GULF WAR ILLNESS

Exercise challenge alters Default Mode Network dynamics in Gulf War Illness.

Rayhan RU[1,2], Washington SD[3], Garner R[3], Zajur K[3], Martinez Addiego F[3], VanMeter JW[4], Baraniuk JN[3].

BMC Neurosci. **2019 Feb 21**;20(1):7. doi: 10.1186/s12868-019-0488-6. PMID: 30791869.

BACKGROUND: Gulf War Illness (GWI) affects 30% of veterans from the 1991 Gulf War and has no known cause. Everyday symptoms include pain, fatigue, migraines, and dyscognition. A striking syndromic feature is post-exertional malaise (PEM). This is recognized as an exacerbation of everyday symptoms following a physically stressful or cognitively demanding activity. The underlying mechanism of PEM is unknown. We previously reported a novel paradigm that possibly captured evidence of PEM by utilizing fMRI scans taken before and after sub-maximal exercises. We hypothesized that A) exercise would be a sufficient physically stressful activity to induce PEM and B) Comparison of brain activity before and after exercise would provide evidence of PEM's effect on cognition. We reported two-exercise induced GWI phenotypes with distinct changes in brain activation patterns during the completion of a 2-back working memory task (also known as two-back > zero-back).

RESULTS: Here we report unanticipated findings from the reverse contrast (zero-back > two-back), which allowed for the identification of task-related deactivation patterns. Following exercise, patients developed a significant increase in deactivation patterns within the Default Mode Network (DMN) that was not seen in controls. The DMN is comprised of regions that are consistently down regulated during external goal-directed activities and is often altered within many neurological disease states.

CONCLUSIONS: Exercise-induced alterations within the DMN provides novel evidence of GWI pathophysiology. More broadly, results suggest that task-related deactivation patterns may have biomarker potential in Gulf War Illness.

Gastrointestinal neuroimmune disruption in a mouse model of Gulf War illness.

Hernandez S[1], Fried DE[1], Grubišić V[1], McClain JL[1], Gulbransen BD[1,2].

FASEB J. **2019 Feb 21**:fj201802572R. doi: 10.1096/fj.201802572R. PMID: 30789759. [Epub ahead of print]

Gulf War illness (GWI) is a chronic multisymptom disorder that is prominent in Gulf War veterans. Major unexplained symptoms of GWI include functional gastrointestinal disorders and undiagnosed illnesses, including neurologic disorders. Exposure to the antinerve gas drug pyridostigmine bromide (PB) is linked to the development of GWI, but the exact mechanisms remain unclear. Here, we tested the hypothesis that PB alters gut function by disrupting the neural and immune systems of the intestine. We exposed male and female mice to physiologically comparable amounts of PB that match the dose, route, and time frame of exposure experienced by Gulf War veterans and assessed the acute and chronic impacts on gastrointestinal functions, the functional architecture of the enteric nervous system, and immune responses in the gut and brain. Exposure to PB drove acute alterations to colonic motility and structure in both male and female mice that transitioned to chronic changes in gut functions. PB drove acute alterations to enteric neural and glial activity, glial reactivity, and neuron survival with glial reactivity persisting into the chronic phase in male mice. Despite having no effect on colonic permeability, exposure to PB caused major shifts in the expression of proinflammatory cytokines and chemokines in the colon and brain that suggest immunosuppressive effects. Interestingly, immune disruption was still evident in the colon and brain in female animals at 1 mo following exposure to PB. Together, our results show that the paradigm of PB exposure experienced by veterans of the Persian Gulf War contributes to long-lasting pathophysiology by driving enteric neuroinflammation, promoting immunosuppression, and altering functional anatomy of the colon in a sex-dependent manner.

CHRONIC FATIGUE SYNDROME

Increased risk of chronic fatigue syndrome in patients with inflammatory bowel disease: a population-based retrospective cohort study.

Tsai SY[1,2,3,4,5], Chen HJ[6,7], Lio CF[8], Kuo CF[9], Kao AC[8], Wang WS[9], Yao WC[10], Chen C[8], Yang TY[11,12,13].

J Transl Med. **2019 Feb 22**;17(1):55. doi: 10.1186/s12967-019-1797-3. PMID: 30795765.

BACKGROUND: Similarities in the symptoms of chronic fatigue syndrome (CFS) and inflammatory bowel disease (IBD) have been observed as follows: severe disease activity in IBD correlates with severe fatigue, major psychiatric signs, the common use of medication, and bacterial translocation. One of several hypotheses for explaining the mechanisms underlying CFS suggests a similarity to the impaired intestinal mucosa of IBD. "This study investigated the risk of incident CFS among patients with IBD".

