pain Syndrome/Interstitial Cystitis criteria, 2 groups of patients were determined: BPS/IC and no BPS/IC. The association between BPS/IC and the wall signal intensity was compared.

RESULTS: In the 106 patients included, 82 had criteria for BPS/IC and 24 did not. A significant difference in the distribution of the signal was found between the 2 groups (p = 0.01). High signal intensity of the bladder wall was related to the presence of a BPS/IC with a sensitivity of 28% and a specificity of 88%. No signal intensity of the bladder wall was related to the absence of a BPS/IC with a sensitivity of 96% and a specificity of 29%.

CONCLUSIONS: In -DWMRI, high bladder wall signal intensity helps to affirm a BPS/IC, whereas the absence of signal helps to exclude the diagnosis. Further studies are needed to confirm these preliminary results.

Associations Between Sleep Disturbance and Chronic Pain Intensity and Function: A Test of Direct and Indirect Pathways.

Burgess HJ[1], Burns JW[2], Buvanendran A[3], Gupta R[4], Chont M[4], Kennedy M[2], Bruehl S[4].

Clin J Pain. **2019 Mar 25**. doi: 10.1097/AJP.0000000000000711. PMID: 30913041. [Epub ahead of print]

OBJECTIVES: Sleep disturbance and chronic pain are related. The present study evaluated both direct and indirect (mediated) pathways through which sleep disturbance might be related to chronic pain intensity and function.

METHODS: Eighty-seven individuals (64% female) with chronic low back pain but not using opioids daily completed questionnaires assessing their sleep disturbance, chronic pain intensity, function, depression, anxiety, positive affect, and catastrophizing.

RESULTS: Greater sleep disturbance was associated with greater pain intensity, worse function, greater emotional distress, lower positive affect and higher levels of catastrophizing. Cross-sectional mediation analyses revealed that the positive associations between sleep disturbance and chronic pain intensity were conveyed statistically not only via significant indirect effects of elevated emotional distress, lower positive affect, and greater catastrophizing associated with sleep disturbance, but also by significant direct effects of sleep disturbance on chronic pain intensity. Similarly, we found that the associations between sleep disturbance and impaired function were conveyed statistically not only via significant indirect effects of elevated chronic pain intensity associated with sleep disturbance, but also via significant direct effects of sleep disturbance on function.

DISCUSSION: Sleep disturbance was related significantly with chronic pain intensity and function via both direct and indirect pathways. These results are consistent with an emerging literature highlighting the potential significance of sleep disturbance in chronic pain patients, and provide further support for addressing sleep disturbance in the assessment and management of chronic pain.

IRRITABLE BOWEL SYNDROME

Noninvasive Diagnosis of Irritable Bowel Syndrome via Bowel Sound Features: Proof of Concept.

Du X[1], Allwood G[1], Webberley KM[1], Inderjeeth AJ[2], Osseiran A[3], Marshall BJ[1,2].

Clin Transl Gastroenterol. **2019 Mar**;10(3):e00017. doi: 10.14309/ctg.0000000000000017. PMID: 30908308.

INTRODUCTION: Irritable bowel syndrome (IBS) is a common and debilitating disorder estimated to affect approximately 11% of the world's population. Typically, IBS is a diagnosis of exclusion after patients undergo a costly and invasive colonoscopy to exclude organic disease. Clinician's and researchers have identified a need for a new cost-effective, accurate, and noninvasive diagnostic test for IBS.

METHODS: Using a diagnostic case-control study, we explored the use of bowel sounds to characterize IBS with a view to diagnostic use. We recruited participants with an existing clinical diagnosis of IBS or healthy (asymptomatic) digestive systems. We recorded bowel sounds for 2 hours after fasting and then for 40 minutes after a standard meal.

RESULTS: We here report our results including our accuracy in characterizing IBS-related bowel sounds and differentiation between participants with IBS and healthy participants. Leave-one-out cross-validation of our model developed using the first 31 IBS and 37 healthy participants gave 90% sensitivity and 92% specificity for IBS diagnosis. Independent testing using the next 15 IBS and 15 healthy participants demonstrated 87% sensitivity and 87% specificity for IBS diagnosis.

