GULF WAR ILLNESS

Improving Health Care for Veterans With Gulf War Illness.

Baldwin N[1], Rudquist RR[1], Lava-Parmele S[1], Trembley JH[1], Butterick TA[1], Bach RR[1].

Fed Pract. **2019 May**;36(5):212-219.

Physicians need to recognize and manage Gulf War illness and similar postdeployment, chronic, multisymptom diseases among veterans of recent military operations.

Many veterans of the Gulf War are experiencing deployment-related chronic illness, known as Gulf War illness (GWI). Symptoms of GWI include cognitive impairments (mood and memory), chronic fatigue, musculoskeletal pain, gastrointestinal (GI) disorders, respiratory problems, and skin rashes.1–4 Three survey studies of the physical and mental health of a large cohort of Gulf War and Gulf era veterans, conducted by the US Department of Veterans Affairs (VA) Office of Public Health, established the increased prevalence of GWI in the decades that followed the end of the conflict.5–7 Thus, GWI has become the signature adverse health-related outcome of the Gulf War. Quality improvement (QI) within the Veterans Health Administration (VHA) is needed in the diagnosis and treatment of GWI.

[See full text, tables, and references for this article excerpt in Federal Practitioner.]

CHRONIC FATIGUE SYNDROME

Shared microglial mechanisms underpinning depression and chronic fatigue syndrome and their comorbidities.

Filho AJMC[1], Macedo DS[2], de Lucena DF[3], Maes M[4].

Behav Brain Res. **2019 May 25**:111975. doi: 10.1016/j.bbr.2019.111975. PMID: 31136774. [Epub ahead of print]

In 2011, it was reviewed that a) there is a strong co-occurrence between major depression and chronic fatigue syndrome (CFS), with fatigue and physio-somatic symptoms being key symptoms of depression, and depressive symptoms appearing during the course of CFS; and b) the comorbidity between both disorders may in part be explained by activated immune-inflammatory pathways, including increased translocation of Gram-negative bacteria and increased levels of pro-inflammatory cytokines, such as interleukin (IL)-1. Nevertheless, the possible involvement of activated microglia in this comorbidity has remained unclear. This paper aims to review microglial disturbances in major depression, CFS and their comorbidity. A comprehensive literature search was conducted using the PubMed / MEDLINE database to identify studies, which are relevant to this current review. Depressed patients present neuroinflammatory alterations, probably related to microglial activation, while animal models show that a microglial response to immune challenges including lipopolysaccharides is accompanied by depressive-like behaviors. Recent evidence from preclinical studies indicates that activated microglia have a key role in the onset of fatigue. In chronic inflammatory conditions, such as infections and senescence, microglia orchestrate an inflammatory microenvironment thereby causing fatigue. In conclusion, based on our review we may posit that shared immune-inflammatory pathways and especially activated microglia underpin comorbid depression and CFS. As such, microglial activation and neuro-inflammation may be promising targets to treat the overlapping manifestations of both depression and CFS.

CHRONIC FATIGUE SYNDROME (Continued)

Autonomic and inflammatory disturbances do not seem to explain symptoms in chronic fatigue.

Wyller VBB[1].

Brain Behav Immun. **2019 May 27**. pii: S0889-1591(19)30533-1. doi: 10.1016/j.bbi.2019.05.037. [Epub ahead of print]

I thank Valenti and Garner for their reflections on our recent paper (Kristiansen et al., 2019) on post-infectious chronic fatigue, including their suggested hypotheses: 1) That autonomic and inflammatory disturbances and inflammatory-autonomic interactions are underlying causal factors for symptoms, and 2) That therapies enhancing parasympathetic activity might inhibit inflammatory activation and thereby improve symptoms.

