GULF WAR ILLNESS

The prevalence of headaches, pain, and other associated symptoms in different Persian Gulf deployment periods and deployment durations.

Lei K[1], Metzger-Smith V[2], Golshan S[2,3], Javors J[2], Leung A[2,4].

SAGE Open Med. **2019 Aug 26**;7:2050312119871418. doi: 10.1177/2050312119871418. PMCID: PMC6712755. PMID: 31489191. eCollection 2019.

Objectives: This study aims to assess (1) the difference in the prevalence of headaches, pain, and other associated symptoms between Gulf War I (1990-1991) and Post-Gulf War I (1992-2015) veterans who served as active military personnel in the Persian Gulf and (2) how the durations of deployment may affect the prevalence ofthose symptoms.

Methods: With institutional human subject committee approval, veterans who were accepted to the Gulf War Registry at the VA San Diego Healthcare System between July 2013 and June 2015 ($N = 367$) were included in this retrospective chart review study and grouped according to the Gulf War period they served under or how long they were deployed to the Persian Gulf. Chi-square was used for categorical data analyses and analysis of variance was conducted for continuous outcomes. All analyses were two-tailed, where applicable, with $\alpha = 0.05$ and Bonferroni for pairwise group comparisons.

Results: Veterans who served during Post-Gulf War I or both Gulf War I and Post-Gulf War I exhibited more pain and neurological symptoms than Gulf War I veterans ($p = 0.005$, $p = 0.003$). In addition, veterans who served $\geqslant$12 months reported more overall pain symptoms and analgesic use than those who served less time ($p < 0.001$, $p = 0.024$).

Conclusion: The findings suggest that the length of deployment and Persian Gulf deployment period may play a role in acquiring headaches, pain, and other associated symptoms with increased analgesic consumption.

CHRONIC FATIGUE SYNDROME

The Efficacy and Safety of Myelophil, an Ethanol Extract Mixture of Astragali Radix and Salviae Radix, for Chronic Fatigue Syndrome: A Randomized Clinical Trial.

Joung JY[1], Lee JS[1], Cho JH[1], Lee DS[2], Ahn YC[3], Son CG[1].

Front Pharmacol. **2019 Sep 10**;10:991. doi: 10.3389/fphar.2019.00991. PMCID: PMC6746924. PMID: 31551788. eCollection 2019.

Background: There is a strong demand for therapeutics to treat chronic fatigue syndrome (CFS), although there are limitations. Myelophil, which is a combination of extracts from *Astragali Radix* and *Salviae Miltiorrhizae Radix*, has been clinically used to treat fatigue-related disorders in South Korea. We conducted a randomized controlled clinical trial of Myelophil in patients with CFS and evaluated its efficacy and safety in two hospitals.

Methods: We enrolled 98 participants (M: 38, F: 60) with CFS in a phase 2 trial of oral Myelophil (2 g daily) or placebo for 12 weeks. The primary end point was a change in the Chalder fatigue scale, as scored by a numeric rating scale (NRS). The secondary end points included changes in the visual analogue scale, fatigue severity scale (FSS), and 36-item short-form health survey (SF-36). Biomarkers of oxidative stress and cytokines were evaluated by blood tests.

Results: Ninety-seven participants (48 in the Myelophil group and 49 in the placebo group) completed the trial. An analysis of all participants showed that Myelophil slightly improved fatigue symptoms compared with those of the placebo, but this effect was not statistically significant ($p > 0.05$ for the NRS, VAS, FSS, and SF-36). By contrast, an analysis of the subpopulation (53 participants, M: 24, F: 29) with severe symptoms (≥63, median NRS value of total participants) showed a statistically significant improvement in fatigue symptoms in the Myelophil group compared with the placebo ($p < 0.05$ for NRS, FSS, and SF-36). There were no significant changes in the biomarkers for oxidative stress and cytokines before or after the treatment. No Myelophil-related adverse response was observed during the trial.

Conclusion: These results support the hypothesis that Myelophil can be a therapeutic candidate to manage CFS and provide the rationale for its progression to a phase 3 clinical trial.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier KCT0002317.

CHRONIC FATIGUE SYNDROME (Continued)

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: From Pathophysiological Insights to Novel Therapeutic Opportunities.

Morris G[1], Puri BK[2], Walker AJ[1], Maes M[1], Carvalho AF[3], Walder K[4], Mazza C[1], Berk M[5].

