GULF WAR ILLNESS

Evidence for Somatic Hypersensitivity in Veterans with Gulf War Illness and Gastrointestinal Symptoms.

Zhou Q[1,2], Verne ML, Zhang B[1,3], Verne GN[1].

Clin J Pain. **2018 Mar 21**. doi: 10.1097/AJP.0000000000000611. PMID: 29570102. [Epub ahead of print]

INTRODUCTION: Over 25% of Persian Gulf War (PGW) veterans with Gulf War Illness (GWI) (chronic health complaints of undetermined etiology) developed GI symptoms (diarrhea and abdominal pain) and somatic complaints.

OBJECTIVES: Our study objective was to determine if veterans with GWI and GI symptoms exhibit heightened patterns of somatic pain perception (hypersensitivity) across nociceptive stimuli modalities.

METHODS: Subjects were previously deployed GW Veterans with GWI and GI symptoms (n=53); veterans with GWI without GI symptom (n=47); and veteran controls (n=38). We determined pain thresholds for contact thermal, cold pressor, and ischemic stimuli.

RESULTS: Veterans with GWI and GI symptoms showed lower pain thresholds (P<0.001) for each stimulus. There was also overlap of somatic hypersensitivities among veterans with GI symptoms with 20% having hypersensitivity to all 3 somatic stimuli. Veterans with GWI and GI symptoms also showed a significant correlation between M-VAS abdominal pain ratings and heat pain threshold, cold pressor threshold, and ischemic pain threshold/tolerance.

DISCUSSION: Our findings show that there is widespread somatic hypersensitivity in veterans with GWI/GI symptoms that is positively correlated with abdominal pain ratings. In addition, veterans with somatic hypersensitivity that overlap have the greatest number of extraintestinal symptoms. These findings may have a translational benefit: strategies for developing more effective therapeutic agents that can reduce and/or prevent somatic and GI symptoms in veterans deployed to future military conflicts.

Epigenetic impacts of stress priming of the neuroinflammatory response to sarin surrogate in mice: a model of Gulf War illness.

Ashbrook DG[1,2], Hing B[1,3], Michalovicz LT[4], Kelly KA[4], Miller JV[4], de Vega WC[1], Miller DB[4], Broderick G[5], O'Callaghan JP[4], McGowan PO [6,7,8].

J Neuroinflammation. **2018 Mar 17**;15(1):86. doi: 10.1186/s12974-018-1113-9. PMCID: PMC5857314. PMID: 29549885.

BACKGROUND: Gulf War illness (GWI) is an archetypal, medically unexplained, chronic condition characterised by persistent sickness behaviour and neuroimmune and neuroinflammatory components. An estimated 25-32% of the over 900,000 veterans of the 1991 Gulf War fulfil the requirements of a GWI diagnosis. It has been hypothesised that the high physical and psychological stress of combat may have increased vulnerability to irreversible acetylcholinesterase (AChE) inhibitors leading to a priming of the neuroimmune system. A number of studies have linked high levels of psychophysiological stress and toxicant exposures to epigenetic modifications that regulate gene expression. Recent research in a mouse model of GWI has shown that pre-exposure with the stress hormone corticosterone (CORT) causes an increase in expression of specific chemokines and cytokines in response to diisopropyl fluorophosphate (DFP), a sarin surrogate and irreversible AChE inhibitor.

METHODS: C57BL/6J mice were exposed to CORT for 4 days, and exposed to DFP on day 5, before sacrifice 6 h later. The transcriptome was examined using RNA-seq, and the epigenome was examined using reduced representation bisulfite sequencing and H3K27ac ChIP-seq.

RESULTS: We show transcriptional, histone modification (H3K27ac) and DNA methylation changes in genes related to the immune and neuronal system, potentially relevant to neuroinflammatory and cognitive symptoms of GWI. Further evidence suggests altered proportions of myelinating oligodendrocytes in the frontal cortex, perhaps connected to white matter deficits seen in GWI sufferers.

CONCLUSIONS: Our findings may reflect the early changes which occurred in GWI veterans, and we observe alterations in several pathways altered in GWI sufferers. These close links to changes seen in veterans with GWI indicates that this model reflects the environmental exposures related to GWI and may provide a model for biomarker development and testing future treatments.

GULF WAR ILLNESS (Continued)

The potential of treating Gulf War Illness with curcumin.

Leibowitz JA[1], Ormerod BK[2].