METHODS: We conducted a population-based retrospective cohort study by using Taiwan's National Health Insurance Research Database to evaluate the subsequent risk of CFS in patients with IBD, according to demographic characteristics and comorbidities. The exposure cohort comprised 2163 patients with new diagnoses of IBD. Each patient was randomly selected and frequency matching according to gender and age with four participants from the general population who had no history of CFS at the index date (control cohort). Cox proportional hazards regression analysis was conducted to estimate the relationship between IBD and the subsequent risk of CFS.

RESULTS: The exposure cohort had a significantly higher overall risk of subsequent CFS than that of the control group [adjusted hazard ratio (Christophi in Inflamm Bowel Dis 18(12):2342-2356, 2012) = 2.25, 95%, confidence interval (Aaron and Buchwald in Ann Intern Med 134(9 Pt 2):868-881, 2001; Farraye et al. in Am J Gastroenterol 112:241, 2017) 1.70-2.99]. Further analysis indicated a significantly higher risk of CFS in patients who were male (HR = 3.23, 95% CI 2.12-4.91), were older than 35 years, and had IBD but without comorbidity status, e.g. Cancers, diabetes, obesity, depression, anxiety, sleep disorder, renal disease (HR = 2.50, 95% CI 1.63-3.84) after adjustment.

CONCLUSION: The findings from this population-based retrospective cohort study suggest that IBD, especially Crohn's disease, is associated with an increased risk of subsequent CFS.

Changes in the transcriptome of circulating immune cells of a New Zealand cohort with myalgic encephalomyelitis/chronic fatigue syndrome.

Sweetman E[1], Ryan M[2], Edgar C[1], MacKay A[1], Vallings R[3], Tate W[1].

Int J Immunopathol Pharmacol. **2019 Jan-Dec**;33:2058738418820402. doi: 10.1177/2058738418820402. PMCID: PMC6350121. PMID: 30791746.

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a poorly understood disease affecting 0.2%-2% of the global population. To gain insight into the pathophysiology of ME/CFS in New Zealand, we examined the transcriptomes of peripheral blood mononuclear cells by RNA-seq analysis in a small well-characterized patient group (10 patients), with age/gender-matched healthy controls (10 control subjects). Twenty-seven gene transcripts were increased 1.5- to sixfold and six decreased three- to sixfold in the patient group ($P < 0.01$). The top enhanced gene transcripts, IL8, NFKBIA and TNFAIP3, are functionally related to inflammation, and significant changes were validated for IL8 and NFKBIA by quantitative polymerase chain reaction (qPCR). Functional network analysis of the altered gene transcripts ($P < 0.01$) detected interactions between the products related to inflammation, circadian clock function, metabolic dysregulation, cellular stress responses and mitochondrial function. Ingenuity pathway analysis ($P < 0.05$) provided further insights into the dysfunctional physiology, highlighting stress and inflammation pathways. This analysis provides novel insights into the molecular changes in ME/CFS and contributes to the understanding of the pathophysiological mechanisms of the disease.

HEADACHE and MIGRAINE

Increased cerebral responses to salient transitions between alternating stimuli in chronic migraine with medication overuse headache and during migraine attacks.

Bogdanov VB[1,2], Bogdanova OV[1,2], Viganò A[2,3,4], Noirhomme Q[5,6], Laureys S[5,6], Dallel R[7,8,9], Phillips C[5,10], Schoenen J[2].

Cephalalgia. **2019 Feb 20**:333102418825359. doi: 10.1177/0333102418825359. PMID: 30786732. [Epub ahead of print]

INTRODUCTION: In a previous study exploring central pain modulation with heterotopic stimuli in healthy volunteers, we found that transitions between sustained noxious and innocuous thermal stimulations on the foot activated the "salience matrix". Knowing that central sensory processing is abnormal in migraine, we searched in the present study for possible abnormalities of these salient transitional responses in different forms of migraine and at different time points of the migraine cycle.

METHODS: Participants of both sexes, mostly females, took part in a conditioned pain modulation experiment: Migraineurs between (n = 14) and during attacks (n = 5), chronic migraine patients with medication overuse headache (n = 7) and healthy volunteers (n = 24). To evoke the salience response, continuous noxious cold or innocuous warm stimulations were alternatively applied on the right foot. Cerebral blood oxygenation level dependent responses were recorded with fMRI.

RESULTS: Switching between the two stimulations caused a significant transition response in the "salience matrix" in all subject groups (effect of the condition). Moreover, some group effects appeared on subsequent post-hoc analyses. Augmented transitional blood oxygenation level dependent responses in the motor cortex and superior temporal sulcus were found in two patient groups compared to healthy controls: chronic migraine with medication overuse headache patients and migraineurs recorded during an attack. In chronic migraine with medication overuse headache patients, salience-related responses were moreover greater in the premotor cortex, supplementary motor area, lingual gyrus and dorso-medial prefrontal cortex and other "salience matrix" areas, such as the anterior cingulate and primary somatosensory cortices.