While I agree that autonomic and inflammatory disturbances are interesting topics for further chronic fatigue studies, I consider existing evidence to count against the suggested hypotheses. For instance, in our recent study, there are no strong associations between autonomic/inflammatory alterations and patients' symptoms; rather, we found a striking discrepancy between the severe symptom burden and functional disability, and the subtle disturbance of biological markers (Kristiansen et al., 2019). More importantly, a previous randomised controlled trial of the sympathetic inhibitor and parasympathetic stimulator drug *clonidine* in chronic fatigue syndrome adolescents demonstrated attenuated sympathetic and inflammatory activity in the intervention group; however, neither symptoms nor function improved (Sulheim et al., 2014). Thus, it seems that autonomic and inflammatory disturbances – while likely present in chronic fatigue and chronic fatigue syndrome – should be regarded secondary phenomena unrelated to patients' complaints, rather than causal factors explaining these complaints. If so, parasympathetic activation might have anti-inflammatory effects without affecting patients' symptoms of having a chronic inflammatory disorder.

[See full text, supplementary data, and references for this article excerpt in Brain, Behavior, and Immunity.]

The involvement of autonomic nervous system and inflammatory mechanisms in chronic fatigue: Perspectives for future studies.

Valenti VE[1], Garner DM[2].

Brain Behav Immun. **2019 May 27**. pii: S0889-1591(19)30464-7. doi: 10.1016/j.bbi.2019.05.036. PMID: 31145975. [Epub ahead of print]

We read with interest the well-designed study performed by Kristiansen et al. (2019) and take this opportunity to commend the authors. This is since autonomic dysfunction has now been shown to be related to several disorders.

As an important conclusion, the authors reported only minor sympathetic predominance in chronic fatigue, which may partially explain increased serum C-Reactive Protein levels. This now allows us to consider some issues for future studies:

1. The parasympathetic anti-inflammatory pathway has been previously described (Borovikova et al., 2000). More recently, Abe et al. (2017) reported that C1 neurons, which are involved in sympathetic regulation; mediate anti-inflammatory reflexes induced by stress in animals. Thus, we propose the following question: Would not the clinical interactions between sympathetic or parasympathetic actions and the inflammatory processes affect the chronic fatigue symptoms?
2. Similarly, non-invasive parasympathetic activation was revealed to improve inflammatory markers (Kong et al., 2018). So, is it logical to investigate this treatment for these chronic fatigue symptoms?

The purpose of this cross-examination is to achieve a better understanding of the physiological roles of interactions between autonomic and inflammatory mechanisms.

[See full text, supplementary data, and references for this article excerpt in Brain, Behavior, and Immunity.]

HEADACHE and MIGRAINE

Response to BotulinumtoxinA in a migraine cohort with multiple comorbidities and widespread pain.

Barad M[1], Sturgeon JA[1], Fish S[1], Dexter F[2], Mackey S[1], Flood PD[3].

Reg Anesth Pain Med. **2019 Jun**; and 44(6):660-668. doi: 10.1136/rapm-2018-100196. PMID: 31101743.

BACKGROUND: The phase III research evaluating migraine prophylaxis therapy (PREEMPT) protocol was developed in low-risk migraine patients. We studied longitudinal response to treatment in a sequential retrospective observational cohort to evaluate predictors of effectiveness in patients with multiple overlapping pain syndromes treated in a quaternary pain management clinic.

METHODS: We evaluated indicators of individual response in 402 consecutive chronic migraine patients who provided demographic information and used the Collaborative Health Outcomes Information Registry.

RESULTS: The patients were middle aged 47 (38-56) median (IQR) years old and 83% women. They reported multiple complex pain problems with 11 (6-18) regions represented on a pain body map. Evaluated with National Institutes of Health Patient-Reported Outcomes Measurement Information System measures, they reported higher scores for sleep impairment and disturbance, anxiety, depression, fatigue, pain behavior, pain interference and worse function and satisfaction with social roles compared with the general US population; $p<0.001$ for all domains. Within 120 days of treatment, 62% of patients reported reduced headache frequency. The best multivariable model developed for prediction of reduced headache frequency in response to treatment included lower treatment number, lower pain interference score, and less depression ($p=0.001$, 0.002, and 0.009). Depression may have been an obstacle to successful treatment; there was no association between depression score and number of treatments ($p=0.54$).

CONCLUSIONS: Our findings point to the importance of identifying and addressing pain interference and depression early in chronic migraine management and, more broadly, highlights the importance of multidisciplinary evaluation and treatment in chronic migraine.

Long-term safety and tolerability of erenumab: Three-plus year results from a five-year open-label extension study in episodic migraine.

