GULF WAR ILLNESS

Corticosterone and pyridostigmine/DEET exposure attenuate peripheral cytokine expression: supporting a dominant role for neuroinflammation in a mouse model of Gulf War Illness.

Michalovicz LT[1], Locker AR[1], Kelly KA[1], Miller JV[1], Barnes Z[2], Fletcher MA[2], Miller DB[1], Klimas NG[2], Morris M[3], Lasley SM[4], O'Callaghan JP[5].

Neurotoxicology. **2018 Oct 16**. pii: S0161-813X(18)30285-7. doi: 10.1016/j.neuro.2018.10.006. [Epub ahead of print]

Gulf War Illness (GWI) is a chronic multi-symptom disorder experienced by as many as a third of the veterans of the 1991 Gulf War; the constellation of "sickness behavior" symptoms observed in ill veterans is suggestive of a neuroimmune involvement. Various chemical exposures and conditions in theater have been implicated in the etiology of the illness. Previously, we found that GW-related organophosphates (OPs), such as the sarin surrogate, DFP, and chlorpyrifos, cause neuroinflammation. The combination of these exposures with exogenous corticosterone (CORT), mimicking high physiological stress, exacerbates the observed neuroinflammation. The potential relationship between the effects of OPs and CORT on the brain versus inflammation in the periphery has not been explored. Here, using our established GWI mouse model, we investigated the effects of CORT and DFP exposure, with or without a chronic application of pyridostigmine bromide (PB) and N,N-diethyl-meta-toluamide (DEET), on cytokines in the liver and serum. While CORT primed DFP-induced neuroinflammation, this effect was largely absent in the periphery. Moreover, the changes found in the peripheral tissues do not correlate with the previously reported neuroinflammation. These results not only support GWI as a neuroimmune disorder, but also highlight the separation between

CHRONIC FATIGUE SYNDROME

Cost-effectiveness of interventions for medically unexplained symptoms: A systematic review.

Wortman MSH[1,2], Lokkerbol J[3,4], van der Wouden JC[2], Visser B[1], van der Horst HE[2], Olde Hartman TC[5].

PLoS One. **2018 Oct 15**;13(10):e0205278. doi: 10.1371/journal.pone.0205278. PMID: 30321193. eCollection 2018.

BACKGROUND: In primary and secondary care medically unexplained symptoms (MUS) or functional somatic syndromes (FSS) constitute a major burden for patients and society with high healthcare costs and societal costs. Objectives were to provide an overview of the evidence regarding the cost-effectiveness of interventions for MUS or FSS, and to assess the quality of these studies.

METHODS: We searched the databases PubMed, PsycINFO, the National Health Service Economic Evaluation Database (NHS-EED) and the CEA registry to conduct a systematic review. Articles with full economic evaluations on interventions focusing on adult patients with undifferentiated MUS or fibromyalgia (FM), irritable bowel syndrome (IBS) and chronic fatigue syndrome (CFS), with no restrictions on comparators, published until 15 June 2018, were included. We excluded preventive interventions. Two reviewers independently extracted study characteristics and cost-effectiveness data and used the Consensus on Health Economic Criteria Checklist to appraise the methodological quality.

RESULTS: A total of 39 studies out of 1,613 articles met the inclusion criteria. Twenty-two studies reported costs per quality-adjusted life year (QALY) gained and cost-utility analyses (CUAs). In 13 CUAs the intervention conditions dominated the control conditions or had an incremental cost-effectiveness ratio below the willingness-to-pay threshold of € 50,000 per QALY, meaning that the interventions were (on average) cost-effective in comparison with the control condition. Group interventions focusing on MUS (n = 3) or FM (n = 4) might be more cost-effective than individual interventions. The included studies were heterogeneous with regard to the included patients, interventions, study design, and outcomes.

CONCLUSION: This review provides an overview of 39 included studies of interventions for patients with MUS and FSS and the methodological quality of these studies. Considering the limited comparability due to the heterogeneity of the studies, group interventions might be more cost-effective than individual interventions.

REGISTRATION: Study methods were documented in an international prospective register of systematic reviews (PROSPERO) protocol, registration number: CRD42017060424.