Pharmacol Res. **2019 Sep 8**:104450. doi: 10.1016/j.phrs.2019.104450. PMID: 31509764. [Epub ahead of print]

Myalgic encephalomyelitis (ME) or chronic fatigue syndrome (CFS) is a common and disabling condition with a paucity of effective and evidence-based therapies reflecting a major unmet need. Cognitive behavioural therapy and graded exercise are of modest benefit for only some ME/CFS patients, and many sufferers report aggravation of symptoms of fatigue with exercise. The presence of a multiplicity of pathophysiological abnormalities, in at least the subgroup of people with ME/CFS diagnosed with the current international consensus "Fukuda" criteria, points to numerous potential therapeutic targets. Such abnormalities include extensive data showing that at least a subgroup has a pro-inflammatory state, increased oxidative and nitrosative stress, disruption of gut mucosal barriers and mitochondrial dysfunction together with dysregulated bioenergetics. In this paper, these pathways are summarised, and data regarding promising therapeutic options that target these pathways are highlighted; they include coenzyme Q_{10}, melatonin, curcumin, molecular hydrogen and N-acetylcysteine. These data are promising yet preliminary, suggesting hopeful avenues to address this major unmet burden of illness.

Phylogenetic Tree-based Microbiome Association Test.

Kim KJ[1], Park J[2], Park SC[3], Won S[1,2,3].

Bioinformatics. **2019 Sep 3**. pii: btz686. doi: 10.1093/bioinformatics/btz686. PMID: 31504188. [Epub ahead of print]

MOTIVATION: Ecological patterns of the human microbiota exhibit high inter-subject variation, with few operational taxonomic units (OTUs) shared across individuals. To overcome these issues, non-parametric approaches, such as the Mann-Whitney U-test and Wilcoxon rank-sum test, have often been used to identify OTUs associated with host diseases. However, these approaches only use the ranks of observed relative abundances, leading to information loss, and are associated with high false-negative rates. In this study, we propose a phylogenetic tree-based microbiome association test (TMAT) to analyze the associations between microbiome OTU abundances and disease phenotypes. Phylogenetic trees illustrate patterns of similarity among different OTUs, and TMAT provides an efficient method for utilizing such information for association analyses. The proposed TMAT provides test statistics for each node, which are combined to identify mutations associated with host diseases.

RESULTS: Power estimates of TMAT were compared with existing methods using extensive simulations based on real absolute abundances. Simulation studies showed that TMAT preserves the nominal type-1 error rate, and estimates of its statistical power generally outperformed existing methods in the considered scenarios. Furthermore, TMAT can be used to detect phylogenetic mutations associated with host diseases, providing more in-depth insight into bacterial pathology.

AVAILABILITY: The 16S rRNA amplicon sequencing metagenomics datasets for colorectal carcinoma and myalgic encephalomyelitis/chronic fatigue syndrome are available from the European Nucleotide Archive (ENA) database under project accession number PRJEB6070 and PRJEB13092, respectively. TMAT was implemented in the R package. Detailed information is available at http://healthstat.snu.ac.kr/software/tmat.

SUPPLEMENTARY INFORMATION: Supplementary data are available at Bioinformatics online.

HEADACHE and MIGRAINE

Migraine and the risk of all-cause dementia, Alzheimer's disease, and vascular dementia: A prospective cohort study in community-dwelling older adults.

Morton RE[1], St John PD[2], Tyas SL[1].

Int J Geriatr Psychiatry. **2019 Sep 4**. doi: 10.1002/gps.5180. PMID: 31486140. [Epub ahead of print]

OBJECTIVES: Dementia is the most common neurological disease in older adults; headaches, including migraines, are the most common neurological disorder across all ages. The objective of this study was to explore the relationship between migraines and dementia, including Alzheimer's disease (AD) and vascular dementia (VaD).

METHODS: Analyses were based on 679 community-dwelling participants 65+ years from the Manitoba Study of Health and Aging, a population-based, prospective cohort study. Participants screened as cognitively intact at baseline had complete data on migraine history and all covariates at baseline and were assessed for cognitive outcomes (all-cause dementia, AD, and VaD) 5 years later. The association of exposure (lifetime history of migraines), confounding (age, gender, education, and depression), and intervening variables (hypertension, myocardial infarction, other heart conditions, stroke, and diabetes) with all-cause dementia and dementia subtypes (AD and VaD) was assessed using multiple logistic regression models.