Brain Behav Immun. **2018 Mar 13**. pii: S0889-1591(18)30067-9. doi: 10.1016/j.bbi.2018.03.017. PMID: 29548999. [Epub ahead of print]

[Note: Leibowitz and Ormerod comment on a Kodali et al. article describing curcumin treatment in a rat model of GWI for which the Abstract was included in RAC-GWVI Research Alerts for February 20, 2018.]

Abstract: A large proportion of Gulf War Veterans suffer from Gulf War Illness (GWI) - a devastating chronic disorder characterized by heterogeneous fatigue, pain and neuropsychological symptoms. In their recent *Brain, Behavior and Immunity* publication entitled "Curcumin Treatment Leads to Better Cognitive and Mood Function in a Model of Gulf War Illness with Enhanced Neurogenesis, and Alleviation of Inflammation and Mitochondrial Dysfunction in the Hippocampus", Kodali and colleagues (2018) report that the polyphenol curcumin improves cognition and mood in a rat model of GWI, potentially by increasing the expression of antioxidant genes and by reversing the effects of chronic combined acetylcholinesterase inhibitor exposure on neuroinflammation, mitochondrial respiration and hippocampal neurogenesis. This preclinical work is encouraging for our veterans who suffer chronically from GWI as well as for developing strategies to protect our troops during future deployments in similar environments.

Brief Commentary: A significant proportion (25–32%) of multinational coalition Veterans returned home from Operation Desert Storm/Desert Shield – the Gulf War – with a devastating chronic syndrome that was eventually coined ‘chronic multisymptom illness’ or ‘Gulf War Illness’ (GWI) for review see (Janulewicz et al., 2017; Nettleman, 2015; White et al., 2016). Given the heterogeneity of symptoms among case studies, the National Academy of Sciences Institute of Medicine has only recently recommended the adoption of both a more clinical GWI definition developed by the Centers for Disease Control and Prevention (CDC) and a more research-focused definition developed by the state of Kansas. The CDC definition requires the self-report of one or more symptoms lasting more than six months from at least two of three symptom categories that include fatigue, musculoskeletal pain and mood/cognition. The Kansas definition requires moderate levels of self-reported symptoms in at least three of six categories that include fatigue/sleep, somatic pain, neurological/cognitive/mood, respiratory, gastrointestinal symptoms and skin symptoms. The etiology of GWI is hypothesized to be mainly chronic exposure to multiple acetylcholinesterase inhibitors that include the nerve gas prophylactic pyridostigmine bromide and the pesticides permethrin (PM) and N, N-diethyl-m-toluamide (DEET). Factors such as chronic smoke, environmental toxin and combat exposure may also contribute to the disease. Research into the etiology of and treatment for GWI is critical for improving quality of life for our Gulf War Veterans as well as for protecting our troops during future deployments in similar environments.

See full text of this commentary article in the 2018 Mar 13 issue of Elsevier Journal *Brain, Behavior, and Immunity*.

CHRONIC FATIGUE SYNDROME

Rethinking the treatment of chronic fatigue syndrome-a reanalysis and evaluation of findings from a recent major trial of graded exercise and CBT.

Wilshire CE[1], Kindlon T[2], Courtney R[3], Matthees A[4], Tuller D[5], Geraghty K[6], Levin B[7].

BMC Psychol. **2018 Mar 22**;6(1):6. doi: 10.1186/s40359-018-0218-3. PMID: 29562932.

BACKGROUND: The PACE trial was a well-powered randomised trial designed to examine the efficacy of graded exercise therapy (GET) and cognitive behavioural therapy (CBT) for chronic fatigue syndrome. Reports concluded that both treatments were moderately effective, each leading to recovery in over a fifth of patients. However, the reported analyses did not consistently follow the procedures set out in the published protocol, and it is unclear whether the conclusions are fully justified by the evidence.

METHODS: Here, we present results based on the original protocol-specified procedures. Data from a recent Freedom of Information request enabled us to closely approximate these procedures. We also evaluate the conclusions from the trial as a whole.

RESULTS: On the original protocol-specified primary outcome measure - overall improvement rates - there was a significant effect of treatment group. However, the groups receiving CBT or GET did not significantly outperform the Control group after correcting for the number of comparisons specified in the trial protocol. Also, rates of recovery were consistently low and not significantly different across treatment groups. Finally, on secondary measures, significant effects were almost entirely confined to self-report measures. These effects did not endure beyond two years.