CONCLUSIONS: These preliminary results provide proof of concept for the use of bowel sound analysis to identify IBS. A prospective study is needed to confirm these findings.

TRANSLATIONAL IMPACT: Our belt and model offer hope of a new approach for IBS diagnosis in primary practice. Combined with screening tests for organic disease, it would offer greater confidence to patients and could reduce the burden of unnecessary colonoscopies for health care systems and patients.

Changes of the postcentral cortex in irritable bowel syndrome patients.

Nan J[1], Yang W[2], Meng P[2], Huang W[2], Zheng Q[2], Xia Y[3], Liu F[4].

Brain Imaging Behav. **2019 Mar 29**. doi: 10.1007/s11682-019-00087-7. PMID: 30927201. [Epub ahead of print]

The postcentral cortex (poCC) is commonly found to respond to visceral stimulation, but researchers usually pay less attention to this role of the poCC in the patients with functional gastrointestinal disorders, because it is a primary receptor for general bodily feeling of touch, such as temperature and pain. The current study focuses on the changes around the poCC in irritable bowel syndrome (IBS) patients based on the resting-state functional magnetic resonance imaging, aiming to investigate whether the poCC-centric brain metrics may be directly related to visceral perception. In the study, we calculated the regional homogeneity, seed-based correlation (SBC) and nodal centralities of the poCC to explore the changes in the regional activity and information flow around the poCC in IBS patients. Moreover, we examined the performance of the poCC-centric features in classifying the IBS group and healthy group in comparison to those features unrelated to the poCC. The results found that central alterations around the poCC in IBS patients were associated with the level of visceral pain, and exhibited a better discriminative power than those around the whole brain and the insula when classifying the IBS group and healthy group. In conclusion, the preliminary investigation provided fundamental advances in understanding the roles of the poCC in the pathphysiology of the IBS.

IRRITABLE BOWEL SYNDROME (Continued)

The experiences of physical activity in Irritable Bowel Syndrome - A qualitative study.

Johannesson E[1,2], Jakobsson Ung E[3,4,5], Ringström G[1,3,4,5], Sadik R[1,2,5].

J Clin Nurs. **2019 Apr 2**. doi: 10.1111/jocn.14880. PMID: 30938882. [Epub ahead of print]

AIMS AND OBJECTIVES: The aim of this study was to explore experiences of physical activity in patients with Irritable bowel syndrome.

BAKGROUND: Irritable bowel syndrome is a common functional bowel disorder. The knowledge of physical activity in Irritable bowel syndrome is limited and has not been qualitatively studied before.

METHODS: We adopted a qualitative approach and a hermeneutic analysis. Fifteen patients with Irritable bowel syndrome (10 women) with a median age of 52 (31-78) years were interviewed. The Consolidated criteria for reporting qualitative research was used.

RESULTS: Two themes emerged from the data: requirements of physical activity and capability for physical activity. The first of these consisted of five subthemes: add additional value, enable transportation, maintain health, cultivate interests, and give a feeling of belonging. These qualities were the patients' requirements of physical activity, and comprised the patients' motives and reasons for being physically active. The second consisted of four subthemes: life situation, earlier experiences, self-image, and symptom variation and described the possibility and resources to be physically active in everyday life. The patients made active choices to adjust their physical activity in terms of type, intensity and amount. The two main themes affect each other reciprocally.

CONCLUSIONS: The requirements of and capabilities for physical activity should be taken into account when giving advice to patients on physical activity. Physical activity for a person with Irritable bowel syndrome is about finding activities which meet the patient's individual requirements of and capability for physical activity.

RELEVANCE TO CLINICAL PRACTICE: This qualitative study on the experience pf physical activity in Irritable bowel syndrome provides knowledge to facilitate promoting physical activity among patients suffering from Irritable bowel syndrome. This knowledge can be used in other diagnosis. This article is protected by copyright. All rights reserved.

OTHER RESEARCH OF INTEREST

Chronic diseases and social risk factors in relation to specific symptoms of depression: Evidence from the U.S. national health and nutrition examination surveys.

Jokela M[1], García-Velázquez R[1], Airaksinen J[1], Gluschkoff K[1], Kivimäki M[2], Rosenström T[3].