CHRONIC FATIGUE SYNDROME (Continued)

Pain is associated with reduced quality of life and functional status in patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.

Strand EB[1], Mengshoel AM[2], Sandvik L[3], Helland IB[4], Abraham S[5], Nes LS[6,7,8].

Scand J Pain. **2018 Oct 16**. pii: /j/sjpain.ahead-of-print/sjpain-2018-0095/sjpain-2018-0095.xml. doi: 10.1515/sjpain-2018-0095. PMID: 30325738.]

Background and aims: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is challenging to live with, often accompanied by pervasive fatigue and pain, accompanied by decreased quality of life (QoL) as well as anxiety and/or depression. Associations between higher pain, lower QoL and higher anxiety and depression have been shown in patients with various chronic pain disorders. Few studies have however examined such associations in a sample of patients with ME/CFS. The aims of the current study were to examine the impact of pain levels and compare levels of pain, health related QoL, anxiety and depression between patients with ME/CFS and healthy controls. In addition, the study aimed and to examine these relationships within the patient group only.

Methods: This is a cross-sectional questionnaire based study comparing 87 well-diagnosed patients with ME/CFS with 94 healthy controls. The De Paul Symptom Questionnaire (DSQ), the Medical Outcomes Study Short-Form Surveys (SF-36) and the Hospital Anxiety and Depression Scale (HADS) were used to examine and compare pain, physical function, QoL, anxiety and depression in patients and healthy controls. Further the pain variables were divided into pain total, pain intensity and a pain frequency score for analyses of the above mentioned variables within the patient group only.

Results: Significantly higher levels of pain, anxiety and depression, and lower levels of QoL were found in the patient group compared with healthy controls. For the patient group alone, pain was significantly associated with lower QoL in terms of physical functioning, bodily pain, general health functioning, vitality and social functioning capacity. In this patient sample, only frequency of joint pain showed significant difference in psychological variables such as depression and anxiety - depression combined.

Conclusions: ME/CFS patients differ significantly from healthy controls in pain, health related QoL, anxiety and depression. Pain is significantly associated with reduced QoL and overall a lower level of functioning. The relation between pain and anxiety and depression appears less clear. Implications Pain is for many ME/CFS patients associated with reduced physical functioning and reduced QoL. A thorough pain assessment can therefore be essential for clinicians, and subsequent medical pain treatment combined with good pain coping skills may increase functioning level and QoL for these patients. The link between joint pain and psychological factors should also be focused in clinical practice in terms of mapping and counseling. Pain should be further examined to understand the importance it may have for functioning level as reduced function is a main criteria when diagnosing the patients.

Exercise-induce hyperalgesia, complement system and elastase activation in Myalgic Encephalo-myelitis/Chronic Fatigue Syndrome - a secondary analysis of experimental comparative studies.

Polli A[1], Van Oosterwijck J[2,3], Meeus M[3,4], Lambrecht L[5], Nijs J[6], Ickmans K[6].

Scand J Pain. **2018 Oct 16**. pii: /j/sjpain.ahead-of-print/sjpain-2018-0075/sjpain-2018-0075.xml. doi: 10.1515/sjpain-2018-0075. PMID: 30325737.

Background and aims: The interaction between the immune system and pain has been thoroughly explored in the recent decades. The release of inflammatory mediators from immune cells has the capability of activating neurons and glial cells, in turn sensitizing the nervous system. Both immune system alterations and pain modulation dysfunctions have been shown in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) following exercise. However, no studies tried to explore whether these two phenomena are linked and can explain exercise-induced symptoms worsening in people with ME/CFS. We hypothesized that exercise-induced changes in descending pain modulation is associated to changes in immune system functions. We used complement system product C4a and elastase activity as indicators of immune system activity.

Methods: The study design was a secondary analysis of controlled experimental studies. Twenty-two patients with ME/CFS and 22 healthy sedentary controls were enrolled. In experiment 1, subjects performed an aerobic submaximal exercise test; in experiment 2 they underwent a self-paced exercise test. One week of rest period were set between the two exercise tests. Before and after each experiment, subjects underwent clinical assessment, pain thresholds (PPTs) measurement, and blood sampling. Immune system function was assessed measuring complement system C4a products and elastase activity.

