GULF WAR ILLNESS

Chronic Multisymptom Illness Among Iraq/Afghanistan-Deployed US Veterans and Their Healthcare Utilization Within the Veterans Health Administration.

Mohanty AF[1,2], McAndrew LM[3,4], Helmer D[3], Samore MH[5,6,7], Gundlapalli AV[5,6,7].

J Gen Intern Med. **2018 May 24**. doi: 10.1007/s11606-018-4479-6. PMID: 29797218. [Epub ahead of print]

Introduction: Little is known regarding the sex-specific CMI prevalence among OEF/OIF/OND deployed veterans or related healthcare utilization. Among OEF/OIF/OND veterans nationwide and stratified by sex, we sought to estimate the prevalence of CMI related diagnoses (hereafter referred to as CMI) and to explore trends in CMI-related (versus non-CMI-related) outpatient healthcare utilization in the Veterans Health Administration (VHA).

Methods: Our serial cross-sectional study included 501,996 males and 69,611 females from the OEF/OIF/OND Roster provided by the Department of Defense who had encounters in any VHA facility nationwide after their last deployment end date from fiscal years 2002–2011. We defined CMI as one or more International Classification of Diseases, 9th edition, Clinical Modification (ICD-9-CM) coded diagnosis of chronic fatigue syndrome (CFS, 780.71), fibromyalgia (FMS, 729.1), or irritable bowel syndrome (IBS, 564.1). We estimated adjusted prevalence ratios (PR) for demographic and military service characteristics associated with CMI. We identified the settings of outpatient encounters including primary care and specialty care clinics such as gastrointestinal, pain, and rheumatology/arthritis. We defined CMI-related outpatient utilization as VHA encounters with a documented ICD-9-CM code for CMI and calculated the yearly mean number.

Results: The prevalence of CMI was 4.2% in males and 8.4% in females. The higher prevalence in females versus males was consistent for CFS (3.3% versus 1.7%), FMS (9.2% versus 2.6%), and IBS (3.5% versus 1.6%). Age ≥ 30 years (PR 1.14, 95% CI 1.11–1.17) and being married (PR 1.13, 95% CI 1.10–1.16) were associated with CMI. Enlisted rank (PR 1.35, 95% CI 1.28–1.42) and Army military branch (PR: 1.22, 95% CI 1.18–1.25) were also associated with CMI in our fully adjusted models. Over the 10-year period, the mean yearly average number of CMI-related outpatient encounters was 11.3 in females and 9.6 in males; visit counts/veteran were higher among females across all years and care settings. Total outpatient utilization was higher among veterans with CMI compared to those without CMI (13.2 versus 7.1 yearly mean visits), regardless of sex. Among veterans with CMI, total outpatient utilization was higher in females versus males (14.3 versus 12.9 yearly mean visits). Among OEF/OIF/OND veterans without CMI, total outpatient utilization was higher among females versus males (7.7 versus 7.0 yearly mean visits).

Discussion: Among 571,607 OEF/OIF/OND veterans who accessed VHA services from fiscal years 2002–2011, 4.7% veterans had CMI. Results from our cross-sectional study of demographic and military characteristics associated with CMI extend these findings to one of the largest nationwide populations of OEF/OIF/OND veterans studied to date. A secondary analysis of yearly prevalence of CMI, stratified by gender, showed that the prevalence increased over the 10-year period. The extent to which more frequent healthcare utilization by females versus males overall, as observed in our study, provides more opportunities for females to receive a CMI diagnosis needs additional investigation. The finding that VHA outpatient care utilization was nearly twice as high for OEF/OIF/OND veterans with versus without CMI underscores the significant burden related to CMI both to patients and the healthcare system. Further work is needed to understand the timing or incidence and severity of symptoms, patterns of healthcare utilization within and outside the VHA, and quality of care received by male and female OEF/OIF/OND veterans with CMI.