CONCLUSIONS: These findings raise serious concerns about the robustness of the claims made about the efficacy of CBT and GET. The modest treatment effects obtained on self-report measures in the PACE trial do not exceed what could be reasonably accounted for by participant reporting biases.

CHRONIC FATIGUE SYNDROME (Continued)

Balance deficits in Chronic Fatigue Syndrome with and without fibromyalgia.

Serrador JM[1,2,3], Quigley KS[4,5], Zhao C[2], Findley T[2], Natelson BH[6].

NeuroRehabilitation. **2018**;42(2):235-246. doi: 10.3233/NRE-172245. PMID: 29562557.

OBJECTIVE: Chronic Fatigue Syndrome (CFS) is a disorder of unknown etiology associated with debilitating fatigue. One symptom commonly reported is disequilibrium. The goal of this study was to determine if CFS patients demonstrated verified balance deficits and if this was effected by comorbid fibromyalgia (FM).

METHODS: Twenty-seven patients with CFS (12 with comorbid FM) and 22 age and gender matched controls performed posturography.

RESULTS: Balance scores were significantly correlated with physical functional status in the CFS group (R2=0.43, P<0.001), which was not found for mental functional status (R2=0.06, P>0.5). CFS patients (regardless of FM) had significantly higher anxiety subscale of the vertigo symptom scale scores. CFS patients, regardless of FM status, demonstrated significantly lower overall composite balance scores (Controls - 78.8±1.5; CFS - 69.0±1.4, P<0.005) even when controlling for anxiety and also had worse preference scores, indicating they relied on visual information preferentially even when visual information was incorrect. Interestingly, the CFS+FM group, not CFS only, demonstrated significantly worse vestibular scores (Controls - 70.2±2.4; CFS only - 67.9±3.8; CFS with FM - 55.4±4.6, P=0.013).

INTERPRETATION: The major findings are that poor balance may be associated with poorer self-reported physical health. In addition, CFS patients seemed to rely preferentially on visual inputs, regardless of whether it was correct. The finding that vestibular function may be impaired in patients with CFS+FM but not in those with CFS alone suggests that the pathophysiology of CFS+FM may differ as has been suggested by some.

HEADACHE and MIGRAINE

Mindfulness Meditation for Primary Headache Pain: A Meta-Analysis.

Gu Q[1], Hou JC[2], Fang XM[1].

Chin Med J (Engl). **2018 Apr 5**;131(7):829-838. doi: 10.4103/0366-6999.228242. PMID: 29578127.

Background: Several studies have reported that mindfulness meditation has a potential effect in controlling headaches, such as migraine and tension-type headache; however, its role remains controversial. This review assessed the evidence regarding the effects of mindfulness meditation for primary headache pain.

Methods: Only English databases (PubMed, Cochrane Central Register of Controlled Trials [the Cochrane Library], PsycINFO, Psychology and behavioral science collection, PsyArticles, Web of Science, and Scopus) were searched from their inception to November 2016 with the keywords ("meditation" or "mindfulness" or "vipassana" or "dzogchen" or "zen" or "integrative body-mind training" or "IBMT" or "mindfulness-based stress reduction" or "MBSR" or "mindfulness-based cognitive therapy" or "MBCT" and "Headache" or "Head pain" or "Cephalodynia" or "Cephalalgia" or "Hemicrania" or "Migraine"). Titles, abstracts, and full-text articles were screened against study inclusion criteria: controlled trials of structured meditation programs for adult patients with primary headache pain. The quality of studies included in the meta-analysis was assessed with the Yates Quality Rating Scale. The meta-analysis was conducted with Revman 5.3.

Results: Ten randomized controlled trials and one controlled clinical trial with a combined study population of 315 patients were included in the study. When compared to control group data, mindfulness meditation induced significant improvement in pain intensity (standardized mean difference, -0.89; 95% confidence interval, -1.63 to -0.15; P = 0.02) and headache frequency (-0.67; -1.24 to -0.10; P = 0.02). In a subgroup analysis of different meditation forms, mindfulness-based stress reduction displayed a significant positive influence on pain intensity (P < 0.000). Moreover, 8-week intervention had a significant positive effect (P < 0.000).

Conclusions: Mindfulness meditation may reduce pain intensity and is a promising treatment option for patients. Clinicians may consider mindfulness meditation as a viable complementary and alternative medical option for primary headache.