Ashina M[1], Goadsby PJ[2], Reuter U[3], Silberstein S[4], Dodick D[5], Rippon GA[6], Klatt J[7], Xue F[6], Chia V[6], Zhang F[6], Cheng S[6], Mikol DD[6].

Cephalalgia. **2019 May 30**:333102419854082. doi: 10.1177/0333102419854082. PMID: 31146544. [Epub ahead of print]

BACKGROUND: Previously published three-month placebo-controlled and one-year open-label clinical trial data have provided information on the efficacy and safety of erenumab.

METHODS: Interim analysis was undertaken from an ongoing five-year open-label treatment phase after all patients completed three years in the open-label treatment phase or discontinued the study. Adult patients with episodic migraine enrolled in the open-label treatment phase initially received 70 mg erenumab monthly. A protocol amendment increased the dosage to 140 mg monthly to assess long-term safety of the higher dose. Safety and tolerability were assessed by monitoring adverse events, electrocardiograms, laboratory assessments, and vital signs.

RESULTS: Of 383 patients enrolled in the open-label treatment phase, at data cutoff 235 (61.3%) remained in the study, all received 140 mg for ≥1 year. Median (Q1, Q3) exposure (70 or 140 mg) for all patients enrolled was 3.2 (1.3, 3.4) years. The most frequent adverse events (≥4.0/100 patient-years) were reported as viral upper respiratory tract infection, sinusitis, influenza, and back pain. Exposure-adjusted serious adverse event rates were 4.2/100 patient-years. There was no increase in cardiovascular events over time.

CONCLUSIONS: In this long-term study of a CGRP-receptor antibody, erenumab was found to be safe and well-tolerated with a spectrum and rate of adverse events consistent with shorter-term placebo-controlled studies.

TRIAL REGISTRATION: ClinicalTrials.gov **NCT01952574**.

HEADACHE and MIGRAINE (Continued)

Pathophysiological Mechanisms in Migraine and the Identification of New Therapeutic Targets.

Haanes KA[1], Edvinsson L[2].

CNS Drugs. **2019 Jun**;33(6):525-537. doi: 10.1007/s40263-019-00630-6. PMID: 30989485.

Migraine is a strongly disabling disease characterized by a unilateral throbbing headache lasting for up to 72 h for each individual attack. There have been many theories on the pathophysiology of migraine throughout the years. Currently, the neurovascular theory dominates, suggesting clear involvement of the trigeminovascular system. The most recent data show that a migraine attack most likely originates in the hypothalamus and activates the trigeminal nucleus caudalis (TNC). Although the mechanisms are unknown, activation of the TNC leads to peripheral release of calcitonin gene-related protein (CGRP), most likely from C-fibers. During the past year monoclonal antibodies against CGRP or the CGRP receptor have emerged as the most promising targets for migraine therapy, and at the same time established the strong involvement of CGRP in the pathophysiology of migraine. The viewpoint presented here focuses further on the activation of the CGRP receptor on the sensory Aδ-fiber, leading to the sensation of pain. The CGRP receptor activates adenylate cyclase, which leads to an increase in cyclic adenosine monophosphate (cAMP). We hypothesize that cAMP activates the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, triggering an action potential sensed as pain. The mechanisms behind migraine pain on a molecular level, particularly their importance to cAMP, provide clues to potential new anti-migraine targets. In this article we focus on the development of targets related to the CGRP system, and further include novel targets such as the pituitary adenylate cyclase-activating peptide (PACAP) system, the serotonin 5-HT_{1F} receptor, purinergic receptors, HCN channels, adenosine triphosphate-sensitive potassium channels (K_{ATP}), and the glutaminergic system.

CHRONIC PAIN

Chronic Pain, Physical Activity, and All-Cause Mortality in the US Adults: The NHANES 1999-2004 Follow-Up Study.

Kim Y[1], Umeda M[2].

Am J Health Promot. **2019 May 30**:890117119854041. doi: 10.1177/0890117119854041. PMID: 31146537. [Epub ahead of print]

PURPOSE: The purposes of this study were (1) to examine the relationship between chronic pain and the risk of all-cause mortality and (2) to explore the role of physical activity (PA) in this relationship.