The neuroinflammatory phenotype in a mouse model of Gulf War Illness is unrelated to brain regional levels of acetylcholine as measured by quantitative HILIC-UPLC-MS/MS.

Miller JV[1], LeBouf RF[2], Kelly KA[1], Michalovicz LT[1], Ranpara A[2], Locker AR[1], Miller DB[1], O'Callaghan JP[1].

Toxicol Sci. **2018 May 28**. doi: 10.1093/toxsci/kfy130. PMID: 29846716. [Epub ahead of print]

Many veterans of the 1991 Persian Gulf War (GW) returned with a chronic multisymptom illness that has been termed Gulf War Illness (GWI). Previous GWI studies have suggested that exposure to acetylcholinesterase inhibitors (AChEIs) in theater, such as sarin and/or pesticides, may have contributed to the symptomatology of GWI. Additionally, concomitant high physiological stress experienced during the war may have contributed to the initiation of the GWI phenotype. While inhibition of AChE leading to accumulation of acetylcholine (ACh) will activate the cholinergic anti-inflammatory pathway, the signature symptomatology of GWI has been shown to be associated with neuroinflammation. To investigate the relationship between ACh and neuroinflammation in discrete brain regions, we used our previously established mouse model of GWI, which combines an exposure to a high physiological stress mimic, corticosterone (CORT), with GW-relevant AChEIs. The AChEIs used in this study were diisopropyl fluorophosphate (DFP), chlorpyrifos oxon (CPO), and physostigmine (PHY). After AChEI exposure, ACh concentrations for cortex (CTX), hippocampus (HIP), and striatum (STR) were determined using hydrophilic interaction liquid chromatography (HILIC) with ultra-performance liquid chromatography (UPLC)-tandem-mass spectrometry (MS/MS). CORT pretreatment ameliorated the DFP-induced ACh increase in HIP and STR, but not CTX. CORT pretreatment did not significantly alter ACh levels for CPO and PHY. Further analysis of STR neuroinflammatory biomarkers revealed an exacerbated CORT+AChEI response, which does not correspond to measured brain ACh. By utilizing this new analytical method for discrete brain region analysis of ACh, this work suggests the exacerbated neuroinflammatory effects in our mouse model of GWI are not driven by the accumulation of brain region-specific ACh.

CHRONIC FATIGUE SYNDROME

Deconstructing post-exertional malaise in myalgic encephalomyelitis/ chronic fatigue syndrome: A patient-centered, cross-sectional survey.

Chu L[1], Valencia IJ[1], Garvert DW[1], Montoya JG[1].

PLoS One. **2018 Jun 1**;13(6):e0197811. doi: 10.1371/journal.pone.0197811. PMID: 29856774. eCollection 2018.

BACKGROUND: Post-exertional malaise (PEM) is considered to be the hallmark characteristic of myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS). Yet, patients have rarely been asked in formal studies to describe their experience of PEM.

OBJECTIVES: To describe symptoms associated with and the time course of PEM.

METHODS: One hundred and fifty subjects, diagnosed via the 1994 Fukuda CFS criteria, completed a survey concerning 11 symptoms they could experience after exposure to two different types of triggers. We also inquired about onset and duration of PEM and included space for subjects to write in any additional symptoms. Results were summarized with descriptive statistics; McNemar's, paired t-, Fisher's exact and chi-square goodness-of-fit tests were used to assess for statistical significance.

RESULTS: One hundred and twenty-nine subjects (90%) experienced PEM with both physical and cognitive exertion and emotional distress. Almost all were affected by exertion but 14 (10%) reported no effect with emotion. Fatigue was the most commonly exacerbated symptom but cognitive difficulties, sleep disturbances, headaches, muscle pain, and flu-like feelings were cited by over 30% of subjects. Sixty percent of subjects experienced at least one inflammatory/ immune-related symptom. Subjects also cited gastrointestinal, orthostatic, mood-related, neurologic and other symptoms. Exertion precipitated significantly more symptoms than emotional distress (7±2.8 vs. 5±3.3 symptoms (median, standard deviation), $p<0.001$). Onset and duration of PEM varied for most subjects. However, 11% reported a consistent post-trigger delay of at least 24 hours before onset and 84% endure PEM for 24 hours or more.