HEADACHE and MIGRAINE (Continued)

Association of Higher Migraine Risk Among Female and Younger Chronic Osteomyelitis Patients: Evidence from a Taiwan Cohort of One Million.

Chen JH[1], Wu SC[2], Muo CH[3], Kao CH[4], Tseng CH[5], Tsai CH[5].

Pain Physician. **2018 Mar**;21(2):E149-E156. PMID: 29565957.

BACKGROUND: Inflammation may trigger migraine development through neurovascular reactions in the brain. Most of the migraine patients, particularly the younger ones, do not have any risk factors for this disease. Hence, we assessed whether chronic osteomyelitis (COM), a chronic inflammatory disease, increases the risk of migraine.

OBJECTIVE: We aim to evaluate the risk of migraine among female and middle-age COM patients with a large patient sample.

STUDY DESIGN: A retrospective cohort study was conducted in this study.

SETTING: The data used in this study were extracted from the Taiwan National Health Insurance (NHI) Research Database.

METHODS: A study group with 2,012 COM patients and 8,048 randomly chosen gender- and age-matched controls were chosen from the Taiwan NHI Research Database (NHIRD) from the start of 2000 to the end of 2009. The risk of migraine was estimated with Cox proportional regression model. Both COM and control groups were followed-up until the occurrence of migraine during the study period (2000-2011). Prevalent covariates, such as age, gender, hypertension, diabetes, hyperlipidemia, stroke, coronary artery disease, depression, anxiety, sleep disorder, bipolar disorder, and epilepsy, were included for further evaluation. The hazard ratio (HR) of migraine was measured with Cox proportional hazard regression model. The primary outcome was the overall migraine risk among COM patients, and the secondary outcome was the migraine risk among COM patients lacking the comorbidities. Additional outcomes included migraine risk among COM patients in different age and gender subgroups.

RESULTS: The overall migraine risk was increased in COM patients (adjusted hazard ratio [aHR] 1.74, 95% confidence interval [CI] 1.14-2.65). Even without any prevalent comorbidities, COM patients still exhibited an increased risk of migraine (aHR 2.05, 95% CI 1.06-3.97) than the controls did. Moreover, this risk was relatively higher in COM patients aged < 40 and 45-54 years (aHR 2.07, 95% CI 0.97-4.46 and aHR 2.11, 95% CI 0.97-4.57, respectively) than in their counterparts. Female COM patients had a relatively higher migraine risk (aHR 1.85, 95% CI 1.05-3.24) than male patients did (aHR 1.68, 95% CI 0.89-3.16).

LIMITATIONS: The messages about personal behaviors were unavailable in the Taiwan NHIRD. Other neurovascular risk factors that might increase migraine cannot be excluded completely in this research.

CONCLUSION: An association between COM and increased risk of migraine was shown in this study. The results suggest that COM is a significant migraine predictor, and thus imply the necessity for rigorous migraine prevention in COM patients, especially female and younger ones.

Radiofrequency Ablation of Pericranial Nerves for Treating Headache Conditions: A Promising Option for Patients.

Abd-Elsayed A[1], Kreuger L[2], Wheeler S[3], Robillard J[3], Seeger S[3], Dulli D[3].

Ochsner J. **2018 Spring**;18(1):59-62. PMCID: PMC5855424. PMID: 29559871.

Background: Chronic daily headache, including chronic migraine, can be challenging to treat. Medications often only provide limited improvement, and surgical interventions can be associated with significant adverse effects. We present our experience with using radiofrequency ablation (RFA) for pericranial nerves to treat chronic headache conditions.

Methods: This retrospective analysis included patients who received RFA for pericranial nerves to treat chronic daily headache conditions from January 1, 2015 to June 1, 2016. Outcomes were pain scores as measured on the visual analog scale (with 0 representing no pain and 10 representing the worst pain imaginable) and the patient-reported percent improvement in headache conditions, including pain scores, severity, duration, frequency, and associated symptoms.

Results: Of the 57 patients who received 72 RFAs for pericranial nerves to treat headache or pericranial neuralgia, 90.3% of patients had improvement in their headache condition after receiving RFA. In addition, pain scores decreased from 6.6 ± 1.7 preprocedure to 1.9 ± 1.9 postprocedure (P<0.001).