Results: Changes in elastase activity were not associated to changes in PPTs. Associations were observed in the ME/CFS group between changes in PPTs and C4a products, following both types of exercise. After submaximal exercise, the change in C4a products was associated with the change in PPT at the thumb in patients (r=0.669, p=0.001). Similarly, after self-paced exercise the change in C4a products was associated with the change in PPT at the calf in patients (r=0.429, p=0.047). No such correlations were found in healthy controls. Regression analysis showed that C4a changes after the submaximal exercise significantly predicted the change in PPTs (R2=0.236; p=0.02).

Conclusions: Moderate associations between exercise-induced changes in PPTs and immune system activity were found only in ME/CFS. The change in the complement system following submaximal exercise might be able to explain part of the change in patient's pain thresholds, providing evidence for a potential link between immune system alteration and dysfunctional endogenous pain modulation. These results have to be taken with caution, as only one out of three measures of PPTs was found associated with C4a changes. We cannot reject the hypothesis that C4a might therefore be a confounding factor, and changes during exercise might be mediated by other mechanism. Implications Immune system changes following exercise might contribute to exercise-induced symptoms worsening in patients with ME/CFS. However, the role of the complement system is questionable.

HEADACHE and MIGRAINE

Comorbidity of migraine with ADHD in adults.

Hansen TF[1,2,3], Hoeffding LK[4], Kogelman L[5], Haspang TM[5], Ullum H[4], Sørensen E[4], Erikstrup C[6], Pedersen OB[7], Nielsen KR[8], Hjalgrim H[9,10], Paarup HM[11], Werge T[12,13,14], Burgdorf K[4].

BMC Neurol. **2018 Oct 16**;18(1):147. doi: 10.1186/s12883-018-1149-6. PMID: 30322380.

BACKGROUND: Migraine and Attention Deficit and Hyperactivity Disorder (ADHD) have been found to be associated in child and adolescent cohorts; however, the association has not been assessed in adults or otherwise healthy population. Assessing the comorbidity between ADHD and migraine may clarify the etiopathology of both diseases. Thus, the objective is to assess whether migraine (with and without visual disturbances) and ADHD are comorbid disorders.

METHODS: Participants from the Danish Blood Donor Study (N = 26,456, age 18-65, 46% female) were assessed for migraine and ADHD using the ASRS ver 1.1 clinically validated questionnaire and self-reported migraine in a cross-sectional study. Logistic regression was used to examine the comorbidity between migraine and ADHD, and their associated endophenotypes.

RESULTS: Migraine was strongly associated with ADHD (OR = 1.8, 95% CI = 1.5-2.1), (238/6152 vs 690/19,376). There was a significant interaction between age and gender, with comorbidity increasing with age and female sex. Post-hoc analysis showed that migraine with visual disturbance was generally associated with a marginally higher risk of ADHD and this was independent of ADHD endophenotypes.

CONCLUSION: Migraine and ADHD were demonstrated to be comorbid disorders; the association with ADHD was most prominent for participants with migraine with visual disturbances. Future studies will elucidate which genetic and environmental factors contribute to migraine-ADHD comorbidity.

Migraine in America Symptoms and Treatment (MAST) Study: Baseline Study Methods, Treatment Patterns, and Gender Differences.

Lipton RB[1,2,3], Munjal S[4], Alam A[4], Buse DC[1] , Fanning KM[5], Reed ML[5], Schwedt TJ[6], Dodick DW[6].

Headache. **2018 Oct 20**. doi: 10.1111/head.13407. PMID: 30341895. [Epub ahead of print]

OBJECTIVES: To summarize the baseline methods for the Migraine in America Symptoms and Treatment (MAST) Study and evaluate gender differences in sociodemographics and headache features; consultation and diagnosis patterns; and patterns of acute and preventive treatment use for migraine among study participants.

BACKGROUND: The MAST Study is a longitudinal, internet-based panel study of symptoms, approaches to management, and unmet treatment needs among US adults with migraine. This analysis focuses on the initial cross-sectional survey, conducted beginning in 2016, and is intended to update results from earlier national epidemiologic surveys of people with migraine in the United States.