CONCLUSIONS: This study provides exact symptom and time patterns for PEM that is generated in the course of patients' lives. PEM involves exacerbation of multiple, atypical symptoms, is occasionally delayed, and persists for extended periods. Highlighting these characteristics may improve diagnosis of ME/CFS. Incorporating them into the design of future research will accelerate our understanding of ME/CFS.

Cerebral blood flow and heart rate variability predict fatigue severity in patients with chronic fatigue syndrome.

Boissoneault J[1], Letzen J[2], Robinson M[1], Staud R[3] .

Brain Imaging Behav. **2018 May 31**. doi: 10.1007/s11682-018-9897-x. PMID: 29855991. [Epub ahead of print]

Prolonged, disabling fatigue is the hallmark of chronic fatigue syndrome (CFS). Previous neuroimaging studies have provided evidence for nervous system involvement in CFS etiology, including perturbations in brain structure/function. In this arterial spin labeling (ASL) MRI study, we examined variability in cerebral blood flow (CBFV) and heart rate (HRV) in 28 women: 14 with CFS and 14 healthy controls. We hypothesized that CBFV would be reduced in individuals with CFS compared to healthy controls, and that increased CBFV and HRV would be associated with lower levels of fatigue in affected individuals. Our results provided support for these hypotheses. Although no group differences in CBFV or HRV were detected, greater CBFV and more HRV power were both associated with lower fatigue symptom severity in individuals with CFS. Exploratory statistical analyses suggested that protective effects of high CBFV were greatest in individuals with low HRV. We also found novel evidence of bidirectional association between the very high frequency (VHF) band of HRV and CBFV. Taken together, the results of this study suggest that CBFV and HRV are potentially important measures of adaptive capacity in chronic illnesses like CFS. Future studies should address these measures as potential therapeutic targets to improve outcomes and reduce symptom severity in individuals with CFS.

CHRONIC FATIGUE SYNDROME (Continued)

Structural brain changes versus self-report: machine-learning classification of chronic fatigue syndrome patients.

Sevel LS[1], Boissoneault J[1], Letzen JE[1], Robinson ME[1] , Staud R[2].

Exp Brain Res. **2018 May 30**. doi: 10.1007/s00221-018-5301-8. PMID: 29846797. [Epub ahead of print]

Chronic fatigue syndrome (CFS) is a disorder associated with fatigue, pain, and structural/functional abnormalities seen during magnetic resonance brain imaging (MRI). Therefore, we evaluated the performance of structural MRI (sMRI) abnormalities in the classification of CFS patients versus healthy controls and compared it to machine learning (ML) classification based upon self-report (SR). Participants included 18 CFS patients and 15 healthy controls (HC). All subjects underwent T1-weighted sMRI and provided visual analogue-scale ratings of fatigue, pain intensity, anxiety, depression, anger, and sleep quality. sMRI data were segmented using FreeSurfer and 61 regions based on functional and structural abnormalities previously reported in patients with CFS. Classification was performed in RapidMiner using a linear support vector machine and bootstrap optimism correction. We compared ML classifiers based on (1) 61 a priori sMRI regional estimates and (2) SR ratings. The sMRI model achieved 79.58% classification accuracy. The SR (accuracy = 95.95%) outperformed both sMRI models. Estimates from multiple brain areas related to cognition, emotion, and memory contributed strongly to group classification. This is the first ML-based group classification of CFS. Our findings suggest that sMRI abnormalities are useful for discriminating CFS patients from HC, but SR ratings remain most effective in classification tasks.