RESULTS: A history of migraines was significantly associated with both all-cause dementia (odds ratio [OR]=2.97; 95% confidence interval [CI]=1.25-6.61) and AD (OR=4.22; 95% CI=1.59-10.42), even after adjustment for confounding and intervening variables. Migraines were not significantly associated with VaD either before (OR=1.83; 95% CI=0.39-8.52) or after (OR=1.52; 95% CI=0.20-7.23) such adjustment.

CONCLUSIONS: Migraines were a significant risk factor for AD and all-cause dementia. Despite the vascular mechanisms involved in migraine physiology, migraines were not significantly associated with VaD in this study. Recognition of the long-term detrimental consequences of migraines for AD and dementia has implications for migraine management, as well as for our understanding of AD etiology.

Development of the TBI-QOL Headache Pain Item Bank and Short Form.

Tulsky DS[1], Tyner CE, Boulton AJ, Kisala PA, Heinemann AW, Roth EJ, Carlozzi NE.

J Head Trauma Rehabil. **2019 Sep/**Oct;34(5):298-307. doi: 10.1097/HTR.0000000000000532. PMID: 31498229.

OBJECTIVE: To develop, calibrate, and evaluate the test-retest reliability of a new patient-reported outcome measure of headache pain relevant for individuals with traumatic brain injury (TBI).

SETTING: Six TBI Model Systems rehabilitation centers in the United States.

PARTICIPANTS: Adults with medically confirmed documentation of TBI.

DESIGN: Cross-sectional calibration field testing and test-retest reliability analyses.

MAIN MEASURES: Traumatic Brain Injury-Quality of Life Headache Pain item bank.

RESULTS: Thirteen headache pain items were calibrated as a unidimensional measure using data from 590 participants. The new measure was reliable (α = .98; item-total correlation range: 0.71-0.91). Item parameter estimates were estimated using Samejima's Graded Response Model and a 10-item calibrated short form was created. Simulation testing confirmed that both the computer-adaptive test and the short-form administrations were equivalent to the full item bank. One- to-2-week test-retest reliability of the computer-adaptive test was high (Pearson r and intraclass correlation coefficients = 0.81). Approximately two-thirds of the sample reported at least 1 headache symptom.

CONCLUSION: The Traumatic Brain Injury-Quality of Life Headache Pain item bank and short form provide researchers and clinicians with reliable measures of the subjective experience of headache symptoms for individuals with a history of TBI.

HEADACHE and MIGRAINE (Continued)

Migraine and gastric disorders: Are they associated?

Hormati A[1,2], Akbari N[3], Sharifipour E[3], Hejazi SA[3], Jafari F[1], Alemi F[1], Mohammadbeigi A[1].

J Res Med Sci. **2019 Jul 24**;24:60. doi: 10.4103/jrms.JRMS_464_18. PMCID: PMC6669996. PMID: 31523246. eCollection 2019.

Background: Migraine is a common disorder which affects quality of life. There has been an increasing interest for discovering the association of gastrointestinal (GI) disorders with migraine during past years. This study aims to evaluate the association of *Helicobacter pylori* contamination, gastroesophageal reflux disease (GERD), gastric ulcer (GU), and duodenal ulcer (DU) with migraine in patients who underwent upper GI endoscopy due to refractory dyspepsia.

Materials and Methods: In this observational cross-sectional study, 341 dyspeptic patients who underwent upper GI endoscopy in Shahid Beheshti Hospital, Qom, Iran, included during 2016-2018. A checklist was used for collecting demographics, symptoms, and results from endoscopy and *H. pylori* testing. Diagnosis of migraine was made according to the International Headache Society criteria in patients who had headache. Data were analyzed using Chi-square and independent samples *t*-tests in SPSS 16 (SPSS Inc., Chicago, IL, USA) with $P < 0.05$ as significance level.

Results: Among 341 patients, 141 (% 41.3) were male and 200 (58.7%) were female. 149 (43.7%) patients were diagnosed with migraine, from which 48 (32.2%) were male and 101 (67.8%) were female. The observed difference in migraine prevalence among male and female was statistically significant ($P = 0.003$). 198 (58.06%) patients were *H. pylori* contaminated, among these 138 (69.7%) suffered from migraine. Among 143 *H. pylori*-negative patients, there were 11 (7.7%) migraineurs. The difference in the prevalence of migraine among *H. pylori* positive and negative patients was significant. *H. pylori* and GERD were associated with migraine with $P < 0.001$. Patients with DU were more commonly suffering from migraine ($P = 0.001$). The association in patients with GU was not statistically significant ($P = 0.863$).