METHODS: Respondents to the MAST Study were recruited from a US nationwide online research panel. Stratified random sampling identified a representative cohort of adults (aged ≥18 years). We administered a validated diagnostic screener based on modified ICHD-3 beta criteria to identify individuals with migraine averaging at least 1 monthly headache day (MHD) over the previous 3 months. A baseline assessment evaluated sociodemographic and headache features, patterns of consultation and diagnosis, and use of acute and preventive medications for migraine. Frequency data and chi-square contrasts ($P < .05$) were used to compare respondents based on gender.

RESULTS: Baseline survey data (N = 95,821) identified 18,353 respondents who met criteria for migraine, including 15,133 (women n = 11,049, men n = 4084) reporting at least 1 MHD for the preceding 3 months. The mean age of the sample was 43.1 (13.6) years; 73.0% of respondents were women, and 81.0% were Caucasian. Compared with men, women were younger (46.1 vs 42.0 years; $P < .001$); had more MHDs (5.6 vs 5.3; $P < .001$); and were more likely to report moderate or severe headache-related disability (45.9% vs 35.8%; $P < .001$) and cutaneous allodynia (43.7% vs 29.5%; $P < .001$). The lifetime rate of medical consultation for headache was 79.8% overall and slightly higher in women than in men. Women were more likely than men to have been diagnosed with migraine (48.3% vs 38.8%, $P < .001$). While 95.1% of people with migraine currently used acute treatment, the majority (58.9%) used over-the-counter (OTC) drugs to the exclusion of prescription drugs, while 11.3% used exclusively prescription drugs, and 20.5% used both. Among acute prescription medication users, women were more likely than men to take triptans (17.7% vs 14.3%, $P < .001$), while men were more likely than women to take opioids (14.5% vs 9.2%, $P < .001$). Oral formulations were used predominately (92.7% of the medication users), but men were more likely to use nasal sprays (13.6% vs 9.4%, $P < .001$) and injectables (7.9% vs 3.4%, $P < .001$). Men (14.5%) were also significantly more likely than women (10.4%) to be taking daily oral preventive medication ($P < .001$).

CONCLUSIONS: The MAST Study identified a large sample of women and men with migraine from a sampling frame that broadly resembles the US population. Low participation rate increases the risk of response bias, however, comparisons with Census data and prior population studies for the demographic and headache characteristics of the current sample suggest that findings are generalizable to the population of people with migraine. Women had more MHDs than men, and they were more likely to report migraine-related disability and cutaneous allodynia. The lifetime consultation rate for headache was relatively high, but many with migraine symptoms reported never having received a diagnosis of migraine from a healthcare professional. Acute prescription and preventive migraine treatments are underused. Migraine persists as an underdiagnosed and undertreated public health problem in 2018, and there are many opportunities to improve the diagnosis and treatment of people with this painful, disabling condition.

HEADACHE and MIGRAINE (Continued)

100% Response Rate to Galcanezumab in Patients With Episodic Migraine: A Post Hoc Analysis of the Results From Phase 3, Randomized, Double-Blind, Placebo-Controlled EVOLVE-1 and EVOLVE-2 Studies.

Rosen N[1], Pearlman E[2], Ruff D[2], Day K[2], Jim Nagy A[3].

Headache. **2018 Oct 20**. doi: 10.1111/head.13427. PMID: 30341990. [Epub ahead of print]

OBJECTIVE: To characterize adult patients with episodic migraine who achieved 100% response to galcanezumab treatment.

BACKGROUND: Galcanezumab is a humanized monoclonal antibody that selectively binds to the calcitonin gene-related peptide (CGRP) and has demonstrated efficacy in reducing migraine headache days (MHD) in patients with episodic and chronic migraine.

METHODS: A post hoc analysis of the proportion of patients with 100% response (100% reduction from baseline in monthly MHD) was calculated for each month from pooled data of 2 double-blind, 6-month galcanezumab studies in patients with episodic migraine (4 to 14 MHD and ≥2 migraine attacks per month at baseline). The patients were randomized (1:1:2) to monthly subcutaneous galcanezumab, 120 mg (after 240 mg initial loading dose) or 240 mg, or placebo. A generalized linear mixed model with effects for baseline MHD, treatment, month, and treatment-by-month interaction was used to estimate the mean monthly response rate.