HEADACHE and MIGRAINE

Evaluation of Galcanezumab for the Prevention of Episodic Migraine: The EVOLVE-1 Randomized Clinical Trial.

Stauffer VL[1], Dodick DW[2], Zhang Q[1], Carter JN[1], Ailani J[3], Conley RR[1,4].

JAMA Neurol. **2018 May 29**. doi: 10.1001/jamaneurol.2018.1212. PMID: 29813147. [Epub ahead of print]

Importance: Migraine is a disabling neurological disease characterized by severe headache attacks. Treatment options reduce migraine frequency for many patients, but adverse effects lead to discontinuation in many patients.

Objective: To demonstrate that galcanezumab is superior to placebo in the prevention of episodic migraine with or without aura.

Design, Setting, and Participants: The EVOLVE-1 (Evaluation of LY2951742 in the Prevention of Episodic Migraine 1) trial was a double-blind, randomized, placebo-controlled (January 11, 2016, to March 22, 2017) trial comparing galcanezumab (120 mg and 240 mg) vs placebo. Patients received treatments once monthly for 6 months (subcutaneous injection via prefilled syringe) and were followed up for 5 months after their last injection. It was a multicenter, clinic-based study involving 90 sites in North America. Participants in the study were adults (aged 18 to 65 years) with at least a 1-year history of migraine, 4 to 14 migraine headache days per month and a mean of at least 2 migraine attacks per month within the past 3 months, and were diagnosed prior to age 50 years. During the study, no other preventive medications were allowed. A total of 1671 patients were assessed; 809 did not meet study entry or baseline criteria, and 858 were included in the intent-to-treat population.

Interventions: Patients were randomized (2:1:1) to monthly placebo, galcanezumab, 120 mg, and galcanezumab, 240 mg.

Main Outcomes and Measures: The primary outcome was overall mean change from baseline in the number of monthly migraine headache days during the treatment period. Secondary measures included at least 50%, at least 75%, and 100% reduction in monthly migraine headache days, migraine headache days with acute medication use, and scores from the Migraine-Specific Quality of Life questionnaire, Patient Global Impression of Severity, and Migraine Disability Assessment. Treatment-emergent adverse events and serious adverse events were reported.

Results: Of the 1671 patients assessed, 858 (mean age, 40.7 years; 718 women [83.7%]) met study entry criteria and received at least 1 dose of investigational product. The primary objective was met for both galcanezumab doses; treatment with galcanezumab significantly reduced monthly migraine headache days (both P < .001) by 4.7 days (120 mg) and 4.6 days (240 mg) compared with placebo (2.8 days). All key secondary objectives were also significant after multiplicity adjustment. There were no meaningful differences between 120-mg and 240-mg doses of galcanezumab on measures of efficacy. Completion rate during treatment was high (81.9%; n = 718), and the incidence of discontinuation owing to adverse events was less than 5% across all treatment groups.

Conclusions and Relevance: Galcanezumab 120-mg and 240-mg monthly injections provided clinical benefits and improved functioning. The incidence rate of adverse events was low, demonstrating the favorable tolerability profile of galcanezumab.

Trial Registration: ClinicalTrials.gov Identifier: NCT02614183.

HEADACHE and MIGRAINE (Continued)

Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial.

Skljarevski V[1], Matharu M[2], Millen BA[1], Ossipov MH[3], Kim BK[4], Yang JY[1].

Cephalalgia. **2018 Jan 1**:333102418779543. doi: 10.1177/0333102418779543. PMID: 29848108. [Epub ahead of print]

Introduction: Galcanezumab is a humanized monoclonal antibody binding calcitonin gene-related peptide, used for migraine prevention.