Conclusion: Migraine might be associated with GERD, *H. pylori* infection, and DU, and the treatment of the underlying GI disorder may control headaches.

Prognosis Following Discontinuation of OnabotulinumA Therapy in "Super-responding" Chronic Migraine Patients.

Ching J[1], Tinsley A[1], Rothrock J[1].

Headache. **2019 Sep 9**. doi: 10.1111/head.13630. PMID: 31498897. [Epub ahead of print]

OBJECTIVE: To determine whether the successful treatment of chronic migraine (CM) with onabotulinumA (BotoxA) may be followed by a continued respite from headache once therapy has been discontinued.

BACKGROUND: The optimal duration of prophylactic therapy for migraine generally and for CM treated with BotoxA specifically is unknown.

METHODS: We conducted a prospective cohort study evaluating a series of patients with CM at a university-affiliated headache subspecialty clinic in Reno, Nevada, all of whom were treated according to a uniform protocol involving serial injections of BotoxA. We followed all positively responding patients who met our stopping rule for a minimum of 6 months after discontinuation of BotoxA, and we assessed the incidence of clinical worsening in that group.

RESULTS: A total of 105/131 patients (80%) for whom complete follow-up was available reported no clinical worsening or need to resume prophylactic therapy over the 6 months following discontinuation of BotoxA therapy. Patients with pre-treatment baseline chronic daily headache (CDH) of greater than 6 months duration were more likely to report clinical deterioration within 6 months of stopping treatment, as compared to patients with CDH of less than 6 months. A greater number of BotoxA treatments required to achieve our stopping rule correlated with clinical deterioration within 6 months of stopping treatment.

CONCLUSIONS: In many CM patients who experience an especially positive response to serial BotoxA injection therapy, clinical improvement may be sustained for a period of at least 6 months following discontinuation of prophylactic therapy.

HEADACHE and MIGRAINE (Continued)

Is There Any MRI Pattern That Discriminates Female From Male Migraine Patients?

Maleki N[1], Androulakis XM[2,3].

Front Neurol. **2019 Sep 6**;10:961. doi: 10.3389/fneur.2019.00961. PMCID: PMC6747047. PMID: 31551917. eCollection 2019.

There has been accumulating evidence on sex disparity in incidence, prevalence, symptomology, and burden of migraine. Several neuroimaging studies on migraine patients attempted to unravel the mechanisms of the disease, yet very few of them examined the sex-related differences. Here, we will first discuss some of the reported neuroimaging patterns that discriminate females from males in migraine. We will then re-examine the salient neuroimaging findings in migraine and discuss them in relation to sex-related influences. Finally, we will discuss some of the intriguing recent data suggesting the presence of sex-specific traits in migraineurs. These findings may have potential implications for future neuroimaging studies to identify underlying correlating patterns in the brain to (1) explain the neural basis for higher prevalence of migraine in women, and (2) better understand migraine-specific changes during different stages of life in both men and women.

CHRONIC PAIN

A complementary and integrative health group-based program pilot demonstrates positive health outcomes with female Veterans.

Haun JN[1], Paykel J[1], Alman AC[2], Patel N[3], Melillo C[4].

Explore (NY). **2019 Aug 12**. CHECK pii: S1550-8307(19)30444-6. doi: 10.1016/j.explore.2019.08.001. PMID: 31477475. [Epub ahead of print]

INTRODUCTION: Transforming Health and Resiliency through Integration of Values-based Experiences (THRIVE) is an evidence-based 14-week curriculum-based group medical appointment clinical program. THRIVE is based on principles of integrative medicine, positive psychology, and acceptance and commitment therapy. The goal of this paper is to review findings from a local THRIVE program implementation piloted in the Women's Health outpatient clinics on mental and physical health indicators.