J Affect Disord. **2019 Mar 22**;251:242-247. doi: 10.1016/j.jad.2019.03.074. PMID: 30928864. [Epub ahead of print]

BACKGROUND: Depression is a heterogeneous mental disorder with multiple symptoms, but only few studies have examined whether associations of risk factors with depression are symptom-specific. We examined whether chronic diseases and social risk factors (poverty, divorce, and perceived lack of emotional support) are differently associated with somatic and cognitive/affective symptoms of depression.

METHODS: Cross-sectional analyses were based on individual-level data from the 31,191 participants of six cross-sectional U.S. National Health and Nutrition Examination Surveys (NHANES) carried out between 2005 and 2016. Depressive symptoms were assessed using the 9-item Patient Health Questionnaire. Information on chronic diseases and social risk factors was self-reported by participants.

RESULTS: After adjustment for sex, age, race/ethnicity, and all the of other symptoms besides the outcome symptom, higher number of chronic diseases was independently related to fatigue, psychomotor retardation/agitation, and sleep problems in a dose-response pattern (range of odds ratios: 1.21 to 2.59). Except for concentration problems, social risk factors were associated with almost all of the cognitive/affective symptoms (range of odds ratios: 1.02 to 2.09) but only sporadically with somatic symptoms.

LIMITATIONS: All measures were self-reported by the participants, which may have introduced bias to the associations. Cross-sectional data did not allow us to study temporal dynamics.

CONCLUSIONS: Specific symptoms of depression may be useful in characterizing the heterogeneous etiology of depression with respect to somatic versus social risk factors.

OTHER RESEARCH OF INTEREST (Continued)

Effectiveness of Implementing a Collaborative Chronic Care Model for Clinician Teams on Patient Outcomes and Health Status in Mental Health: A Randomized Clinical Trial.

Bauer MS[1,2], Miller CJ[1,2], Kim B[1,2], Lew R[1,3], Stolzmann K[1], Sullivan J[1,4], Riendeau R[1,5], Pitcock J[6], Williamson A[7], Connolly S[1,2], Elwy AR[1,8], Weaver K[9].

JAMA Netw Open. **2019 Mar 1**;2(3):e190230. doi: 10.1001/jamanetworkopen.2019.0230. PMID: 30821830.

Importance: Collaborative chronic care models (CCMs) have extensive randomized clinical trial evidence for effectiveness in serious mental illnesses, but little evidence exists regarding their feasibility or effect in typical practice conditions.

Objective: To determine the effectiveness of implementation facilitation in establishing the CCM in mental health teams and the impact on health outcomes of team-treated individuals.

Design, Setting, and Participants: This quasi-experimental, randomized stepped-wedge implementation trial was conducted from February 2016 through February 2018, in partnership with the US Department of Veterans Affairs (VA) Office of Mental Health and Suicide Prevention. Nine facilities were enrolled from all VA facilities in the United States to receive CCM implementation support. All veterans (n = 5596) treated by designated outpatient general mental health teams were included for hospitalization analyses, and a randomly selected sample (n = 1050) was identified for health status interviews. Individuals with dementia were excluded. Clinicians (n = 62) at the facilities were surveyed, and site process summaries were rated for concordance with the CCM process. The CCM implementation start time was randomly assigned across 3 waves. Data analysis of this evaluable population was performed from June to September 2018.

Interventions: Internal-external facilitation, combining a study-funded external facilitator and a facility-funded internal facilitator working with a designated team for 1 year.

Main Outcomes and Measures: Facilitation was hypothesized to be associated with improvements in both implementation and intervention outcomes (hybrid type II trial). Implementation outcomes included the clinician Team Development Measure (TDM) and proportion of CCM-concordant team care processes. The study was powered for the primary health outcome, mental component score (MCS). Hospitalization rate was derived from administrative data.