Methods: A global, double-blind, 6-month study of patients with episodic migraine was undertaken with 915 intent-to-treat patients randomized to monthly galcanezumab 120 mg (n = 231) or 240 mg (n = 223) or placebo (n = 461) subcutaneous injections. Primary endpoint was overall mean change from baseline in monthly migraine headache days. Key secondary endpoints were ≥50%, ≥ 75%, and 100% response rates; monthly migraine headache days with acute migraine medication use; Patient Global Impression of Severity rating; the Role Function-Restrictive score of the Migraine-Specific Quality of Life Questionnaire.

Results: Mean monthly migraine headache days were reduced by 4.3 and 4.2 days by galcanezumab 120 and 240 mg, respectively, and 2.3 days by placebo. The group differences (95% CIs) versus placebo were 2.0 (-2.6, -1.5) and 1.9 (-2.4, -1.4), respectively. Both doses were superior to placebo for all key secondary endpoints. Injection site pain was the most common treatment-emergent adverse event, reported at similar rates in all treatment groups. Both galcanezumab doses had significantly more injection site reactions and injection site pruritus, and the 240 mg group had significantly more injection site erythema versus placebo.

Conclusions: Galcanezumab 120 or 240 mg given once monthly was efficacious, safe, and well tolerated. Study identification EVOLVE-2; Trial Registration NCT02614196.

Sphenopalatine Ganglion Block for the Treatment of Acute Migraine Headache.

Binfalah M[1], Alghawi E[2], Shosha E[3], Alhilly A[4], Bakhiet M[5].

Pain Res Treat. **2018 May 7**;2018:2516953. doi: 10.1155/2018/2516953. PMCID: PMC5971252. PMID: 29862074. eCollection 2018.

Transnasal sphenopalatine ganglion block is emerging as is an attractive and effective treatment modality for acute migraine headaches, cluster headache, trigeminal neuralgia, and several other conditions. We assessed the efficacy and safety of this treatment using the Sphenocath® device. 55 patients with acute migraine headaches underwent this procedure, receiving 2 ml of 2% lidocaine in each nostril. Pain numeric rating scale (baseline, 15 minutes, 2 hours, and 24 hours) and patient global impression of change (2 hours and 24 hours after treatment) were recorded. The majority of patients became headache-free at 15 minutes, 2 hours, and 24 hours after procedure (70.9%, 78.2%, and 70.4%, resp.). The rate of headache relief (50% or more reduction in headache intensity) was 27.3% at 15 minutes, 20% at 2 hours, and 22.2% at 24 hours. The mean pain numeric rating scale decreased significantly at 15 minutes, 2 hours, and 24 hours, respectively. Most patients rated the results as very good or good. The procedure was well-tolerated with few adverse events. This treatment is emerging as an effective and safe option for management of acute migraine attacks.

CHRONIC PAIN

An Interdisciplinary Pain Rehabilitation Program for Veterans with Chronic Pain: Description and Initial Evaluation of Outcomes.

Anamkath NS[1,2], Palyo SA[1,2], Jacobs SC[1,2], Lartigue A[1,2], Schopmeyer K[1], Strigo IA[1,2].

Pain Res Manag. **2018 Apr 17**;2018:3941682. doi: 10.1155/2018/3941682. PMCID: PMC5932417. PMID: 29849842. eCollection 2018.

Objective: Chronic pain conditions are prominent among Veterans. To leverage the biopsychosocial model of pain and comprehensively serve Veterans with chronic pain, the San Francisco Veterans Affairs Healthcare System has implemented the interdisciplinary pain rehabilitation program (IPRP). This study aims to (1) understand initial changes in treatment outcomes following IPRP, (2) investigate relationships between psychological factors and pain outcomes, and (3) explore whether changes in psychological factors predict changes in pain outcomes.

Methods: A retrospective study evaluated relationships between clinical pain outcomes (pain intensity, pain disability, and opioid use) and psychological factors (depressive symptoms, catastrophizing, and "acceptable" level of pain) and changes in these outcomes following treatment. Multiple regression analysis explored whether changes in psychological variables significantly predicted changes in pain disability.