MATERIALS AND METHODS: Pilot data were obtained for 14 THRIVE cohorts of female veterans enrolled from outpatient clinics at the James A. Haley veterans' Hospital in Tampa, FL between 2016 and 2018 (N = 201). THRIVE assessments were conducted as part of the THRIVE program, at the first visit (baseline), mid-way, and at the end of the program. Data were collected using self-administered paper-pencil method on standardized scales for physical and mental health (Patient Health Questionnaire, Generalized Anxiety Disorder Questionnaire, Acceptance and Action Questionnaire-II, Satisfaction With Life Scale, and the physical and mental function components of the Short Form Survey). Linear mixed effects models were used to examine change in physical and mental health scales over time while adjusting for age, race (white vs. other), and cohort. In addition, we examined whether the rate of change differed by age or race.

RESULTS: Improvement was seen for most scales across the 3 assessments ($p < 0.05$) with the exception of physical composite score of the Short Form Survey ($p = 0.487$). Participants reported that pain interfering with work significantly decreased from "quite a bit" at baseline to "moderately" by assessment 3 ($p = 0.042$). Older ages had lower baseline scores on the Patient Health Questionnaire and Acceptance and Action Questionnaire than younger ages, but younger ages had a greater rate of improvement over the intervention (p for interaction 0.016 and 0.056, respectively). Whites reported greater improvement in life satisfaction than non-whites (p for interaction 0.043). For physical composite score, whites had higher baseline score, but did not report significant improvement in physical function over the assessment period, while non-whites had lower baseline score, but did report significant improvement in physical function (p for interaction 0.059). Non-white veterans reported more pain interfering with work relative to white veterans (OR 5.9, 95% CI 1.79-19.43, $p = 0.004$).

CONCLUSIONS: We found significant improvement on self-reported mental health scales as well as improvement in how much pain interferes with work in a pilot sample of women veterans over the 14-week program.

CHRONIC PAIN (Continued)

Mindfulness Training for Chronic Non-malignant Pain Management: A Review of the Clinical Effectiveness, Cost-effectiveness and Guidelines [Internet].

Editors Lachance CC, McCormack S. CADTH Rapid Response Reports.

Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; **2019 Jun**. PMID: 31498576

Excerpt: Chronic pain is a pervasive health issue that adversely affects both the patient and society, including loss of productivity, decreased quality of life, and an increased burden on the health care system.[1–4] The International Classification of Diseases (ICD) of the World Health Organization defines chronic pain as persistent or recurrent pain lasting longer than three months.[5] Non-malignant (non-cancer) related types of chronic pain may include low back pain, osteoarthritis, rheumatoid arthritis, headache, neck pain, fibromyalgia, and irritable bowel syndrome.[6] The prevalence of chronic pain is estimated to be 21% among the general Canadian population, a prevalence rate that has increased over time.[2] Chronic pain has substantial economic implications and has been estimated to cost Canada over six billion dollars per year in direct health care costs and 37 billion per year in productivity costs (e.g., job loss, sick days).[1,7,8] Given the prevalence and burden of chronic pain, a variety of treatment options have been explored to help patients manage their symptoms of pain, including pharmacological approaches (i.e., prescription or non-prescription drugs), physical therapy, exercise, surgery, psychological therapy, and complementary and alternative therapies.[4] In order to decide what treatment is best for the patient, careful consideration should be given to the benefits and risks of the available treatment options.[9] Medications, such as opioids, are commonly prescribed for pain, with approximately three to four percent of the adult population in the United States prescribed long-term opioid therapy.[9,10] However, long-term opioid therapy presents some serious risks, including addiction, accidental overdose, hyperalgesia, and diversion for non-medical use.[10] Mindfulness training is another potential treatment option for individuals who suffer from chronic pain.[11] Mindfulness is defined as the intentional and non-judgmental conscious awareness of the present moment.[12] A previous CADTH rapid response report that was published in 2012[11] examined the clinical effectiveness and evidence-based guidelines regarding the use of mindfulness training for chronic pain management in adults and found insufficient evidence to draw conclusions about its potential effectiveness. An update is needed to determine if the evidence surrounding mindfulness for chronic pain management is more conclusive to inform future policy decisions. The aim of this report is to summarize the evidence regarding both the clinical and cost-effectiveness, as well as guidelines for the use of mindfulness training for chronic non-malignant pain management.

IRRITABLE BOWEL SYNDROME

The Dietary Management of Patients with Irritable Bowel Syndrome: A Narrative Review of the Existing and Emerging Evidence.

Algera J[1,2], Colomier E[3,4], Simrén M[5].