CONCLUSION: This study shows salience-related hyperactivation of affective and motor control areas in chronic migraine with medication overuse headache patients and, to a lesser extent, in episodic migraine patients during an attack. The greater extension of exaggerated blood oxygenation level dependent responses to unspecific salient stimuli in chronic migraine with medication overuse headache than during a migraine attack could be relevant for headache chronification.

Cross-Sectional Evaluation of the Psychometric Properties of the Headache-Specific Locus of Control Scale in People With Migraine.

Grinberg AS[1], Seng EK[2,3].

Headache. **2019 Feb 19**. doi: 10.1111/head.13485. PMID: 30784040. [Epub ahead of print]

OBJECTIVE: This study aims to investigate the psychometric properties (component structure, reliability, and construct validity) of the Headache-Specific Locus of Control scale in several clinical migraine populations.

BACKGROUND: Headache-specific locus of control beliefs may impact a person's behavioral decisions that affect the likelihood of migraine attack onset, emotional responses to migraine attacks, coping strategies used, and treatment adherence. The 33-item Headache-Specific Locus of Control scale is the most widely used measure of locus of control specific to headache yet psychometric evaluations remain limited.

METHODS: Six hundred and ninety-five adults with a diagnosis of migraine from 5 different research studies completed cross-sectional self-report measures including the Headache-Specific Locus of Control scale and measures of quality of life and disability (Migraine-Specific Quality of Life Questionnaire and Migraine Disability Assessment).

RESULTS: Five Headache-Specific Locus of Control components emerged from Horn's Parallel Analysis, Minimum Average Partial test, and Principal Component Analysis (eigenvalues: Presence of Internal = 5.7, Lack of Internal = 4.0, Luck = 2.9, Doctor = 2.0, and Treatment = 1.5). The 33 Headache-Specific Locus of Control items demonstrated adequate internal consistency for total (α = 0.79) and subscale scores (α's = 0.69 to 0.88). This study found preliminary evidence of convergent validity. For example, Lack of Internal (r = -0.12, P = 0.004), Doctor (r = -0.20, P < .001), and Treatment (r = -0.12, P = .004) beliefs were associated with higher overall migraine-specific quality of life impairments.

CONCLUSIONS: The Headache-Specific Locus of Control scale is a reliable and valid measure of headache-specific locus of control. Findings suggest that headache-specific locus of control is more multidimensional than previous conceptualizations and contribute to our understanding of control beliefs as a potential mechanism for migraine treatment.

HEADACHE and MIGRAINE (Continued)

The efficacy of magnesium oxide and sodium valproate in prevention of migraine headache: a randomized, controlled, double-blind, crossover study.

Karimi N[1], Razian A[2], Heidari M[3].

Acta Neurol Belg. **2019 Feb 23**. doi: 10.1007/s13760-019-01101-x. PMID: 30798472. [Epub ahead of print]

Migraine is a disabling disorder that affects the quality of life of patients. Different medications have been used in prevention of migraine headache. In this study, we evaluated the effectiveness of magnesium oxide in comparison with valproate sodium in preventing migraine headache attacks. This is a single-center, randomized, controlled, crossover trial which is double-blind, 24-week, 2-sequence, 2-period, 2-treatment. After patient randomization into two sequences, the intervention group received magnesium oxide 500 mg and the control group received valproate sodium 400 mg two tablets each day (every 12 h) for 8 weeks. The primary efficacy variable was reduction in the number of migraine attacks and number of days with moderate or severe headache and hours with headache (duration) per month in the final of 8 weeks in comparison with baseline. Seventy patients were randomized and seven dropped out, leaving 63 for analysis. In an intention-to-treat analysis, 31 patients were in group 1 (magnesium oxide-valproate) and 32 patients were in group 2 (valproate-magnesium oxide). The mean number of migraine attacks and days per month was 1.72 ± 1.18 and 2.09 ± 1.70, with a mean duration of 15.50 ± 21.80 h in magnesium group and 1.27 ± 1.27 and 2.22 ± 1.96, with a mean duration 13.38 ± 14.10 in valproate group. This study has shown that 500 mg magnesium oxide appears to be effective in migraine prophylaxis similar to valproate sodium without significant adverse effect.

Saliva molecular inflammatory profiling in female migraine patients responsive to adjunctive cervical non-invasive vagus nerve stimulation: the MOXY Study.

Boström A[1,2], Scheele D[3,4,2], Stoffel-Wagner B[5,2], Hönig F[1,2], Chaudhry SR[1,2], Muhammad S[6], Hurlemann R[3,4,2], Krauss JK[7], Lendvai IS[3,4,2], Chakravarthy KV[8], Kinfe TM[9,10,11].

J Transl Med. **2019 Feb 22**;17(1):53. doi: 10.1186/s12967-019-1801-y. PMID: 30795781.