DESIGN: Prospective cohort study.

SETTING: The National Health and Nutrition Examination Survey (NHANES) conducted between 1999 and 2004.

PARTICIPANTS: A total of 7384 adults aged ≥40 years old.

MEASURES: Chronic pain and PA were assessed based on the responses to miscellaneous pain and leisure-time PA questionnaires collected during the household interview. The 2011 mortality data from the National Center for Health Statistics were linked to the NHANES participants.

ANALYSIS: Cox proportional hazard analyses after accounting for the complex sampling design of the NHANES.

RESULTS: After adjusting for several key covariates including sociodemographic variables, chronic health conditions, and unhealthy lifestyle behaviors, individuals with localized or widespread chronic pains showed greater risk of all-cause mortality when compared to individuals with no chronic pain (hazard ratios [HRs] = 1.26 and 1.41, respectively). However, the association was attenuated by further adjustment of PA levels, where engagement of PA ≥150 min/wk was associated with reduced risk of mortality regardless of chronic pain conditions (P for trends between <.001 and .028). The joint analysis further demonstrated that individuals with localized or widespread chronic pains who had PA ≥150 min/wk had lower risk of mortality (HRs = 0.53 and 0.58, respectively) when compared to those without chronic pain who reported no leisure time PA.

CONCLUSION: This study highlighted the important role of PA in reducing the risk of mortality for individuals with chronic pain. Further public health efforts to promote PA in this vulnerable population group are required.

CHRONIC PAIN (Continued)

Yoga improves occupational performance, depression, and daily activities for people with chronic pain.

Schmid AA[1], Van Puymbroeck M[2], Fruhauf CA[3], Bair MJ[4], Portz JD[5,6].

Work. **2019 May 27**. doi: 10.3233/WOR-192919. PMID: 31156199. [Epub ahead of print]

BACKGROUND: Chronic pain is a complex accumulation of physical, psychological, and social conditions, thus interventions that address pain and promote occupational performance are needed. A holistic intervention, with mind and body components, is likely necessary to best treat the complexities of chronic pain. Thus, we developed and tested a yoga intervention for people with chronic pain.

OBJECTIVES: In a randomized control trial (RCT), participants with chronic pain were randomized to a yoga intervention or usual care group. Between and within group differences for pre-and post-outcome measure scores were assessed for: occupational performance, completion of activities, and depression.

METHODS: Pilot RCT with participant allocation to 8 weeks of yoga or usual care. Both groups received ongoing monthly self-management programming. Data were collected before and after the 8-week intervention. Participants were randomized to yoga or usual care after baseline assessments. Demographics were collected and measures included: Canadian Occupational Performance Measure (COPM) to assess occupational performance; the 15-item Frenchay Activities Index (FAI)(activities); and the 9-item Patient Health Questionnaire (PHQ-9) for depression. Independent t-tests were used to assess differences between groups. Paired t-tests were used to assess differences between pre- and post 8-week intervention for both the yoga and the usual care groups. Percent change scores and effect sizes were calculated.

RESULTS: 83 people were recruited for the study and completed baseline assessments; 44 individuals were randomized to yoga and 39 to the control group. The average age of all participants was 51.4±10.5 years, 68% were female; and 60% had at least some college education. There were no significant differences in demographics or outcome measures between groups at baseline or 8 weeks; however, the study was not powered to see such differences. Individuals randomized to the control group did not significantly improve in any outcome measure over the 8 weeks. There were significant improvements in COPM performance and COPM satisfaction scores for individuals randomized to the yoga group; both scores significantly improved. COPM performance improved by 27% with a moderate to large effect size (3.66±1.85 vs 4.66±1.93, $p < 0.001$, $d = 0.76$). COPM satisfaction significantly improved by 78% (2.14±2.31 vs. 3.80±2.50, $p < 0.001$) and had a large effects size ($d = 1.02$). FAI scores improved, indicating increased activity or engagement in daily occupation during the 8-week intervention. Scores increased by 5% (38.13±8.48 vs. 39.90±8.57, $p = 0.024$) with a small effect size ($d = 0.37$). Depression significantly decreased from 13.21±5.60 to 11.41±5.82, $p = 0.041$, with a small effect size.