Nutrients. **2019 Sep 9**;11(9). pii: E2162. doi: 10.3390/nu11092162. PMCID: PMC6770052. PMID: 31505870.

Even though irritable bowel syndrome (IBS) has been known for more than 150 years, it still remains one of the research challenges of the 21st century. According to the current diagnostic Rome IV criteria, IBS is characterized by abdominal pain associated with defecation and/or a change in bowel habit, in the absence of detectable organic causes. Symptoms interfere with the daily life of patients, reduce health-related quality of life and lower the work productivity. Despite the high prevalence of approximately 10%, its pathophysiology is only partly understood and seems multifactorial. However, many patients report symptoms to be meal-related and certain ingested foods may generate an exaggerated gastrointestinal response. Patients tend to avoid and even exclude certain food products to relieve their symptoms, which could affect nutritional quality. We performed a narrative paper review of the existing and emerging evidence regarding dietary management of IBS patients, with the aim to enhance our understanding of how to move towards an individualized dietary approach for IBS patients in the near future.

IRRITABLE BOWEL SYNDROME (Continued)

Sucrase-Isomaltase Deficiency as a Potential Masquerader in Irritable Bowel Syndrome.

Kim SB[1], Calmet FH[2], Garrido J[3], Garcia-Buitrago MT[4], Moshiree B[5].

Dig Dis Sci. **2019 Sep 6**. doi: 10.1007/s10620-019-05780-7. PMID: 31493040. [Epub ahead of print]

BACKGROUND: Patients with irritable bowel syndrome (IBS) frequently have meal-related symptoms and can recognize specific trigger foods. Lactose intolerance is a well-established carbohydrate malabsorption syndrome that causes symptoms similar to IBS such as bloating, abdominal pain, and diarrhea. However, the prevalence of sucrase-isomaltase deficiency (SID) in this population is poorly defined. SID is a condition in which sucrase-isomaltase, an enzyme produced by brush border of small intestine to metabolize sucrose, is deficient. Just like lactase deficiency, SID causes symptoms of maldigestion syndromes including abdominal pain, bloating, gas, and diarrhea. In this study, we aim to determine the prevalence of SID in patients with presumed IBS-D/M and characterize its clinical presentation.

METHODS: Patients with a presumed diagnosis of IBS-D/M based on symptoms of abdominal pain, diarrhea, and/or bloating who underwent esophagogastroduodenoscopy with duodenal biopsies and testing for disaccharidase deficiency were included. Patients with a history of inflammatory bowel disease, gastrointestinal malignancy, or celiac disease were excluded. Odds ratio was calculated for abdominal pain, diarrhea, and bloating in patients with versus without SID.

RESULTS: A total of 31 patients with clinical suspicion for IBS-D/M were included with a median age of 46 years (IQR 30.5-60) and with 61% females. SID was present in 35% of patients. Among patients with SID, 63.6% had diarrhea, 45.4% had abdominal pain, and 36.4% had bloating. Patients with SID were less likely than controls to have abdominal pain (OR 0.16, 95% CI 0.03-0.81, p = 0.04) although no difference in diarrhea or bloating was found. Only two patients with SID underwent sucrose breath testing of which only one had a positive result. However, this patient also had a positive glucose breath test and may have had small intestinal bacterial overgrowth as a confounder.

CONCLUSION: SID was found in 35% of patients with presumed IBS-D/M and should be considered in the differential diagnosis of patients presenting with abdominal pain, diarrhea, or bloating. Further studies should better characterize the clinical features of SID and investigate the effects of dietary modification in this group of patients.

Protease-activated receptor signaling in intestinal permeability regulation.

Pontarollo G[1], Mann A[1], Brandão I[1,2], Malinarich F[1], Schöpf M[1], Reinhardt C[1,3].