Conclusion: Our study demonstrates the efficacy and safety of RFA in treating pericranial neuralgias associated with chronic daily headache.

CHRONIC PAIN

Research Agenda for the Prevention of Pain and Its Impact: Report of the Work Group on the Prevention of Acute and Chronic Pain of the Federal Pain Research Strategy.

Gatchel RJ, Reuben DB, Dagenais S, Turk DC, Chou R, Hershey A, Hicks G, Licciardone JC, Horn SD.

J Pain. **2018 Mar 22**. pii: S1526-5900(18)30107-X. doi: 10.1016/j.jpain.2018.02.015. PMID: 29578089. [Epub ahead of print]

Following the 2011 Institute of Medicine report on chronic pain, the Interagency Pain Research Coordinating Committee (IPRCC) was created to enhance research efforts among federal agencies. The IPRCC and Office of Pain Policy at the NIH collaborated to identify gaps in knowledge and address them via a Federal Pain Research Strategy (FPRS). The FPRS appointed Interdisciplinary Work Groups (WGs) to make research recommendations in 5 areas: prevention of acute and chronic pain; acute pain and acute pain management; transition from acute to chronic pain; chronic pain and chronic pain management; and disparities in pain and pain care; cross-cutting issues were also considered. Findings from the Prevention of Acute and Chronic Pain WG are summarized in this article. The objective was to provide guidance on current research and to make recommendations about addressing identified gaps. The WG created different subgroups within the WG to make recommendations on specific aspects of prevention of acute and chronic pain, including: public education; primary prevention; secondary prevention; tertiary prevention; transition from acute to chronic pain, and cross-cutting mediators. No formal literature review was conducted; however, external advisors were available and consulted as needed. The WG identified 7 key research priorities. The one deemed "greatest near-term value" was to optimize public health strategies to educate patients on managing pain; that deemed "most impactful" was to determine an association between patient and intervention factors. Other recommendations were related to: the epidemiology of acute pain from healthcare procedures; the epidemiology of acute pain from work-related injuries; safety and effectiveness of management of pain associated with healthcare procedures; optimizing approaches to acute postsurgical pain; and safety and effectiveness of early interventions for tertiary prevention. Stakeholders, including federally-sponsored research programs, researchers, healthcare providers, policy makers, patients, and others should work together to implement these recommendations and address these important gaps.

Pain and mortality: mechanisms for a relationship.

Smith D[1], Wilkie R[1], Croft P[1], Parmar S[2], McBeth J[3].

Pain. **2018 Mar 19**. doi: 10.1097/j.pain.0000000000001193. PMID: 29570110. [Epub ahead of print]

Moderate to severe chronic pain affects one in five adults and its impact increases with age. People with chronic pain that interferes with their lives have an increased risk of mortality. Identifying how interfering chronic pain can lead to mortality may highlight potential intervention strategies. This study uses a novel approach to test whether lifestyle, health, social and psychological factors mediate the relationship between pain and mortality. Survival analyses (Cox's proportional hazard modelling and a technique to assess mediation within survival models) were conducted on a large population study of adults aged ≥50 years from the English Longitudinal Study of Ageing (ELSA) (n=6324). Data collected at Wave 2 (2004) were used as baseline and follow-up was until 2012. The relationship between being "often troubled with pain" and mortality was examined. Lifestyle, health, social and psychological factors were tested as potential mediators. The strongest mediating factors for the relationship between troubling pain and mortality were functional limitation (Hazard Ratio 1.31; 95%CI (1.20, 1.39)), symptoms preventing walking quarter of a mile (1.45 (1.35, 1.58)), physical inactivity (1.14 (1.10, 1.20)) and poor self-rated health (1.32 (1.23, 1.41)). Mediators of the relationship between troubling pain and mortality provide targets for preventive health programmes. Interventions to improve general health, activity and function could improve long-term survival in patients with this clinical problem.

CHRONIC PAIN (Continued)

Pain catastrophizing, neuroticism, fear of pain, and anxiety: Defining the genetic and environmental factors in a sample of female twins.

Burri A[1,2], Ogata S[3,4,5], Rice D[1,2], Williams F[6].

PLoS One. **2018 Mar 22**;13(3):e0194562. doi: 10.1371/journal.pone.0194562. PMID: 29566063. eCollection 2018.