CONCLUSION: Data from this pilot RCT indicate yoga may be an effective therapeutic intervention with people in chronic pain to improve occupational performance, increase engagement in activities, and decrease depression. Occupational therapy practitioners may consider adding yoga as a treatment intervention to address the needs of people with pain.

IRRITABLE BOWEL SYNDROME

Serum zonulin is elevated in IBS and correlates with stool frequency in IBS-D.

Singh P[1], Silvester J[1,2], Chen X[1], Xu H[1], Sawhney V[1], Rangan V[1], Iturrino J[1], Nee J[1], Duerksen DR[3], Lembo A[1].

United European Gastroenterol J. **2019 Jun**;7(5):709-715. doi: 10.1177/2050640619826419. PMCID: PMC6545708. PMID: 31210949.

Background: Studies have shown increased intestinal permeability in irritable bowel syndrome. Validating serum biomarkers for altered intestinal permeability in irritable bowel syndrome will facilitate research and pathophysiology-based therapy.

Objective: To measure serum zonulin and intestinal fatty acid binding protein levels in diarrhea-predominant irritable bowel syndrome and constipation-predominant irritable bowel syndrome and compare with healthy controls and celiac disease.

Methods: Serum zonulin and intestinal fatty acid binding protein levels were measured using enzyme-linked immunosorbent assays in constipation-predominant irritable bowel syndrome ($n = 50$), diarrhea-predominant irritable bowel syndrome ($n = 50$), celiac disease ($n = 53$) and healthy controls ($n = 42$). Irritable bowel syndrome symptom severity was measured using the irritable bowel syndrome-symptom severity scale.

Results: Patients with constipation-predominant irritable bowel syndrome and diarrhea-predominant irritable bowel syndrome had higher zonulin levels compared with healthy controls ($p = 0.006$ and 0.009 respectively), which was comparable to those with active celiac disease. Although zonulin levels did not correlate with the overall irritable bowel syndrome symptom severity scale, it positively correlated with stool frequency per week ($p = 0.03$) and dissatisfaction with bowel habits ($p = 0.007$) in diarrhea-predominant irritable bowel syndrome. Patients with diarrhea-predominant irritable bowel syndrome and constipation-predominant irritable bowel syndrome had lower intestinal fatty acid binding protein levels compared with celiac patients ($p = 0.005$ and $p = 0.047$ respectively).

Conclusion: Serum zonulin is upregulated in irritable bowel syndrome and the levels are comparable to those in celiac disease. Zonulin levels correlated with severity of bowel habits in diarrhea-predominant irritable bowel syndrome. Intestinal fatty acid binding protein levels in irritable bowel syndrome patients were not increased suggesting no significant increase in enterocyte death.

OTHER RESEARCH OF INTEREST

Reproducibility and Replicability in Science

Consensus Study Report (**May 2019**)

Contributors: National Academies of Sciences, Engineering, and Medicine; Division of Behavioral and Social Sciences and Education; Division on Earth and Life Studies; Division on Engineering and Physical Sciences; Policy and Global Affairs; Committee on National Statistics; Board on Behavioral, Cognitive, and Sensory Sciences; Nuclear and Radiation Studies Board; Committee on Applied and Theoretical Statistics; Board on Mathematical Sciences and Analytics; Committee on Science, Engineering, Medicine, and Public Policy; Board on Research Data and Information; Committee on Reproducibility and Replicability in Science.

National Academies of Sciences, Engineering, and Medicine. 2019. *Reproducibility and Replicability in Science*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25303.

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One of the pathways by which the scientific community confirms the validity of a new scientific discovery is by repeating the research that produced it. When a scientific effort fails to independently confirm the computations or results of a previous study, some fear that it may be a symptom of a lack of rigor in science, while others argue that such an observed inconsistency can be an important precursor to new discovery.

Concerns about reproducibility and replicability have been expressed in both scientific and popular media. As these concerns came to light, Congress requested that the National Academies of Sciences, Engineering, and Medicine conduct a study to assess the extent of issues related to reproducibility and replicability and to offer recommendations for improving rigor and transparency in scientific research.