BACKGROUND: Rising evidence indicate that oxytocin and IL-1β impact trigemino-nociceptive signaling. Current perspectives on migraine physiopathology emphasize a cytokine bias towards a pro-inflammatory status. The anti-nociceptive impact of oxytocin has been reported in preclinical and human trials. Cervical non-invasive vagus nerve stimulation (nVNS) emerges as an add-on treatment for the preventive and abortive use in migraine. Less is known about its potential to modulate saliva inflammatory signaling in migraine patients. The rationale was to perform inter-ictal saliva measures of oxytocin and IL-1ß along with headache assessment in migraine patients with 10 weeks adjunctive nVNS compared to healthy controls.

METHODS: 12 migraineurs and 12 suitably matched healthy control were studied with inter-ictal saliva assay of pro- and anti-neuroinflammatory cytokines using enzyme-linked immuno assay techniques along with assessment of headache severity/frequency and associated functional capacity at baseline and after 10 weeks adjunctive cervical nVNS.

RESULTS: nVNS significantly reduced headache severity (VAS), frequency (headache days and total number of attacks) and significantly improved sleep quality compared to baseline ($p < 0.01$). Inter-ictal saliva oxytocin and IL-1β were significantly elevated pre- as well as post-nVNS compared to healthy controls ($p < 0.01$) and similarly showed changes that may reflect the observed clinical effects.

CONCLUSIONS: Our results add to accumulating evidence for a therapeutic efficacy of adjunct cervical non-invasive vagus nerve stimulation in migraine patients. This study failed to provide an evidence-derived conclusion addressed to the predictive value and usefulness of saliva assays due to its uncontrolled study design. However, saliva screening of mediators associated with trigemino-nociceptive traffic represents a novel approach, thus deserve future targeted headache research. Trial registration This study was indexed at the German Register for Clinical Trials (DRKS No. 00011089) registered on 21.09.2016.

CHRONIC PAIN

Systematic review and neural network analysis to define predictive variables in implantable motor cortex stimulation to treat chronic intractable pain.

Henssen DJHA[1], Witkam RL[2], Dao JCML[2], Comes DJ[2], van Walsum AMVC[3], Kozicz T[4], van Dongen R[5], Vissers K[5], Bartels RHMA[6], de Jong G[6], Kurt E[7].

J Pain. **2019 Feb 13**. pii: S1526-5900(18)30686-2. doi: 10.1016/j.jpain.2019.02.004. PMID: 30771593. [Epub ahead of print]

Implantable Motor Cortex Stimulation (iMCS) has been performed for over 25 years to treat various intractable pain syndromes. Its effectiveness shows to be highly variable and although various studies revealed predictive variables, none of these were found repeatedly. This study uses neural network analysis (NNA) to identify predictive factors of iMCS treatment of intractable pain. A systematic review provided a database of patient data on an individual level of patients who underwent iMCS to treat refractory pain between 1991 and 2017. Responders were defined as patients with a pain relief >40% as measured by numerical rating scale (NRS) score. NNA was carried out to predict outcome of iMCS and to identify predictive factors that impacted the outcome of iMCS. The outcome prediction value of the NNA was expressed as mean accuracy, sensitivity and specificity. The NNA furthermore provided the mean weight of predictive variables, which shows the impact of the predictive variable on the prediction. The mean weight was converted into the mean relative influence (M), a value that varies between 0-100%. A total of 358 patients were included (202 males (56.4%); mean age: 54.2 ±13.3), 201 of which were responders to iMCS. NNA had a mean accuracy of 66.3% and a sensitivity and specificity of 69.8% and 69.4%, respectively. NNA further identified six predictive variables that had a relatively high M: 1) the sex of the patients (M=19.7%); 2) the origin of the lesion (M=15.1%); 3) the preoperative NRS score (M= 9.2%); 4) preoperative use of rTMS (M=7.3%); 5) preoperative intake of opioids (M=7.1%) and; 6) the follow-up period (M= 13.1%). The results from the present study show that these six predictive variables influence the outcome of iMCS and that based on these variables, a fair prediction model can be built to predict outcome after iMCS surgery.

PERSPECTIVE: The presented neural network analysis (NNA) analyzed the functioning of computational models and modeled non-linear statistical data. Based on this NNA, six predictive variables were identified which are suggested to be of importance in the improvement of future implantable motor cortex stimulation (iMCS) to treat chronic pain.

Gender Differences in the Prevalence and Characteristics of Pain in Spain: Report from a Population-Based Study.

Jiménez-Trujillo I[1], López-de-Andrés A[1], Del Barrio JL[1], Hernández-Barrera V[1], Valero-de-Bernabé M[2], Jiménez-García R[1].