The objective of the present study was to establish the heritability of pain catastrophizing and its subdomains of helplessness, magnification, and rumination and to further explore the genetic and environmental sources that may contribute to pain catastrophizing as well as to its commonly reported psycho-affective correlates, including neuroticism, anxiety sensitivity, and fear of pain. N = 2,401 female twin individuals from the TwinsUK registry were subject to univariate and multivariate twin analyses. Well validated questionnaires including the Pain Catastrophizing Scale, the Pain Anxiety Symptom Scale, the Ten Item Personality Index, and the Anxiety Sensitivity Index were used to assess the study variables. Moderate estimates of heritability for pain catastrophizing (36%) and the three subdomains of helplessness (35%), rumination (27%), and magnification (36%) were detected. The high correlations observed between the three subdomains were explained mainly by overlapping genetic factors, with a single factor loading on all three phenotypes. High genetic correlations between pain catastrophizing and its psycho-affective correlates of fear of pain and anxiety sensitivity were found, while the genetic overlap between neuroticism and pain catastrophizing was low. Each measure of negative affect demonstrated relatively distinct environmental contributing factors, with very little overlap. This is the first study to show shared genetic factors in the observed association between pain catastrophizing and other measures of negative affect. Our findings provide deeper insight into the aetiology of pain catastrophizing and confirm that it is at least partially distinct from other measures of negative affect and personality that may influence the development and treatment of chronic pain conditions. Further research in males is warranted to check the comparability of the findings.

Confirmatory factor analysis of the Coping Strategies Questionnaire-Revised for veterans with pain.

Freed RD[1], Emmert-Aronson BO[2], Alschuler KN[3], Otis JD[2].

Psychol Serv. **2018 Mar 26**. doi: 10.1037/ser0000237. PMID: 29578740. [Epub ahead of print]

As the need for appropriate assessment and treatment of veterans with chronic pain continues to grow, it is important to ensure that the instruments we use to complete these assessments, such as the Coping Strategies Questionnaire-Revised (CSQ-R), are validated on this population. The purpose of the present study was to confirm the factor structure of the CSQ-R in veterans. Secondary analyses examined associations between various pain coping strategies and measures of mood and health functioning. Participants consisted of 281 veterans who were referred to and evaluated by a Psychology Pain Management Program in a northeastern Department of Veterans Affairs health care facility. Participants completed self-report questionnaires including the CSQ-R and measures of disability, mood, and health. Confirmatory factor analysis (CFA) compared the 6-factor solution to models identified in other studies. The CFA indicated that the 6-factor solution of the CSQ-R proposed by Riley and Robinson (1997) is valid and has the best fit of all models tested when used with veterans. The results of the secondary correlational analyses were consistent with previous research indicating that coping self-statements and ignoring pain are adaptive pain coping strategies. Our findings support the psychometric soundness of the 6-factor CSQ-R when used with veterans with chronic pain. (PsycINFO Database Record.

CHRONIC PAIN (Continued)

Grey Matter Correlates of Pressure Pain Thresholds and Self-Rated Pain Sensitivity: A Voxel-Based Morphometry Study.

Ruscheweyh R[1,2,3], Wersching H[4], Kugel H[5], Sundermann B[5], Teuber A[4].

Pain. **2018 Mar 16**. doi: 10.1097/j.pain.0000000000001219. PMID: 29557929. [Epub ahead of print]

Individual differences in sensitivity to pain are large and have clinical and scientific importance. Although heavily influenced by situational factors, they also relate to genetic factors and psychological traits, and are reflected by differences in functional activation in pain-related brain regions. Here, we used voxel-based morphometry to investigate if individual pain sensitivity is related to local grey matter volumes. Pain sensitivity was determined using (1) index finger pressure pain thresholds (PPTs) and (2) pain intensity ratings of imagined painful situations as assessed by the Pain Sensitivity Questionnaire (PSQ) in 501 population-based subjects participating in the BiDirect Study. PSQ scores were positively associated with grey matter in two symmetrical clusters, with a focus on the parahippocampal gyrus, extending to hippocampus, fusiform gyrus, BA19, putamen and insula ($p < 0.05$ corrected), but the effect was small ($R = 0.045$ to 0.039). No negative associations with the PSQ and no associations with the PPT reached significance. Parahippocampal activation during pain, and altered parahippocampal grey matter in chronic pain have been reported, which would be consistent with positive associations with PSQ scores. Alternatively, associations of PSQ scores with parahippocampal and fusiform grey matter could relate to the visual imagination of painful situations required by the PSQ, not to pain sensitivity itself. Regarding PPTs, the present data obtained in a large sample strongly suggest an absence of associations of this parameter with grey matter volume. In conclusion, the present results argue against a strong association between pain sensitivity and local grey matter volumes.