Results: Catastrophizing and depressive symptoms were positively related to pain disability, while "acceptable" level of pain was idiosyncratically related to pain intensity. Pain disability and psychological variables showed significant changes in their expected directions. Regression analysis indicated that only changes in depressive symptoms significantly predicted changes in pain disability.

Conclusion: Our results are consistent with evidence-based clinical practice guidelines for the management of chronic pain in Veterans. Further investigation of interdisciplinary treatment programs in Veterans is warranted.

CHRONIC PAIN (Continued)

Insomnia Symptoms Among Female Veterans: Prevalence, Risk Factors, and the Impact on Psychosocial Functioning and Health Care Utilization.

Babson KA, Wong AC, Morabito D, Kimerling R.

J Clin Sleep Med. **2018 May 29**. pii: jc-17-00399. PMID: 29852900. [Epub ahead of print]

STUDY OBJECTIVES: To examine the prevalence of self-reported insomnia symptoms, identify subgroups of female veterans with clinically significant insomnia symptoms, and examine the effect on psychosocial functioning and health care utilization.

METHODS: Cross-sectional analysis of insomnia symptoms and associated characteristics among a stratified random sample of female veterans using Department of Veterans Affairs primary care facilities between October 1, 2010 and September 30, 2011 (n = 6,261) throughout the United States. The primary outcome was reported presence of insomnia symptoms. Other variables included psychological disorders, chronic conditions, chronic pain, and demographic variables.

RESULTS: Overall, 47.39% of female veterans screened positively for insomnia symptoms. They differed demographically from those without insomnia symptoms and reported more substance use, chronic physical conditions, and psychological conditions. Receiver operating characteristic analysis indicated the primary factor that differentiated those with versus those without insomnia symptoms was depression. Individuals were further differentiated based on presence of pain and posttraumatic stress disorder. Results yielded eight homogenous subgroups of women at low and high risk of experiencing insomnia symptoms.

CONCLUSIONS: Sleep problems are common among female veterans (47.39%) despite limited diagnosis of sleep disorders (0.90%). Eight unique subgroups of female veterans with both low and high insomnia symptoms were observed. These subgroups differed in terms of psychosocial functioning and health care utilization, with those with depression, posttraumatic stress disorder, and pain having the poorest outcomes. These results shed light on the prevalence of insomnia symptoms experienced among female veterans and the effect on psychosocial functioning and health care utilization. Results can inform targeted detection and customized treatment among female veterans.

A randomized controlled trial on the long-term effects of proprioceptive neuromuscular facilitation training, on pain-related outcomes and back muscle activity, in patients with chronic low back pain.

Areeudomwong P[1,2], Wongrat W[1], Neammesri N[1], Thongsakul T[1].

Musculoskeletal Care. **2017 Sep**;15(3):218-229. doi: 10.1002/msc.1165. Epub 2016 Oct 28. PMID: 27791345.

BACKGROUND: The role of exercise therapy in improving pain-related clinical outcomes and trunk muscle activity in patients with chronic low back pain (CLBP) has been widely reported. There is little information on the effect of proprioceptive neuromuscular facilitation (PNF) training in patients with CLBP. The purpose of the present study was therefore to investigate the persistence of the effects of PNF training on pain intensity, functional disability, patient satisfaction, health-related quality of life (HRQOL) and lower back muscle activity in patients with CLBP.

METHODS: Forty-two participants with CLBP were randomly assigned either to 4-week PNF training or to a control group receiving a Low back pain educational booklet. Pain-related outcomes, including pain intensity, functional disability, patient satisfaction, HRQOL and lumbar erector spinae (LES) muscle activity, were measured before and after the intervention, and at a follow-up session 12 weeks after the last intervention session.