Pain Med. **2019 Feb 21**. pii: pnz004. doi: 10.1093/pm/pnz004. PMID: 30789640. [Epub ahead of print]

OBJECTIVE: To assess the prevalence and characteristics of chronic neck pain, chronic low back pain, and migraine or frequent headaches among Spanish adults in 2014 according to gender, to identify predictors for each of these types of pains, and to compare the prevalence with those found in 2009.

DESIGN: Cross-sectional study.

SETTING: Spain.

METHODS: We used data collected from the 2014 European Health Interview Survey (N = 22,842). Sociodemographic features, self-rated health status, lifestyle habits, comorbid conditions, pain characteristics, and self-reported use of medications were analyzed.

RESULTS: The prevalence of all types of pain was significantly higher among women than men. For chronic neck pain, the figures were 25.68% vs 12.54%, for chronic low back pain, 27.03% vs 18.83%, and for migraine or frequent headaches, 15.93% vs 6.74%, in women and men, respectively. Predictors of these types of pain included female gender, advanced age, poor self-rated health, psychological distress, comorbidities, and obesity. The prevalence of neck pain and low back pain increased from 2009 to 2014 for both sexes, and the prevalence of migraine or frequent headaches remained stable over time.

CONCLUSIONS: The prevalence and intensity of all the forms of chronic pain were higher among women. Women experiencing pain used prescribed medications for pain, anxiety, and/or depression and sleeping pills more than men. The prevalence of chronic neck and low back has increased in the last five years in Spain, and the prevalence of migraine or frequent headaches has remained stable.

CHRONIC PAIN (Continued)

Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial.

Haight BR[1], Learned SM[1], Laffont CM[1], Fudala PJ[1], Zhao Y[1], Garofalo AS[1], Greenwald MK[2], Nadipelli VR[1], Ling W[3], Heidbreder C[1]; RB-US-13-0001 Study Investigators, Collaborators (36).

Lancet. **2019 Feb 23**;393(10173):778-790. doi: 10.1016/S0140-6736(18)32259-1. PMID: 30792007. Epub 2019 Feb 18.

BACKGROUND: RBP-6000, referred to as BUP-XR (extended-release buprenorphine), is a subcutaneously injected, monthly buprenorphine treatment for opioid use disorder. BUP-XR provides sustained buprenorphine plasma concentrations to block drug-liking of abused opioids over the entire monthly dosing period, while controlling withdrawal and craving symptoms. Administration of BUP-XR in a health-care setting also mitigates abuse, misuse, diversion, and unintentional exposure. We aimed to investigate the efficacy of different BUP-XR dosing regimens in participants with opioid use disorder.

METHODS: This randomised, double-blind, placebo-controlled, phase 3 trial was done at 36 treatment centres in the USA. Treatment-seeking adults aged 18-65 years who had moderate or severe opioid use disorder (as defined by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders) entered an open-label run-in phase of up to 2 weeks' treatment with buprenorphine-naloxone sublingual film. Eligible participants were then randomly assigned (4:4:1:1) with an interactive voice/web-response system to receive BUP-XR 300 mg/300 mg (six injections of 300 mg), BUP-XR 300 mg/100 mg (two injections of 300 mg plus four injections of 100 mg), or volume-matched placebo every 28 days, and received weekly individual drug counselling. No supplemental buprenorphine was allowed. The primary efficacy endpoint was participants' percentage abstinence from opioid use, defined as the percentage of each participant's negative urine samples and self-reports of illicit opioid use from week 5 to week 24, analysed in the full analysis set. Safety was assessed in all participants who received at least one dose of BUP-XR or placebo. This study is registered with **ClinicalTrials.gov**, number **NCT02357901**.

FINDINGS: From Jan 28, 2015, to Nov 12, 2015, 1187 potential participants were screened, 665 entered run-in, and 504 received BUP-XR 300 mg/300 mg (n=201), BUP-XR 300 mg/100 mg (n=203), or placebo (n=100). Mean participants' percentage abstinence was 41·3% (SD 39·7) for BUP-XR 300 mg/300 mg and 42·7% (38·5) for 300 mg/100 mg, compared with 5·0% (17·0) for placebo (p<0·0001 for both BUP-XR regimens). No compensatory non-opioid drug use was observed during BUP-XR treatment. The most common adverse events were headache (17 [8%] participants in the BUP-XR 300 mg/300 mg group vs 19 [9%] participants in the BUP-XR 300 mg/100 mg group vs six [6%] participants in the placebo group), constipation (16 [8%] vs 19 [9%] vs 0), nausea (16 [8%] vs 18 [9%] vs five [5%]), and injection-site pruritis (19 [9%] vs 13 [6%] vs four [4%]). The BUP-XR safety profile was consistent with other buprenorphine products for treatment of opioid use disorder, except for injection-site reactions, which were reported in more than 5% of all participants who received BUP-XR, but were mostly mild and not treatment-limiting. INTERPRETATION: Participants' percentage abstinence was significantly higher in both BUP-XR groups than in the placebo group. Treatment with BUP-XR was also well tolerated. The availability of this monthly formulation, delivered by health-care providers, represents an advance in treatment for opioid use disorder that enhances the benefits of buprenorphine by delivering sustained, optimal exposure, while reducing risks of current buprenorphine products. FUNDING: Indivior.