OTHER RESEARCH OF INTEREST

VA Announces Plan to Improve Worst-Performing Medical Centers.

Rubin R.

JAMA. **2018 Mar 27**;319(12):1189. doi: 10.1001/jama.2018.2784. PMID: 29584827.

The US Department of Veterans Affairs (VA) recently announced steps it plans to take to rapidly improve its low-performing medical centers.

There are 15 such facilities, all of which received a 1 star out of 5 rating on the VA's Strategic Analytics for Improvement and Learning (SAIL) rating system. They are located in Hampton, Virginia; Phoenix; Denver; Harlingen, El Paso, and Big Spring, Texas; Roseburg, Oregon; Washington, DC; Memphis, Murfreesboro, and Nashville, Tennessee; Dublin, Georgia; Jackson, Mississippi; Loma Linda, California; and Walla Walla, Washington.

The SAIL rating system assesses 25 quality measures, including death rate, complications, and patient satisfaction as well as overall efficiency and physician capacity. VA Medical centers are rated based on how they compare with other VA hospitals and with their own performance the previous year.

The VA has designated Peter Almenoff, MD, director of the its Office of Reporting, Analytics, Performance, Improvement, and Deployment (RAPID) Healthcare Improvement Center to oversee improvement at all 15 medical centers. The agency is also implementing a Strategic Action Transformation (STAT) initiative to identify vulnerabilities in each of the centers and set specific targets for improvement. RAPID experts will track progress toward reaching those targets and, if necessary, go to the medical centers to help them meet those goals. The VA will change the leadership at centers that fail to make rapid, substantial progress.

A recent High Risk Report by the US Government Accountability Office (GAO) noted that the VA's Office of the Inspector General, the GAO, and others have reported on VA facilities failing to provide timely health care.

OTHER RESEARCH OF INTEREST (Continued)

Advancing Therapeutic Development for Pain and Opioid Use Disorders Through Public–Private Partnerships: Proceedings of a Workshop.

Released March 23, 2018. Proceedings of a Workshop (2018): National Academies of Sciences, Engineering, and Medicine. 2018. *Advancing Therapeutic Development for Pain and Opioid Use Disorders Through Public-Private Partnerships: Proceedings of a Workshop*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25060.

Contributors: National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Forum on Neuroscience and Nervous System Disorders; Lisa Bain, Sheena M. Posey Norris, and Clare Stroud, Rapporteurs. Download PDF. Read Online.

Chronic pain is one of the most prevalent, costly, and disabling health conditions in the United States. Estimates show that more than 11 percent of the American population suffer from chronic pain, yet the federal pain research investment has been minimal. In parallel with a gradual increased recognition of the problems of treating chronic pain, the opioid epidemic has emerged as a growing public health emergency. The intersection of these two crises lies in the fact that an unintended consequence of treating pain has been an increasing number of opioid prescriptions and diversion of drugs for illicit purposes.

In May 2017, the National Institutes of Health (NIH), and the National Institute on Drug Abuse announced a public–private partnership to develop solutions to the opioid crisis and cut in half the time it takes to develop non-addictive analgesics. To advance the planning of NIH's anticipated public–private partnerships, the National Academies' Forum on Neuroscience and Nervous Systems Disorders hosted a public workshop that brought together a diverse group of stakeholders from academia, federal agencies, advocacy organizations and companies developing therapeutics for pain and opioid use disorders. Participants discussed potential strategies to accelerate development of non-addictive pain medications and treatments for opioid use disorders. This publication summarizes the presentations and discussions from the workshop.

Manfredo Vieira S[1], Hiltensperger M[1], Kumar V[2], Zegarra-Ruiz D[1], Dehner C[1], Khan N[1], Costa FRC[1], Tiniakou E[1], Greiling T[1], Ruff W[1], Barbieri A[3], Kriegel C[1], Mehta SS[4], Knight JR[4], Jain D[3], Goodman AL[5], Kriegel MA[6,2].

Science. **2018 Mar 9**;359(6380):1156-1161. doi: 10.1126/science.aar7201. PMID: 29590047.