FEBS J. **2019 Sep 8**. doi: 10.1111/febs.15055. PMID: 31495063. [Epub ahead of print]

Protease-activated receptors (PARs) are a unique class of G-protein-coupled transmembrane receptors, which revolutionized the perception of proteases from degradative enzymes to context-specific signaling factors. Although PARs are traditionally known to affect several vascular responses, recent investigations have started to pinpoint the functional role of PAR signaling in the gastrointestinal (GI) tract. This organ is exposed to the highest number of proteases, either from the gut lumen or from the mucosa. Luminal proteases include the host's digestive enzymes and the proteases released by the commensal microbiota, while mucosal proteases entail extravascular clotting factors and the enzymes released from resident and infiltrating immune cells. Active proteases and, in case of a disrupted gut barrier, even entire microorganisms are capable to translocate the intestinal epithelium, particularly under inflammatory conditions. Especially PAR-1 and PAR-2, expressed throughout the GI tract, impact gut permeability regulation, a major factor affecting intestinal physiology and metabolic inflammation. In addition, PARs are critically involved in the onset of inflammatory bowel diseases, irritable bowel syndrome, and tumor progression. Due to the number of proteases involved and the multiple cell types affected, selective regulation of intestinal PARs represents an interesting therapeutic strategy. The analysis of tissue/cell-specific knockout animal models will be of crucial importance to unravel the intrinsic complexity of this signaling network. Here, we provide an overview on the implication of PARs in intestinal permeability regulation under physiologic and disease conditions.

OTHER RESEARCH OF INTEREST

Usual Care Among Providers Treating Women Veterans: Managing Complexity and Multimorbidity in the Era of Evidence-Based Practice.

Hamilton AB[1,2], Wiltsey-Stirman S[3,4], Finley EP[5,6], Klap R[7,8], Mittman BS[9], Yano EM[7,10], Oishi S[7].

Adm Policy Ment Health. **2019 Aug 29**. doi: 10.1007/s10488-019-00961-y. PMID: 31468284. [Epub ahead of print]

To better understand VA providers' approaches to and perspectives on providing care to women Veterans, providers (n = 97) in primary care and mental health settings were interviewed about women's perceived treatment needs, types of care provided, and perceptions of evidence-based treatments (EBTs) for this population. Providers perceived that women Veteran VA users are often diagnostically complex and require a coordinated approach to treatment planning. They struggled with decisions about how to offer services such as EBTs and collaborative care in light of comorbidity and psychosocial stressors, and endorsed the belief that a tailored approach and consideration of these factors is essential in providing care.

The Impact of Sexual Trauma on the Sexual Health of Women Veterans: A Comprehensive Review.

Pulverman CS[1,2], Creech SK[1,2].

Trauma Violence Abuse. **2019 Aug 22**:1524838019870912. doi: 10.1177/1524838019870912. PMID: 31438778. [Epub ahead of print]

Sexual trauma, particularly childhood sexual trauma, is a potent risk factor for sexual health difficulties among civilian women. Women veterans report elevated rates of sexual trauma compared to their civilian peers, including sexual trauma during military service, perhaps making women veterans *even more* vulnerable to sexual health difficulties. A comprehensive review of the peer-reviewed literature on the relationship between sexual trauma and sexual health in women veterans was conducted. Inclusion criteria were measurement of sexual trauma and sexual health (i.e., sexual function or sexual satisfaction), a U.S. veteran sample including women veterans, and written in English. This process identified 18 articles. Results indicated that similar to the pattern observed among civilian women, sexual trauma was associated with an increased risk of sexual dysfunction and low sexual satisfaction among women veterans. Sexual pain was the most common sexual dysfunction among women veterans. Comorbid post-traumatic stress disorder and depression were identified as correlates of sexual dysfunction. Gaps in the literature included limited use of validated measures of sexual health and inconsistencies in the assessment of sexual trauma history. Future research is needed on the interrelationships between sexual trauma, sexual health, and mental health to inform treatment recommendations for improving sexual health among women veterans.

Characterizing VA Users with the OMOP Common Data Model.

Viernes B[1,2], Lynch KE[1,2], South B[1,2], Coronado G[1,2], DuVall SL[1,2].

Stud Health Technol Inform. **2019 Aug 21**;264:1614-1615. doi: 10.3233/SHTI190561. PMID: 31438258.

In 2015, the VA Informatics and Computing Infrastructure, a resource center of the Department of Veterans Affairs, began to transform parts of its Corporate Data Warehouse (CDW) into the Observational Medical Outcomes Partnership) Common Data Model for use by its research and operations communities. Using the hierarchical relationships within the clinical vocabularies in OMOP we found differences in visits, disease prevalence, and medications prescribed between male and female veterans seen between VA fiscal years 2000-17.

OTHER RESEARCH OF INTEREST (Continued)

Trial of SAGE-217 in Patients with Major Depressive Disorder.