Results: The veteran population (n = 5596) included 881 women (15.7%), and the mean (SD) age was 52.2 (14.5) years. The interviewed sample (n = 1050) was similar but was oversampled for women (n = 210 [20.0%]). Facilitation was associated with improvements in TDM subscales for role clarity (53.4%-68.6%; δ = 15.3; 95% CI, 4.4-26.2; P = .01) and team primacy (50.0%-68.6%; δ = 18.6; 95% CI, 8.3-28.9; P = .001). The percentage of CCM-concordant processes achieved varied, ranging from 44% to 89%. No improvement was seen in veteran self-ratings, including the primary outcome. In post hoc analyses, MCS improved in veterans with 3 or more treated mental health diagnoses compared with others (β = 5.03; 95% CI, 2.24-7.82; P < .001). Mental health hospitalizations demonstrated a robust decrease during facilitation (β = -0.12; 95% CI, -0.16 to -0.07; P < .001); this finding withstood 4 internal validity tests.

Conclusions and Relevance: Implementation facilitation that engages clinicians under typical practice conditions can enhance evidence-based team processes; its effect on self-reported overall population health status was negligible, although health status improved for individuals with complex conditions and hospitalization rate declined.

Trial Registration: ClinicalTrials.gov Identifier: NCT02543840.

Potential Effects on Mortality of Replacing Sedentary Time With Short Sedentary Bouts or Physical Activity: A National Cohort Study.

Diaz KM[1], Duran AT[1], Colabianchi N[2], Judd SE[3], Howard VJ[4], Hooker SP[5].

Am J Epidemiol. **2019 Mar 1**;188(3):537-544. doi: 10.1093/aje/kwy271. PMCID: PMC6395167. PMID: 30551177.

Little is known concerning the type of activity that should be substituted for sedentary time and its potentially most hazardous form (prolonged sedentary bouts) to impart health benefit. We used isotemporal substitution techniques to examine whether 1) replacing total sedentary time with light-intensity or moderate to vigorous physical activity (LIPA or MVPA) or 2) replacing prolonged sedentary bouts with shorter sedentary bouts is associated with reductions in all-cause mortality risk. Participants (n = 7,999) from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a national cohort of US adults aged ≥45 years, were studied. Sedentary time was measured by accelerometry between 2009 and 2013. There was a beneficial association with mortality risk for replacing total sedentary time with both LIPA (per 30 minutes, hazard ratio (HR) = 0.83; 95% confidence interval (CI): 0.80, 0.87) and MVPA (per 30 minutes, HR = 0.65; 95% CI: 0.50, 0.85). Similarly, there was a beneficial association for replacing prolonged sedentary-bout time with LIPA and MVPA but not for replacement with shorter sedentary bouts (per 30 minutes, HR = 1.00; 95% CI: 0.96, 1.03). These findings suggest short sedentary bouts still carry mortality risk and are not a healthful alternative to prolonged sedentary bouts. Instead, physical activity of any intensity is needed to mitigate the mortality risks incurred by sedentary time.

OTHER RESEARCH OF INTEREST (Continued)

Adapting summary scores for the PROMIS-29 v2.0 for use among older adults with multiple chronic conditions.

Huang W[1], Rose AJ[2,3], Bayliss E[4,5], Baseman L[6], Butcher E[7], Garcia RE[7], Edelen MO[2].

Qual Life Res. **2019 Jan**;28(1):199-210. doi: 10.1007/s11136-018-1988-z. PMCID: PMC6374169. Epub 2018 Sep 12.

PURPOSE: The patient-reported outcomes measurement information system 29-item profile (PROMIS-29 v2.0) is a widely used health-related quality of life (HRQoL) measure. Summary scores for physical and mental HRQoL have recently been developed for the PROMIS-29 using a general population. Our purpose was to adapt these summary scores to a population of older adults with multiple chronic conditions.

METHODS: We collected the PROMIS-29 v2.0 for 1359 primary care patients age 65+ with at least 2 of 13 chronic conditions. PROMIS-29 has 7 domains, plus a single-item pain intensity scale. We used exploratory factor analysis (EFA), followed by confirmatory factor analysis (CFA), to examine the number of factors that best captured these eight scores. We used previous results from a recent study by Hays et al. (Qual Life Res 27:1885-1891, 2018) to standardize scoring coefficients, normed to the general population.

RESULTS: The mean age was 80.7, and 67% of participants were age 80 or older. Our results indicated a 2-factor solution, with these factors representing physical and mental HRQoL, respectively. We call these factors the physical health score (PHS) and the mental health score (MHS). We normed these summary scores to the general US population. The mean MHS for our population of was 50.1, similar to the US population, while the mean PHS was 42.2, almost a full standard deviation below the US population.