Despite multiple associations between the microbiota and immune diseases, their role in autoimmunity is poorly understood. We found that translocation of a gut pathobiont, *Enterococcus gallinarum*, to the liver and other systemic tissues triggers autoimmune responses in a genetic background predisposing to autoimmunity. Antibiotic treatment prevented mortality in this model, suppressed growth of *E. gallinarum* in tissues, and eliminated pathogenic autoantibodies and T cells. Hepatocyte-*E. gallinarum* cocultures induced autoimmune-promoting factors. Pathobiont translocation in monocolonized and autoimmune-prone mice induced autoantibodies and caused mortality, which could be prevented by an intramuscular vaccine targeting the pathobiont. *E. gallinarum*-specific DNA was recovered from liver biopsies of autoimmune patients, and cocultures with human hepatocytes replicated the murine findings; hence, similar processes apparently occur in susceptible humans. These discoveries show that a gut pathobiont can translocate and promote autoimmunity in genetically predisposed hosts.

OTHER RESEARCH OF INTEREST (Continued)

Effect of tai chi versus aerobic exercise for fibromyalgia: comparative effectiveness randomized controlled trial.

Wang C[1], Schmid CH[2], Fielding RA[3], Harvey WF[4], Reid KF[3], Price LL[5], Driban JB[4], Kalish R[6], Rones R[7], McAlindon T[4].

BMJ. **2018 Mar 21**; 360:k851. doi: 10.1136/bmj.k851. PMCID: PMC5861462. PMID: 29563100.

OBJECTIVES: To determine the effectiveness of tai chi interventions compared with aerobic exercise, a current core standard treatment in patients with fibromyalgia, and to test whether the effectiveness of tai chi depends on its dosage or duration.

DESIGN: Prospective, randomized, 52 week, single blind comparative effectiveness trial.

SETTING: Urban tertiary care academic hospital in the United States between March 2012 and September 2016.

PARTICIPANTS: 226 adults with fibromyalgia (as defined by the American College of Rheumatology 1990 and 2010 criteria) were included in the intention to treat analyses: 151 were assigned to one of four tai chi groups and 75 to an aerobic exercise group.

INTERVENTIONS: Participants were randomly assigned to either supervised aerobic exercise (24 weeks, twice weekly) or one of four classic Yang style supervised tai chi interventions (12 or 24 weeks, once or twice weekly). Participants were followed for 52 weeks. Adherence was rigorously encouraged in person and by telephone.

MAIN OUTCOME MEASURES: The primary outcome was change in the revised fibromyalgia impact questionnaire (FIQR) scores at 24 weeks compared with baseline. Secondary outcomes included changes of scores in patient's global assessment, anxiety, depression, self efficacy, coping strategies, physical functional performance, functional limitation, sleep, and health related quality of life.

RESULTS: FIQR scores improved in all five treatment groups, but the combined tai chi groups improved statistically significantly more than the aerobic exercise group in FIQR scores at 24 weeks (difference between groups=5.5 points, 95% confidence interval 0.6 to 10.4, P=0.03) and several secondary outcomes (patient's global assessment=0.9 points, 0.3 to 1.4, P=0.005; anxiety=1.2 points, 0.3 to 2.1, P=0.006; self efficacy=1.0 points, 0.5 to 1.6, P=0.0004; and coping strategies, 2.6 points, 0.8 to 4.3, P=0.005). Tai chi treatment compared with aerobic exercise administered with the same intensity and duration (24 weeks, twice weekly) had greater benefit (between group difference in FIQR scores=16.2 points, 8.7 to 23.6, P<0.001). The groups who received tai chi for 24 weeks showed greater improvements than those who received it for 12 weeks (difference in FIQR scores=9.6 points, 2.6 to 16.6, P=0.007). There was no significant increase in benefit for groups who received tai chi twice weekly compared with once weekly. Participants attended the tai chi training sessions more often than participants attended aerobic exercise. The effects of tai chi were consistent across all instructors. No serious adverse events related to the interventions were reported.

CONCLUSION: Tai chi mind-body treatment results in similar or greater improvement in symptoms than aerobic exercise, the current most commonly prescribed non-drug treatment, for a variety of outcomes for patients with fibromyalgia. Longer duration of tai chi showed greater improvement. This mind-body approach may be considered a therapeutic option in the multidisciplinary management of fibromyalgia.

TRIAL REGISTRATION: ClinicalTrials.gov NCT01420640.

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