RESULTS: The analysis included 1739 patients treated with galcanezumab, 120 mg (n = 436) or 240 mg (n = 428), or placebo (n = 875). The mean monthly 100% response rate on an average month in the 6-month double-blind phase was greater for galcanezumab 120 mg (13.5%) and 240 mg (14.3%) groups vs placebo (5.9%) with odds ratios of 2.5 (95% confidence interval [CI] 1.9, 3.2) and 2.6 (95% CI 2.0, 3.4), respectively (P < .001). The rate of 100% monthly response increased at each month over the 6-month double-blind phase with higher rates for galcanezumab dose groups (9 to 21%) than placebo (2 to 10%) (P < .02). Evaluation of 100% response by the number of months showed a greater proportion of galcanezumab-treated patients in either dose group, compared to placebo, were able to achieve a 100% response (P < .001 up to 3 months); however, though greater than placebo, few galcanezumab patients had ≥4 months of 100% response (P < .02). The proportions of patients with 100% response were greatest in the last 3 months of the treatment. Considering the average number days between nonconsecutive MHD across the 6-month period (not just during the times of 100% response), the duration of migraine headache-free periods in the galcanezumab groups was 29 days for those with at least 1 month of 100% response and 55 days for those with at least 3 months of 100% response. This gap was approximately 6 to 11 times greater than the mean gap of 5 days observed at baseline.

CONCLUSIONS: More than a third of the patients with episodic migraine treated with galcanezumab 120 mg or 240 mg achieved 100% response for at least 1 month. More patients had 100% monthly response in the last 3 months of the 6-month double-blind period. For those with 100% response for at least 1 month, the average time between nonconsecutive MHD for the entire treatment period was nearly 1 month and approached 2 months for patients with 3 or more months of 100% response.

Changes in brainstem pain modulation circuitry function over the migraine cycle.

Marciszewski KK[1], Meylakh N[1], Di Pietro F[1], Mills EP[1], Macefield VG[2], Macey PM[3], Henderson LA[4].

J Neurosci. **2018 Oct 19**. pii: 1088-18. doi: 10.1523/JNEUROSCI.1088-18.2018. PMID: 30341182. [Epub ahead of print]

The neural mechanism responsible for migraine remains unclear. Whilst an external trigger has been proposed to initiate a migraine, it has also been proposed that changes in brainstem function are critical for migraine headache initiation and maintenance. Although the idea of altered brainstem function has some indirect support, no study has directly measured brainstem pain modulation circuitry function in migraineurs particularly immediately prior to a migraine. In male and female humans, we performed functional magnetic resonance imaging in 31 control and 31 migraineurs at various times in their migraine cycle. We measured brainstem function during noxious orofacial stimulation and assessed resting-state functional connectivity. Firstly, we found that in individual migraineurs, pain sensitivity increased over the interictal period, but then dramatically decreased immediately prior to a migraine. Secondly, despite overall similar pain intensity ratings between groups, in the period immediately prior to a migraine, compared to controls and other migraine phases, migraineurs displayed greater activation during noxious orofacial stimulation in the spinal trigeminal nucleus and reduced functional connectivity of this region with the rostral ventromedial medulla. Additionally, during the interictal phase, migraineurs displayed reduced activation of the midbrain periaqueductal gray matter and enhanced periaqueductal gray connectivity with the rostral ventromedial medulla. These data support the hypothesis that brainstem sensitivity fluctuates throughout the migraine cycle. However in contrast to the prevailing hypothesis, our data suggest that immediately prior to a migraine attack, endogenous analgesic mechanisms are enhanced and incoming noxious inputs are less likely to reach higher brain centres.