CONCLUSIONS: We describe the adaptation of physical and mental health summary scores of the PROMIS-29 for use with a population of older adults with multiple chronic conditions.

Comparative study of PROMIS® self-efficacy for managing chronic conditions across chronic neurologic disorders.

Shulman LM[1], Velozo C[2], Romero S[3,4], Gruber-Baldini AL[5].

Qual Life Res. **2019 Mar 26**. doi: 10.1007/s11136-019-02164-2. PMID: 30915674. [Epub ahead of print]

PURPOSE: Self-efficacy (SE) for managing chronic conditions is the belief that one can carry out behaviors to reach health goals. The study objective is to investigate (1) SE for managing chronic conditions across diverse neurologic conditions, (2) demographic and disease determinants of SE, and (3) SE as a predictor of health and disability.

METHODS: Patients with chronic neurologic conditions (epilepsy, multiple sclerosis, neuropathy, Parkinson disease, stroke; n = 834) completed five SE for Managing Chronic Conditions instruments (Patient-Reported Outcomes Measurement Information System®; PROMIS®). Other assessments included PROMIS depression, fatigue, physical function, and global health.

RESULTS: Two of the five SE domains showed differences across the five disorders (ANOVA; SE for Managing Daily Activities $p < .001$ and Managing Symptoms $p < .01$). The three domains with no differences were Managing Medications/Treatments, Emotions, and Social Interactions. Lowest SE was in neuropathy, and highest in epilepsy (Managing Activities) and stroke (Managing Symptoms). Multivariate regression showed SE measures to be better predictors of mental health, global health, and disability than either disease severity or diagnosis.

CONCLUSIONS: SE for managing chronic conditions differs across neurologic disorders, with lowest SE for managing activities and symptoms in neuropathy, and highest in patients with epilepsy and stroke. PROMIS SE measures are better predictors of mental health, disability, and quality of life than disease severity or diagnosis.

OTHER RESEARCH OF INTEREST (Continued)

Do people with arthritis differ from healthy controls in their internal comparison standards for self-reports of health, fatigue, and pain?

Junghaenel DU[1], Schneider S[2], Stone AA[2,3].

J Patient Rep Outcomes. **2019 Mar 27**;3(1):21. doi: 10.1186/s41687-019-0108-3. PMID: 30919113.

OBJECTIVE: Patient-reported outcomes are central for the assessment and treatment of people with chronic disease. The primary aim of this study was to determine if people with arthritis differed from healthy individuals in their use of internal comparison standards when answering questions about their health and symptomatology. A secondary aim was to determine if average levels of the patient-reported outcomes were associated with the use of internal comparison standards, regardless of whether a participant had arthritis or no chronic medical condition.

METHODS: People with a self-report diagnosis of any type of arthritis (n = 588) and healthy controls (n = 567) were recruited from an Internet panel and were randomly assigned to rate two of three outcomes: health, fatigue, and pain. After completing their rating, participants were presented with internal comparison standards and indicated which ones, if any, they used for the ratings they provided. The internal comparison standards were: Interpersonal (comparisons with other people); Historical (comparisons with the past); Imaginary comparisons (comparisons with a hypothetical scenario); or that none of the three were used.

RESULTS: After controlling for group differences in demographic characteristics and outcome levels by including them in the analyses as covariates, people with arthritis were more likely to make Historical comparisons than healthy controls when rating their health. No other group differences in the use of internal comparison standards were found. We further found that the use of internal comparison standards was associated with health and symptom levels, regardless of whether a participant had arthritis or no medical condition. Poorer self-rated health, greater fatigue, and higher pain were associated with a greater likelihood of making a Historical comparison. Furthermore, poorer self-rated health was associated with a greater likelihood of making an Interpersonal comparison, and higher fatigue and pain with a greater likelihood of making an Imaginary comparison.

CONCLUSION: People with arthritis differed in their use of Historical comparison standards compared to those with no chronic medical condition for health ratings. In addition, poorer health and more severe symptomatology were associated with the use of internal comparison standards in both groups of participants, people with arthritis and healthy controls.