The impact of anxiety on chronic musculoskeletal pain and the role of astrocyte activation.

Burston JJ[1,2], Valdes AM[1,3], Woodhams SG[1,2], Mapp PI[1, 3], Stocks J[1,3], Watson DJG[1,2], Gowler PRW[1,2], Xu L[1,2], Sagar DR[1,2], Fernandes G[3,4], Frowd N[1,3], Marshall L[1,3], Zhang W[1,3,4], Doherty M[1,3,4,5], Walsh DA[1,3,4,5], Chapman V[1,2,4].

Pain. **2019 Mar**;160(3):658-669. doi: 10.1097/j.pain.0000000000001445. PMID: 30779717.

Anxiety and depression are associated with increased pain responses in chronic pain states. The extent to which anxiety drives chronic pain, or vice versa, remains an important question that has implications for analgesic treatment strategies. Here, the effect of existing anxiety on future osteoarthritis (OA) pain was investigated, and potential mechanisms were studied in an animal model. Pressure pain detection thresholds, anxiety, and depression were assessed in people with (n = 130) or without (n = 100) painful knee OA. Separately, knee pain and anxiety scores were also measured twice over 12 months in 4730 individuals recruited from the general population. A preclinical investigation of a model of OA pain in normo-anxiety Sprague-Dawley (SD) and high-anxiety Wistar Kyoto (WKY) rats assessed underlying neurobiological mechanisms. Higher anxiety, independently from depression, was associated with significantly lower pressure pain detection thresholds at sites local to ($P < 0.01$) and distant from ($P < 0.05$) the painful knee in patients with OA. Separately, high anxiety scores predicted increased risk of knee pain onset in 3274 originally pain-free people over the 1-year period (odds ratio = 1.71; 95% confidence interval = 1.25-2.34, $P < 0.00083$). Similarly, WKY rats developed significantly lower ipsilateral and contralateral hind paw withdrawal thresholds in the monosodium iodoacetate model of OA pain, compared with SD rats ($P = 0.0005$). Linear regressions revealed that baseline anxiety-like behaviour was predictive of lowered paw withdrawal thresholds in WKY rats, mirroring the human data. This augmented pain phenotype was significantly associated with increased glial fibrillary acidic protein immunofluorescence in pain-associated brain regions, identifying supraspinal astrocyte activation as a significant mechanism underlying anxiety-augmented pain behaviour.

CHRONIC PAIN (Continued)

National Trends in Prescription Opioid Risk Mitigation Practices: Implications for Prescriber Education.

Alford DP[1,2], Lazure P[3], Murray S[3], Hardesty I[1], Krause JR[1], White JL[1].

Pain Med. **2019 Feb 21**. pii: pny298. doi: 10.1093/pm/pny298. PMID: 30789651. [Epub ahead of print]

OBJECTIVES: To assess national trends in selected prescription opioid risk mitigation practices and associations with prescriber type, state-specific opioid overdose severity, and required pain education.

METHODS: Analysis of the national SCOPE of Pain registrants' baseline self-report of five safer opioid prescribing practices over three years (March 2013-Februrary 2016).

RESULTS: Of 6,889 registrants for SCOPE of Pain, 70-94% reported performing each of five opioid risk mitigation practices for "most or all" patients, with 49% doing so for all five practices. Only 28% performed all five practices for "all" patients prescribed opioids. There were few differences among three yearly cohorts. Advanced practice nurses reported performing practices for "all" patients more often than physicians or physician assistants. Clinicians from states with high opioid overdose rates reported significantly higher implementation of most practices, compared with clinicians from states with low rates.

CONCLUSIONS: Prescribers report low levels of employing five opioid risk mitigation practices for all patients prescribed opioids before attending a safer opioid prescribing training. Policy Implications. Safer opioid prescribing education should transition from knowledge acquisition toward universal implementation of opioid risk mitigation practices.

OTHER RESEARCH OF INTEREST

Gender differences in rates and predictors of individual psychotherapy initiation and completion among Veterans Health Administration users recently diagnosed with PTSD.

Valenstein-Mah H[1], Kehle-Forbes S[1], Nelson D[1], Danan ER[1], Vogt D[2], Spoont M[1].

Psychol Trauma. **2019 Jan 28**. doi: 10.1037/tra0000428. PMID: 30688508. [Epub ahead of print]

OBJECTIVE: Most veterans with posttraumatic stress disorder (PTSD) who receive care from the Veterans Health Administration (VHA) do not receive individual psychotherapy. The purpose of this study was to explore gender differences in initiation and completion of a sufficient course (defined as attending 8 or more sessions) of individual psychotherapy among male and female VHA users recently diagnosed with PTSD.