Gunduz-Bruce H[1], Silber C[1], Kaul I[1], Rothschild AJ[1], Riesenberg R[1], Sankoh AJ[1], Li H[1], Lasser R[1], Zorumski CF[1], Rubinow DR[1], Paul SM[1], Jonas J[1], Doherty JJ[1], Kanes SJ[1].

N Engl J Med. **2019 Sep 5**;381(10):903-911. doi: 10.1056/NEJMoa1815981. PMID: 31483961.

BACKGROUND: Altered neurotransmission of γ-aminobutyric acid (GABA) has been implicated in the pathogenesis of depression. Whether SAGE-217, an oral, positive allosteric modulator of GABA type A receptors, is effective and safe for the treatment of major depressive disorder is unknown.

METHODS: In this double-blind, phase 2 trial, we enrolled patients with major depression and randomly assigned them in a 1:1 ratio to receive 30 mg of SAGE-217 or placebo once daily. The primary end point was the change from baseline to day 15 in the score on the 17-item Hamilton Depression Rating Scale (HAM-D; scores range from 0 to 52, with higher scores indicating more severe depression). Secondary efficacy end points, which were assessed on days 2 through 8 and on days 15, 21, 28, 35, and 42, included changes from baseline in scores on additional depression and anxiety scales, a reduction from baseline of more than 50% in the HAM-D score, a HAM-D score of 7 or lower, and a Clinical Global Impression of Improvement score of 1 (very much improved) or 2 (much improved) (on a scale of 1 to 7, with a score of 7 indicating that symptoms are very much worse).

RESULTS: A total of 89 patients underwent randomization: 45 patients were assigned to the SAGE-217 group, and 44 to the placebo group. The mean baseline HAM-D score was 25.2 in the SAGE-217 group and 25.7 in the placebo group. The least-squares mean (±SE) change in the HAM-D score from baseline to day 15 was -17.4±1.3 points in the SAGE-217 group and -10.3±1.3 points in the placebo group (least-squares mean difference in change, -7.0 points; 95% confidence interval, -10.2 to -3.9; P<0.001). The differences in secondary end points were generally in the same direction as those of the primary end point. There were no serious adverse events. The most common adverse events in the SAGE-217 group were headache, dizziness, nausea, and somnolence.

CONCLUSIONS: Administration of SAGE-217 daily for 14 days resulted in a reduction in depressive symptoms at day 15. Adverse events were more common in the SAGE-217 group than in the placebo group. Further trials are needed to determine the durability and safety of SAGE-217 in major depressive disorder and to compare SAGE-217 with available treatments. (Funded by Sage Therapeutics; ClinicalTrials.gov number, NCT03000530.).

Cognitive behavioural therapy for MS-related fatigue explained: A longitudinal mediation analysis.

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BACKGROUND: Cognitive behavioural therapy (CBT) effectively reduces fatigue directly following treatment in patients with Multiple Sclerosis (MS), but little is known about the process of change during and after CBT.

DESIGN: Additional analysis of a randomized clinical trial.

OBJECTIVE: To investigate which psychological factors mediate change in fatigue during and after CBT.

METHODS: TREFAMS-CBT studied the effectiveness of a 16-week CBT treatment for MS-related fatigue. Ninety-one patients were randomized (44 to CBT, 47 to the MS-nurse consultations). Mediation during CBT treatment was studied using assessments at baseline, 8 and 16weeks. Mediation of the change in fatigue from post-treatment to follow-up was studied separately using assessments at 16, 26 and 52weeks. Proposed mediators were: changes in illness cognitions, general self-efficacy, coping styles, daytime sleepiness, concentration and physical activity, fear of disease progression, fatigue perceptions, depression and physical functioning. Mediators were separately analysed according to the product-of-coefficients approach. Confidence intervals were calculated with a bootstrap procedure.

RESULTS: During treatment the decrease in fatigue brought on by CBT was mediated by improved fatigue perceptions, increased physical activity, less sleepiness, less helplessness, and improved physical functioning. Post-treatment increases in fatigue levels were mediated by reduced physical activity, reduced concentration, and increased sleepiness.

CONCLUSION: These results suggests that focusing on improving fatigue perceptions, perceived physical activity, daytime sleepiness, helplessness, and physical functioning may further improve the effectiveness of CBT for fatigue in patients with MS. Maintenance of treatment effects may be obtained by focusing on improving physical activity, concentration and sleepiness.

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