RESULTS: Compared with the control group, after undergoing a 4-week PNF training intervention, participants showed a significant reduction in pain intensity and functional disability, and improved patient satisfaction and HRQOL ($p < 0.01$). These effects were still significant at the 12-week follow-up assessment ($p < 0.01$). LES muscle activity in the PNF training group was significantly increased throughout the measurement periods compared with controls ($p < 0.01$).

CONCLUSIONS: The study found that 4-week PNF training has positive long-term effects on pain-related outcomes, and increases lower back muscle activity in patients with CLBP.

OTHER RESEARCH OF INTEREST

Gut microbiota regulates maturation of the adult enteric nervous system via enteric serotonin networks.

De Vadder F[1], Grasset E[1], Mannerås Holm L[1], Karsenty G[2], Macpherson AJ[3], Olofsson LE[1], Bäckhed F[4,5].

Proc Natl Acad Sci U S A. **2018 Jun 4**. pii: 201720017. doi: 10.1073/pnas.1720017115. PMID: 29866843. [Epub ahead of print]

The enteric nervous system (ENS) is crucial for essential gastrointestinal physiologic functions such as motility, fluid secretion, and blood flow. The gut is colonized by trillions of bacteria that regulate host production of several signaling molecules including serotonin (5-HT) and other hormones and neurotransmitters. Approximately 90% of 5-HT originates from the intestine, and activation of the 5-HT_4 receptor in the ENS has been linked to adult neurogenesis and neuroprotection. Here, we tested the hypothesis that the gut microbiota could induce maturation of the adult ENS through release of 5-HT and activation of 5-HT_4 receptors. Colonization of germ-free mice with a microbiota from conventionally raised mice modified the neuroanatomy of the ENS and increased intestinal transit rates, which was associated with neuronal and mucosal 5-HT production and the proliferation of enteric neuronal progenitors in the adult intestine. Pharmacological modulation of the 5-HT_4 receptor, as well as depletion of endogenous 5-HT, identified a mechanistic link between the gut microbiota and maturation of the adult ENS through the release of 5-HT and activation of the 5-HT_4 receptor. Taken together, these findings show that the microbiota modulates the anatomy of the adult ENS in a 5-HT-dependent fashion with concomitant changes in intestinal transit.

Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells.

Ma C[1], Han M[1], Heinrich B[1], Fu Q[1], Zhang Q[1], Sandhu M[1], Agdashian D[1], Terabe M[2], Berzofsky JA[2], Fako V[3], Ritz T[4], Longerich T[4,5], Theriot CM[6], McCulloch JA[7], Roy S[7], Yuan W[7,8], Thovarai V[7,8], Sen SK[7,8], Ruchirawat M[9], Korangy F[1], Wang XW[3,10], Trinchieri G[7], Greten TF[11,10].

Science. **2018 May 25**;360(6391). pii: eaan5931. doi: 10.1126/science.aan5931. PMID: 29798856.

Comment in **Cancer immunity thwarted by the microbiome.** [Science. 2018]

Primary liver tumors and liver metastasis currently represent the leading cause of cancer-related death. Commensal bacteria are important regulators of antitumor immunity, and although the liver is exposed to gut bacteria, their role in antitumor surveillance of liver tumors is poorly understood. We found that altering commensal gut bacteria in mice induced a liver-selective antitumor effect, with an increase of hepatic $CXCR6^+$ natural killer T (NKT) cells and heightened interferon-γ production upon antigen stimulation. In vivo functional studies showed that NKT cells mediated liver-selective tumor inhibition. NKT cell accumulation was regulated by CXCL16 expression of liver sinusoidal endothelial cells, which was controlled by gut microbiome-mediated primary-to-secondary bile acid conversion. Our study suggests a link between gut bacteria-controlled bile acid metabolism and liver antitumor immunosurveillance.

OTHER RESEARCH OF INTEREST (Continued)

Systematic review: probiotics in the management of lower gastrointestinal symptoms - an updated evidence-based international consensus.