METHOD: Participants (N = 7,218) were veterans in a prospective national cohort survey of VHA users diagnosed with PTSD; oversampling was used to increase representation of women and minority veterans.

RESULTS: Forty-two percent of the sample (40.1% of men, 52.3% of women) initiated individual psychotherapy within 6 months of their index PTSD diagnosis. Of those who initiated, 12.1% (10.8% of men, 17.7% of women) completed a sufficient course of individual psychotherapy. Women were generally more likely than men to initiate individual psychotherapy. However, we found an interaction between gender and age, such that younger men were more likely to initiate psychotherapy than older men; age was not significantly associated with initiation among women. Regarding completion of individual psychotherapy, an interaction between gender and beliefs about psychotherapy was found, such that men were less likely to complete individual psychotherapy when they held more negative beliefs about psychotherapy; these beliefs did not significantly impact female veterans' likelihood of completing psychotherapy.

CONCLUSIONS: Overall, while female veterans are more likely than male veterans with PTSD to initiate individual psychotherapy, rates of initiation and completion of individual psychotherapy for both genders remain relatively low. Interventions are needed to increase engagement in individual psychotherapy, particularly for male veterans with PTSD.

OTHER RESEARCH OF INTEREST (Continued)

Diagnostic algorithms to study post-concussion syndrome using electronic health records: validating a method to capture an important patient population.

Dennis J[1], Yengo-Kahn AM[2], Kirby P[3], Solomon GS[4], Cox NJ[5], Zuckerman SL[6].

J Neurotrauma. **2019 Feb 16**. doi: 10.1089/neu.2018.5916. PMID: 30773988. [Epub ahead of print]

Post-concussion syndrome (PCS) is characterized by persistent cognitive, somatic, and emotional symptoms after a mild traumatic brain injury (mTBI). Genetic and other biological variables may contribute to PCS etiology, and the emergence of biobanks linked to electronic health records (EHR) offers new opportunities for research on PCS. We sought to validate the use of EHR data of PCS patients by comparing two diagnostic algorithms deployed in the Vanderbilt University Medical Center de-identified database of 2.8 million patient EHR. The algorithms identified individuals with PCS by: (i) natural language processing (NLP) of narrative text in the EHR combined with structured demographic, diagnostic, and encounter data; or (ii) coded billing and procedure data. The predictive value of each algorithm was assessed, and cases and controls identified by each approach were compared on demographic and medical characteristics. The (i) NLP algorithm identified 507 cases and 10,857 controls. The positive predictive value (PPV) in the cases was 82% and the negative predictive value in the controls was 78%. Conversely, the (ii) coded algorithm identified 1,142 patients with two or more PCS billing codes and had a PPV of 76%. Comparisons of PCS controls to both case groups recovered known epidemiology of PCS: cases were more likely than controls to be female and to have pre-morbid diagnoses of anxiety, migraine, and PTSD. In contrast, controls and cases were equally likely to have ADHD and learning disabilities, in accordance with the findings of recent systematic reviews of PCS risk factors. We conclude that EHR are a valuable research tool for PCS. Ascertainment based on coded data alone had a predictive value comparable to an NLP algorithm, recovered known PCS risk factors, and maximized the number of included patients.

Patient Perspectives on Osseointegration: A National Survey of Veterans with Upper Limb Amputation.

Resnik L[1,2], Benz H[3], Borgia M[1], Clark MA[3,4].

PM R. **2019 Feb 19**. doi: 10.1002/pmrj.12147. PMID: 30784201. [Epub ahead of print]

INTRODUCTION: Osseointegrated (OI) prostheses have a unique benefit-risk profile among prosthetic alternatives and have been marketed in the U.S. under a Humanitarian Device Exemption since 2015. Information about upper limb prosthesis user perspectives on benefits and risks, prosthesis-user subpopulations for whom OI is most acceptable, and outcomes that matter most to patients could help inform clinical and regulatory decision-making. Recent 21st Century Cures legislation expanded the role of patient experience data in the FDA decision-making process, recognizing that patient perspectives may be informative to regulators.

OBJECTIVE: To better understand prosthesis user perspectives about the benefits and risks associated with upper limb OI prostheses.

DESIGN: Patient perspective survey

SETTING: Telephone administration

PARTICIPANTS: National sample of Veterans with upper limb loss.