SIGNIFICANCE STATEMENT: It has been hypothesised that alterations in brainstem function are critical for the generation of migraine. In particular, modulation of orofacial pain pathways by brainstem circuits alter the propensity of external triggers or on-going spontaneous activity to evoke a migraine attack. We sought to obtain empirical evidence to support this theory. Contrary to our hypothesis, we found pain sensitivity decreased immediately prior to a migraine and this was coupled with increased sensitivity of the spinal trigeminal nucleus to noxious stimuli and resting connectivity within endogenous pain modulation circuitry alters across the migraine cycle. These changes may reflect enhanced and diminished neural tone states proposed to be critical for the generation of a migraine and underlie cyclic fluctuations in migraine brainstem sensitivity.

HEADACHE and MIGRAINE (Continued)

Anxiety, Incentives, and Adherence to Self-Monitoring on a Mobile Health Platform: A Naturalistic Longitudinal Cohort Study in People With Headache.

Seng EK[1,2,3], Prieto P[4], Boucher G[4], Vives-Mestres M[4].

Headache. **2018 Oct 18**. doi: 10.1111/head.13422. PMID: 30334248. [Epub ahead of print]

OBJECTIVE: To evaluate factors associated naturalistically with adherence to a mobile headache diary.

BACKGROUND: Self-monitoring (keeping a headache diary) is commonly used in headache to enhance diagnostic accuracy and evaluate the effectiveness of headache therapies. Mobile applications are increasingly used to facilitate keeping a headache diary. Little is known about the factors associated with adherence to mobile headache diaries.

METHODS: In this naturalistic longitudinal cohort study, people with headache (n = 1561) registered to use Curelator Headache® (now called N1-Headache®), an application that includes a mobile headache diary, through their physician (coupon), or directly through the website or app store using either a paid or free version of the application. Participants completed baseline questionnaires and were asked to complete daily recordings of headache symptoms and other factors for at least 90 days. Baseline questionnaires included headache characteristics and migraine disability. Daily recordings included headache symptoms and anxiety ratings. Adherence to keeping the headache diary was conceptualized as completion (kept the headache diary for 90 days), adherence rate (proportion of diary days completed 90 days after registration), and completion delay (the number of days past 90 days after registration required to complete 90 days of headache diary).

RESULTS: The majority of participants reported migraine as the most common headache type (90.0%), and reported an average of 30.8 headache days/90 days (SD = 24.2). One-third of participants completed 90 days of headache diary (32.4%). Endorsing higher daily anxiety scores (8/10 OR = 0.97 [95% CI = 0.96, 0.99]; 10/10 OR = 0.96 [95% CI = 0.91, 0.99]) was associated with lower odds of completion, whereas higher age (OR = 1.04 [95% CI = 1.03, 1.05]), and downloading the app paid vs free (OR = 4.27 [95% CI = 2.62, 7.06]), paid vs coupon (OR = 2.43, 95% CI = 1.41, 4.26]), or through a physician coupon vs free (OR = 1.75 [95% CI = 1.27, 2.42]) were associated with higher odds of completion. The median adherence rate at 90 days was 0.34 (IQR = 0.10-0.88), indicating that half of participants kept 34 or fewer days 90 diary days after registration. Endorsing high daily anxiety scores (5/10 OR = 0.98 [95% CI = 0.97, 1.00]; 8/10 OR = 0.96 [95% CI = 0.94, 0.98]; 10/10 OR = 0.96 [9% CI = 0.92, 0.98]) and higher age (OR = 1.05 [95% CI = 1.04, 1.07]) were associated with lower odds of adhering at 90 days, whereas downloading the app paid vs free (OR = 9.63 [95% CI = 4.61, 25.51]), paid vs coupon (OR = 2.39, 95% CI = 1.27, 5.10]), or through a physician coupon vs free (OR = 4.01 [95% CI = 2.54, 7.26]) were associated with higher odds of adhering at 90 days. Among completers, the median completion delay was 6.0 days (IQR = 2.0-15.0). Among completers, endorsing high daily anxiety scores (9/10 OR = 1/06 [95% CI = 1.01, 1.12]) and younger age (OR = 0.98 [95% CI = 0.97, 1.00]) was associated with completion delay; downloading the app through physician coupon vs free (OR = 0.40 [95% CI = 0.22, 0.71]) or paid vs free (OR = 0.38 [95% CI = 0.20, 0.72]) was associated with lower odds of completing 90 diary days in 90 calendar days.