Revisiting protein aggregation as pathogenic in sporadic Parkinson and Alzheimer diseases.

Espay AJ[1], Vizcarra JA[2], Marsili L[2], Lang AE[2], Simon DK[2], Merola A[2], Josephs KA[2], Fasano A[2], Morgante F[2], Savica R[2], Greenamyre JT[2], Cambi F[2], Yamasaki TR[2], Tanner CM[2], Gan-Or Z[2], Litvan I[2], Mata IF[2], Zabetian CP[2], Brundin P[2], Fernandez HH[2], Standaert DG[2], Kauffman MA[2], Schwarzschild MA[2], Sardi SP[2], Sherer T[2], Perry G[2], Leverenz JB[2].

Neurology. **2019 Feb 12**;92(7):329-337. doi: 10.1212/WNL.0000000000006926. PMCID: PMC6382364. PMID: 30745444.

The gold standard for a definitive diagnosis of Parkinson disease (PD) is the pathologic finding of aggregated α-synuclein into Lewy bodies and for Alzheimer disease (AD) aggregated amyloid into plaques and hyperphosphorylated tau into tangles. Implicit in this clinicopathologic-based nosology is the assumption that pathologic protein aggregation at autopsy reflects pathogenesis at disease onset. While these aggregates may in exceptional cases be on a causal pathway in humans (e.g., aggregated α-synuclein in *SNCA* gene multiplication or aggregated β-amyloid in *APP* mutations), their near universality at postmortem in sporadic PD and AD suggests they may alternatively represent common outcomes from upstream mechanisms or compensatory responses to cellular stress in order to delay cell death. These 3 conceptual frameworks of protein aggregation (pathogenic, epiphenomenon, protective) are difficult to resolve because of the inability to probe brain tissue in real time. Whereas animal models, in which neither PD nor AD occur in natural states, consistently support a pathogenic role of protein aggregation, indirect evidence from human studies does not. We hypothesize that (1) current biomarkers of protein aggregates may be relevant to common pathology but not to subgroup pathogenesis and (2) disease-modifying treatments targeting oligomers or fibrils might be futile or deleterious because these proteins are epiphenomena or protective in the human brain under molecular stress. Future precision medicine efforts for molecular targeting of neurodegenerative diseases may require analyses not anchored on current clinicopathologic criteria but instead on biological signals generated from large deeply phenotyped aging populations or from smaller but well-defined genetic-molecular cohorts.

OTHER RESEARCH OF INTEREST (Continued)

Magnetic Resonance Imaging-Guided Phase 1 Trial of Putaminal AADC Gene Therapy for Parkinson's Disease.

Christine CW[1], Bankiewicz KS[2], Van Laar AD[3], Richardson RM[4], Ravina B[5], Kells AP[5], Boot B[5], Martin AJ[6], Nutt J[7], Thompson ME[2], Larson PS[2].

Ann Neurol. **2019 Feb 25**. doi: 10.1002/ana.25450. PMID: 30802998. [Epub ahead of print]

OBJECTIVE: To understand the safety, putaminal coverage, and enzyme expression of adeno-associated viral vector serotype-2 encoding the complementary DNA for the enzyme, aromatic L-amino acid decarboxylase (VY-AADC01), delivered using novel intraoperative monitoring to optimize delivery.

METHODS: Fifteen subjects (three cohorts of 5) with moderately advanced Parkinson's disease and medically refractory motor fluctuations received VY-AADC01 bilaterally coadministered with gadoteridol to the putamen using intraoperative magnetic resonance imaging (MRI) guidance to visualize the anatomic spread of the infusate and calculate coverage. Cohort 1 received 8.3×10^{11} vg/ml and ≤450 µl per putamen (total dose, $\leq 7.5 \times 10^{11}$ vg); cohort 2 received the same concentration (8.3×10^{11} vg/ml) and ≤900 µl per putamen (total dose, $\leq 1.5 \times 10^{12}$ vg); and cohort 3 received 2.6×10^{12} vg/ml and ≤900 µl per putamen (total dose, $\leq 4.7 \times 10^{12}$ vg). (18)F-fluoro-L-dihydroxyphenylalanine positron emission tomography (PET) at baseline and 6 months postprocedure assessed enzyme activity; standard assessments measured clinical outcomes.