Reproducibility and Replicability in Science defines reproducibility and replicability and examines the factors that may lead to non-reproducibility and non-replicability in research. Unlike the typical expectation of reproducibility between two computations, expectations about replicability are more nuanced, and in some cases a lack of replicability can aid the process of scientific discovery. This report provides recommendations to researchers, academic institutions, journals, and funders on steps they can take to improve reproducibility and replicability in science.

OTHER RESEARCH OF INTEREST (Continued)

Use of PROMIS-29® in US Veterans: Diagnostic Concordance and Domain Comparisons with the General Population.

LaVela SL[1,2], Etingen B[3], Miskevics S[3], Cella D[4] .

J Gen Intern Med. **2019 May 29**. doi: 10.1007/s11606-019-05011-9. PMID: 31144276. [Epub ahead of print]

BACKGROUND: PROMIS® items have not been widely or systematically used within the Veterans Health Administration (VA).

OBJECTIVE: To examine the concordance of PROMIS-29® scores and medical record diagnosis in US Veterans and to compare Veteran scores relative to US population norms.

DESIGN/PARTICIPANTS: Cross-sectional multi-site survey of Veterans (n = 3221) provided sociodemographic and PROMIS-29® domain data. Electronic medical records provided health condition (depression, anxiety, sleep disorders, pain disorders) diagnosis data.

MAIN MEASURES: For each domain, we calculated PROMIS® standardized T scores and used t tests to compare PROMIS® scores for Veterans diagnosed with each targeted health condition vs. those without that documented clinical diagnosis and compare mean Veterans' PROMIS-29® with US adult population norms.

KEY RESULTS: Veterans with (vs. without) a depression diagnosis reported significantly higher PROMIS® depression scores (60.3 vs. 49.6, p < .0001); those with an anxiety diagnosis (vs. without) reported higher average PROMIS® anxiety scores (62.7 vs. 50.9, p < .0001). Veterans with (vs. without) a pain disorder reported higher pain interference (65.3 vs. 57.7, p < .0001) and pain intensity (6.4 vs. 4.4, p < .0001). Veterans with (vs. without) a sleep disorder reported higher sleep disturbance (55.8 vs. 51.2, p < .0001) and fatigue (57.5 vs. 51.8, p < .0001) PROMIS® scores. Compared with the general population norms, Veterans scored worse across all PROMIS-29® domains.

CONCLUSIONS: We found that PROMIS-29® domains are selectively sensitive to expected differences between clinically-defined groups, suggesting their appropriateness as indicators of condition symptomology among Veterans. Notably, Veterans scored worse across all PROMIS-29(R) domains compared with population norms. Taken collectively, our findings suggest that PROMIS-29® may be a useful tool for VA providers to assess patient's physical and mental health, and because PROMIS® items are normed to the general population, this offers a way to compare the health of Veterans with the adult population at large and identify disparate areas for intervention.

Is there any harm in administering extra-doses of vaccine to a person? Excess doses of vaccine reported to the Vaccine Adverse Event Reporting System (VAERS), 2007-2017.

Moro PL[1], Arana J[2], Marquez PL[2], Ng C[2], Barash F[3], Hibbs BF[2], Cano M[2].

Vaccine. **2019 May 30**. pii: S0264-410X(19)30576-6. doi: 10.1016/j.vaccine.2019.04.088. PMID: 31155414. [Epub ahead of print]

BACKGROUND: The administration of an extra dose of a vaccine may occur due to a programmatic error (e.g., vaccination error) when there is need to provide one of the antigens of a combination vaccine not readily available as a single antigen, or when there is need to provide immunization in a person with uncertain vaccination histories (e.g., refugees). There is little data available on the safety of an extra dose of vaccine.

OBJECTIVE: To assess for the presence of adverse events (AEs) most commonly reported following the administration of excess doses of vaccine in the Vaccine Adverse Event Reporting System (VAERS).

METHODS: We searched VAERS for US reports where an excess dose of vaccine was administered to a person received from 1/1/2007 through 1/26/2018. We reviewed medical records for all serious reports and a random sample of non-serious reports. The most common AEs among reports of excess dose of vaccine administered were compared with the corresponding AEs for all vaccines reported to VAERS during the same period.