INTERVENTIONS: NA

MAIN OUTCOME MEASURES: Benefit-Risk survey developed for this study

RESULTS: 28% of unilateral and 13% of bilateral amputees were willing to consider osseointegration surgery. Multivariate logistic regression models (OR; 95%CI) showed that transhumeral amputation level (OR 1.40; 1.01-1.98) was associated with greater willingness to consider surgery, while older age (OR 0.17; 0.09-0.32) and higher VR-12 MCS (OR 0.53; 0.35-0.81) were associated with less willingness. Having a durable/reliable device, the ability to do more activities, and having a comfortable device were rated as very important or somewhat important by 98% or more for every risk condition

CONCLUSIONS: Persons who were older, had transradial amputation (compared to transhumeral), and those who had better mental functioning were less willing to consider this surgery. Respondents who were willing to consider surgery indicated that the most important potential benefits were obtaining a durable/reliable device, the ability to do more activities, and having a comfortable device. Most were willing to accept one or more risks of surgery, with long term risks including chronic pain, loss of nerve function or device failure, considered the most unacceptable.

OTHER RESEARCH OF INTEREST (Continued)

Cholecystokinin and Alzheimer's disease: a biomarker of metabolic function, neural integrity, and cognitive performance.

Plagman A[1], Hoscheidt S[2], McLimans KE[1], Klinedinst B[3], Pappas C[1], Anantharam V[4], Kanthasamy A[4], Willette AA[5]; Alzheimer's Disease Neuroimaging Initiative.

Neurobiol Aging. **2019 Apr**;76:201-207. doi: 10.1016/j.neurobiolaging.2019.01.002. PMID: 30739077. Epub 2019 Jan 9.

Cholecystokinin (CCK) is a satiety hormone that is highly expressed in brain regions like the hippocampus. CCK is integral for maintaining or enhancing memory and thus may be a useful marker of cognitive and neural integrity in participants with normal cognition, mild cognitive impairment, and Alzheimer's disease (AD). Cerebrospinal fluid (CSF) CCK levels were examined in 287 subjects from the Alzheimer's Disease Neuroimaging Initiative. Linear or voxelwise regression was used to examine associations between CCK, regional gray matter, CSF AD biomarkers, and cognitive outcomes. Briefly, higher CCK was related to a decreased likelihood of having mild cognitive impairment or AD, better global and memory scores, and more gray matter volume primarily spanning posterior cingulate cortex, parahippocampal gyrus, and medial prefrontal cortex. CSF CCK was also strongly related to higher CSF total tau (R^2 = 0.342) and p-tau-181 (R^2 = 0.256) but not Aβ1-42. Tau levels partially mediated CCK and cognition associations. In conclusion, CCK levels may reflect compensatory protection as AD pathology progresses.

Artificially Sweetened Beverages and Stroke, Coronary Heart Disease, and All-Cause Mortality in the Women's Health Initiative.

Mossavar-Rahmani Y[1], Kamensky V[1], Manson JE[2], Silver B[3], Rapp SR[4], Haring B[5], Beresford SAA[6], Snetselaar L[7], Wassertheil-Smoller S[1].

Stroke. **2019 Mar**;50(3):555-562. doi: 10.1161/STROKEAHA.118.023100. PMID: 30802187.

Background and Purpose- We examine the association between self-reported consumption of artificially sweetened beverages (ASB) and stroke and its subtypes, coronary heart disease, and all-cause mortality in a cohort of postmenopausal US women.

Methods- The analytic cohort included 81 714 women from the Women's Health Initiative Observational Study, a multicenter longitudinal study of the health of 93 676 postmenopausal women of ages 50 to 79 years at baseline who enrolled in 1993 to 1998. This prospective study had a mean follow-up time of 11.9 years (SD of 5.3 years.) Participants who completed a follow-up visit 3 years after baseline were included in the study.

Results- Most participants (64.1%) were infrequent consumers (never or <1/week) of ASB, with only 5.1% consuming ≥2 ASBs/day. In multivariate analyses, those consuming the highest level of ASB compared to never or rarely (<1/wk) had significantly greater likelihood of all end points (except hemorrhagic stroke), after controlling for multiple covariates. Adjusted models indicated that hazard ratios and 95% confidence intervals were 1.23 (1.02-1.47) for all stroke; 1.31 (1.06-1.63) for ischemic stroke; 1.29 (1.11-1.51) for coronary heart disease; and 1.16 (1.07-1.26) for all-cause mortality. In women with no prior history of cardiovascular disease or diabetes mellitus, high consumption of ASB was associated with more than a 2-fold increased risk of small artery occlusion ischemic stroke hazard ratio =2.44 (95% confidence interval, 1.47-4.04.) High consumption of ASBs was associated with significantly increased risk of ischemic stroke in women with body mass index ≥30; hazard ratio =2.03 (95% confidence interval, 1.38-2.98).

Conclusions- Higher intake of ASB was associated with increased risk of stroke, particularly small artery occlusion subtype, coronary heart disease, and all-cause mortality. Although requiring replication, these new findings add to the potentially harmful association of consuming high quantities of ASB with these health outcomes.

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