CONCLUSION: This naturalistic observational study confirmed evidence from clinical observation and research: adherence to mobile headache diaries is a challenge for a significant proportion of people with headache. Endorsing higher levels of daily anxiety, younger age, and downloading the app for free (vs either paying for the self-monitoring app or receiving a physician referral coupon) were associated with poorer adherence to keeping a mobile headache diary.

CHRONIC PAIN

Gender Differences in Use of Complementary and Integrative Health by U.S. Military Veterans with Chronic Musculoskeletal Pain.

Evans EA[1], Herman PM[2], Washington DL[3], Lorenz KA[4], Yuan A[5], Upchurch DM[6], Marshall N[7], Hamilton AB[8], Taylor SL[9].

Womens Health Issues. **2018 Sep - Oct**;28(5):379-386. doi: 10.1016/j.whi.2018.07.003. PMID: 30174254. Epub 2018 Aug 31.

AIMS: The Veterans Health Administration promotes evidence-based complementary and integrative health (CIH) therapies as nonpharmacologic approaches for chronic pain. We aimed to examine CIH use by gender among veterans with chronic musculoskeletal pain, and variations in gender differences by race/ethnicity and age.

METHODS: We conducted a secondary analysis of electronic health records provided by all women (n = 79,537) and men (n = 389,269) veterans age 18 to 54 years with chronic musculoskeletal pain who received Veterans Health Administration-provided care between 2010 and 2013. Using gender-stratified multivariate binary logistic regression, we examined predictors of CIH use, tested a race/ethnicity-by-age interaction term, and conducted pairwise comparisons of predicted probabilities.

RESULTS: Among veterans with chronic musculoskeletal pain, more women than men use CIH (36% vs. 26%), with rates ranging from 25% to 42% among women and 15% to 29% among men, depending on race/ethnicity and age. Among women, patients under age 44 who were Hispanic, White, or patients of other race/ethnicities are similarly likely to use CIH; in contrast, Black women, regardless of age, are least likely to use CIH. Among men, White and Black patients, and especially Black men under age 44, are less likely to use CIH than men of Hispanic or other racial/ethnic identities.

CONCLUSIONS: Women veteran patients with chronic musculoskeletal pain are more likely than men to use CIH therapies, with variations in CIH use rates by race/ethnicity and age. Tailoring CIH therapy engagement efforts to be sensitive to gender, race/ethnicity, and age could reduce differential CIH use and thereby help to diminish existing health disparities among veterans.

CHRONIC PAIN (Continued)

Influence of family history on prognosis of spinal pain and the role of leisure time physical activity and body mass index: a prospective study using family-linkage data from the Norwegian HUNT study.

Amorim AB[1], Ferreira PH[1], Ferreira ML[2], Lier R[3], Simic M[1], Pappas E[1], Zadro JR[1], Mork PJ[3], Nilsen TI[3,4].

BMJ Open. **2018 Oct 18**;8(10):e022785. doi: 10.1136/bmjopen-2018-022785. PMID: 30341129.

OBJECTIVES: To investigate the influence of parental chronic spinal pain on prognosis of chronic spinal pain in adult offspring, and whether offspring physical activity level and body mass index (BMI) modified this association.

DESIGN: Prospective cohort study.

SETTING: We used family-linked longitudinal data from the Norwegian HUNT study collected in HUNT2 (1995-1997) and HUNT3 (2006-2008).

PARTICIPANTS: A total of 1529 offspring who reported spinal pain in HUNT2 were linked with parental data and followed up in HUNT3.

OUTCOMES: We estimated relative risk (RR) with 95% CI for recovery from chronic spinal pain, and also from activity limiting spinal pain, in offspring related to chronic spinal pain in parents. We also investigated whether offspring leisure time physical activity and BMI modified these intergenerational associations in spinal pain.