RESULTS: Out of 366,815 total VAERS reports received, 5067 (1.4%) reported an excess dose of vaccine was administered; 3898 (76.9%) did not describe an adverse health event (AHE). The most common vaccines reported were trivalent inactivated influenza (15.4%), varicella (13.9%), hepatitis A (11.4%), and measles, mumps, rubella, varicella (11.1%). Among reports where only AHEs were reported, the most common were pyrexia (12.8%), injection site erythema (9.7%), injection site pain (8.9%), and headache (6.6%). The percentage of AHEs among these reports was comparable to all reports submitted to VAERS during the same study period.

CONCLUSION: More than three-fourths of reports of an excess dose of vaccine did not describe an AHE. Among reports where an AHE event was reported, we did not observe any unexpected conditions or clustering of AEs.

OTHER RESEARCH OF INTEREST (Continued)

Noninvasive ultrasound stimulation of the spleen to treat inflammatory arthritis.

Zachs DP[1], Offutt SJ[2], Graham RS[3], Kim Y[2], Mueller J[2], Auger JL[3], Schuldt NJ[3], Kaiser CRW[4], Heiller AP[4], Dutta R[3], Guo H[4], Alford JK[2], Binstadt BA[3], Lim HH[5,6,7].

Nat Commun. **2019 Mar 12**;10(1):951. doi: 10.1038/s41467-019-08721-0. PMCID: PMC6414603. PMID: 30862842.

Targeted noninvasive control of the nervous system and end-organs may enable safer and more effective treatment of multiple diseases compared to invasive devices or systemic medications. One target is the cholinergic anti-inflammatory pathway that consists of the vagus nerve to spleen circuit, which has been stimulated with implantable devices to improve autoimmune conditions such as rheumatoid arthritis. Here we report that daily noninvasive ultrasound (US) stimulation targeting the spleen significantly reduces disease severity in a mouse model of inflammatory arthritis. Improvements are observed only with specific parameters, in which US can provide both protective and therapeutic effects. Single cell RNA sequencing of splenocytes and experiments in genetically-immunodeficient mice reveal the importance of both T and B cell populations in the anti-inflammatory pathway. These findings demonstrate the potential for US stimulation of the spleen to treat inflammatory diseases.

Noninvasive sub-organ ultrasound stimulation for targeted neuromodulation.

Cotero V[1], Fan Y[1], Tsaava T[2], Kressel AM[2], Hancu I[1], Fitzgerald P[1], Wallace K[1], Kaanumalle S[1], Graf J[1], Rigby W[1], Kao TJ[1], Roberts J[1], Bhushan C[1], Joel S[1], Coleman TR[2], Zanos S[2], Tracey KJ[2], Ashe J[1], Chavan SS[2], Puleo C[3].

Nat Commun. **2019 Mar 12**;10(1):952. doi: 10.1038/s41467-019-08750-9. PMCID: PMC6414607. PMID: 30862827.

Comment in: **Peripheral Focused Ultrasound Stimulation (pFUS): New Competitor in Pharmaceutical Markets?** [SLAS Technol. 2019]

Tools for noninvasively modulating neural signaling in peripheral organs will advance the study of nerves and their effect on homeostasis and disease. Herein, we demonstrate a noninvasive method to modulate specific signaling pathways within organs using ultrasound (U/S). U/S is first applied to spleen to modulate the cholinergic anti-inflammatory pathway (CAP), and US stimulation is shown to reduce cytokine response to endotoxin to the same levels as implant-based vagus nerve stimulation (VNS). Next, hepatic U/S stimulation is shown to modulate pathways that regulate blood glucose and is as effective as VNS in suppressing the hyperglycemic effect of endotoxin exposure. This response to hepatic U/S is only found when targeting specific sub-organ locations known to contain glucose sensory neurons, and both molecular (i.e. neurotransmitter concentration and cFOS expression) and neuroimaging results indicate US induced signaling to metabolism-related hypothalamic sub-nuclei. These data demonstrate that U/S stimulation within organs provides a new method for site-selective neuromodulation to regulate specific physiological functions.

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