RESULTS: MRI-guided administration of ascending VY-AADC01 doses resulted in putaminal coverage of 21% (cohort 1), 34% (cohort 2), and 42% (cohort 3). Cohorts 1, 2, and 3 showed corresponding increases in enzyme activity assessed by PET of 13%, 56%, and 79%, and reductions in antiparkinsonian medication of -15%, -33%, and -42%, respectively, at 6 months. At 12 months, there were dose-related improvements in clinical outcomes, including increases in patient-reported ON-time without troublesome dyskinesia (1.6, 3.3, and 1.5 hours, respectively) and quality of life.

INTERPRETATION: Novel intraoperative monitoring of administration facilitated targeted delivery of VY-AADC01 in this phase 1 study, which was well tolerated. Increases in enzyme expression and clinical improvements were dose dependent. ClinicalTrials.gov Identifier: NCT01973543 ANN NEUROL 2019.

The GC-MS metabolomics signature in patients with fibromyalgia syndrome directs to dysbiosis as an aspect contributing factor of FMS pathophysiology.

Malatji BG[1], Mason S[2], Mienie LJ[1], Wevers RA[3], Meyer H[4], van Reenen M[1], Reinecke CJ[1].

Metabolomics. **2019 Mar 27**;15(4):54. doi: 10.1007/s11306-019-1513-6. PMID: 30919098.

INTRODUCTION: Fibromyalgia syndrome (FMS) is a chronic pain syndrome. Previous analyses of untargeted metabolomics data indicated altered metabolic profile in FMS patients.

OBJECTIVES: We report a semi-targeted explorative metabolomics study on the urinary metabolite profile of FMS patients; exploring the potential of urinary metabolite information to augment existing medical diagnosis.

METHODS: All cases were females. Patients had a medical history of persistent FMS (n = 18). Control groups were first-generation family members of the patients (n = 11), age-related individuals without indications of FMS (n = 10), and healthy, young (18-22 years) individuals (n = 41). The biofluid investigated was early morning urine samples. Data generation was done through gas chromatography-mass spectrometry (GC-MS) analysis and data processing and analyses were performed using Matlab, R, SPSS and SAS software.

RESULTS: Quantitative analysis revealed the presence of 196 metabolites. Unsupervised and supervised multivariate analyses distinguished all three control groups and the FMS patients, which could be related to 14 significantly increased metabolites. These metabolites are associated with energy metabolism, digestion and metabolism of carbohydrates and other host and gut metabolites.

CONCLUSIONS: Overall, urinary metabolite profiles in the FMS patients suggest: (1) energy utilization is a central aspect of this pain disorder, (2) dysbiosis seems to prevail in FMS patients, indicated by disrupted microbiota metabolites, supporting the model that microbiota may alter brain function through the gut-brain axis, with the gut being a gateway to generalized pain, and (3) screening of urine from FMS is an avenue to explore for adding non-invasive clinical information for diagnosis and treatment of FMS.

OTHER RESEARCH OF INTEREST (Continued)

The Association between Mushroom Consumption and Mild Cognitive Impairment: A Community-Based Cross-Sectional Study in Singapore.

Feng L[1], Cheah IK[2], Ng MM[3], Li J[3], Chan SM[4], Lim SL[5], Mahendran R[1,6], Kua EH[1], Halliwell B[2].

J Alzheimers Dis. **2019**;68(1):197-203. doi: 10.3233/JAD-180959. PMID: 30775990.

We examined the cross-sectional association between mushroom intake and mild cognitive impairment (MCI) using data from 663 participants aged 60 and above from the Diet and Healthy Aging (DaHA) study in Singapore. Compared with participants who consumed mushrooms less than once per week, participants who consumed mushrooms >2 portions per week had reduced odds of having MCI (odds ratio=0.43, 95% CI 0.23-0.78, p=0.006) and this association was independent of age, gender, education, cigarette smoking, alcohol consumption, hypertension, diabetes, heart disease, stroke, physical activities, and social activities. Our cross-sectional data support the potential role of mushrooms and their bioactive compounds in delaying neurodegeneration.

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