RESULTS: A total of 540 (35%) offspring were defined as recovered after approximately 11 years of follow-up. Offspring with both parents reporting chronic spinal pain were less likely to recover from chronic spinal pain (RR 0.83, 95% CI 0.69 to 0.99) and activity limiting spinal pain (RR 0.71, 95% CI 0.54 to 0.94), compared with offspring of parents without chronic spinal pain. Analyses stratified by BMI and physical activity showed no strong evidence of effect modification on these associations. However, offspring who were overweight/obese and with both parents reporting chronic spinal pain had particularly low probability of recovery from activity limiting spinal pain, compared with those who were normal weight and had parents without chronic spinal pain (RR 0.57, 95% CI 0.39 to 0.84).

CONCLUSION: Offspring with chronic spinal pain are less likely to recover if they have parents with chronic spinal pain, particularly if offspring are overweight/obese.

OTHER RESEARCH OF INTEREST

Clearance of senescent glial cells prevents tau-dependent pathology and cognitive decline.

Bussian TJ[1], Aziz A[2], Meyer CF[2], Swenson BL[2], van Deursen JM[1,2], Baker DJ[3,4].

Nature. **2018 Sep 19**. doi: 10.1038/s41586-018-0543-y. PMID: 30232451. [Epub ahead of print]

Cellular senescence, which is characterized by an irreversible cell-cycle arrest accompanied by a distinctive secretory phenotype, can be induced through various intracellular and extracellular factors. Senescent cells that express the cell cycle inhibitory protein $p16^{INK4A}$ have been found to actively drive naturally occurring age-related tissue deterioration and contribute to several diseases associated with ageing, including atherosclerosis and osteoarthritis. Various markers of senescence have been observed in patients with neurodegenerative diseases; however, a role for senescent cells in the aetiology of these pathologies is unknown. Here we show a causal link between the accumulation of senescent cells and cognition-associated neuronal loss. We found that the $MAPT^{P301S}$PS19 mouse model of tau-dependent neurodegenerative disease accumulates $p16^{INK4A}$-positive senescent astrocytes and microglia. Clearance of these cells as they arise using INK-ATTAC transgenic mice prevents gliosis, hyperphosphorylation of both soluble and insoluble tau leading to neurofibrillary tangle deposition, and degeneration of cortical and hippocampal neurons, thus preserving cognitive function. Pharmacological intervention with a first-generation senolytic modulates tau aggregation. Collectively, these results show that senescent cells have a role in the initiation and progression of tau-mediated disease, and suggest that targeting senescent cells may provide a therapeutic avenue for the treatment of these pathologies.

OTHER RESEARCH OF INTEREST (Continued)

Military sexual trauma and suicidal behavior among National Guard personnel.

White KL[1], Harris JA[1], Bryan AO[1], Reynolds M[1], Fuessel-Herrmann D[2], Bryan CJ[3].

Compr Psychiatry. **2018 Aug 18**;87:1-6. doi: 10.1016/j.comppsych.2018.08.008. PMID: 30172073. [Epub ahead of print]

BACKGROUND: Preliminary evidence suggests military sexual trauma (MST) may be associated with increased risk for suicidal behaviors among active duty military personnel and veterans. Among National Guard personnel, a high-risk subgroup, MST and suicide risk have not received much empirical attention.

PURPOSE: To examine the association of MST with suicide ideation and suicide attempts among National Guard personnel.

PROCEDURES: N = 997 National Guard personnel from Idaho and Utah participated in an anonymous online survey. Weighted analyses were conducted to minimize sampling bias.

MAIN FINDINGS: 9% of participants had a history of MST (6% of men, 28% of women). Among participants reporting MST, 68% reported a service member perpetrator and 44% reported a civilian perpetrator (12% reported both). A history of MST was associated with significantly increased risk for lifetime suicide attempt. MST remained a significant predictor of lifetime suicide attempt even when restricting the sample to the subgroup with a history of suicidal thoughts (n = 257, 27% of full sample). When adjusting for premilitary sexual victimization, MST was no longer significantly associated with lifetime suicide attempts, but premilitary sexual victimization was.

CONCLUSIONS: The rate of MST among National Guard personnel is comparable to rates among active duty military personnel, although the perpetrators of MST are less likely to be service members. MST is a risk factor for suicide attempts, but premilitary sexual victimization is a relatively stronger risk factor.

###