Hungin APS[1], Mitchell CR[2], Whorwell P[3], Mulligan C[4], Cole O[2], Agréus L[5], Fracasso P[6], Lionis C[7], Mendive J[8], Philippart de Foy JM[9], Seifert B[10], Wensaas KA[11], Winchester C[2], de Wit N[12]; European Society for Primary Care Gastroenterology.

Aliment Pharmacol Ther. **2018 Apr**;47(8):1054-1070. doi: 10.1111/apt.14539. PMCID: PMC5900870. PMID: 29460487. Epub 2018 Feb 20.

BACKGROUND: In 2013, a systematic review and Delphi consensus reported that specific probiotics can benefit adult patients with irritable bowel syndrome (IBS) and other gastrointestinal (GI) problems.

AIM: To update the consensus with new evidence.

METHODS: A systematic review identified randomised, placebo-controlled trials published between January 2012 and June 2017. Evidence was graded, previously developed statements were reassessed by an 8-expert panel, and agreement was reached via Delphi consensus.

RESULTS: A total of 70 studies were included (IBS, 34; diarrhoea associated with antibiotics, 13; diarrhoea associated with Helicobacter pylori eradication therapy, 7; other conditions, 16). Of 15 studies that examined global IBS symptoms as a primary endpoint, 8 reported significant benefits of probiotics vs placebo. Consensus statements with 100% agreement and "high" evidence level indicated that specific probiotics help reduce overall symptom burden and abdominal pain in some patients with IBS and duration/intensity of diarrhoea in patients prescribed antibiotics or H. pylori eradication therapy, and have favourable safety. Statements with 70%-100% agreement and "moderate" evidence indicated that, in some patients with IBS, specific probiotics help reduce bloating/distension and improve bowel movement frequency/consistency.

CONCLUSIONS: This updated review indicates that specific probiotics are beneficial in certain lower GI problems, although many of the new publications did not report benefits of probiotics, possibly due to inclusion of new, less efficacious preparations. Specific probiotics can relieve lower GI symptoms in IBS, prevent diarrhoea associated with antibiotics and H. pylori eradication therapy, and show favourable safety. This study will help clinicians recommend/prescribe probiotics for specific symptoms.

Posttraumatic stress disorder, depression, and suicidal ideation in veterans: Results from the mind your heart study.

Arenson MB[1], Whooley MA[2], Neylan TC[2], Maguen S[2], Metzler TJ[2], Cohen BE[3].

Psychiatry Res. **2018 Jul**;265:224-230. doi: 10.1016/j.psychres.2018.04.046. PMID: 29753254. Epub 2018 Apr 22.

Veterans with PTSD or depression are at increased risk for suicidal ideation. However, few studies have examined that risk in those with comorbid PTSD and depression, instead focusing on these disorders individually. This study investigates the association of suicidal ideation with comorbid PTSD and depression and examines the role of military and psychosocial covariates. We evaluated 746 veterans using the CAPS to assess PTSD and the PHQ-9 to measure depression and suicidal ideation. Covariates were assessed via validated self-report measures. 49% of veterans with comorbid PTSD and depression endorsed suicidal ideation, making them more likely to do so than those with depression alone (34%), PTSD alone (11%), or neither (2%). In multivariate logistic regression models, this association remained significant after controlling for demographics and symptom severity. Anger, hostility, anxiety, alcohol use, optimism and social support did not explain the elevated risk of suicidal ideation in the comorbid group in fully adjusted models. As suicidal ideation is a known risk factor for suicide attempts and completions, veterans with comorbid PTSD and depression represent a vulnerable group who may need more intensive monitoring and treatment to reduce risk of suicide.

OTHER RESEARCH OF INTEREST (Continued)

A 12-Year Analysis of Nonbattle Injury Among US Service Members Deployed to Iraq and Afghanistan.

Le TD[1], Gurney JM[1,2,3], Nnamani NS[1], Gross KR[3,4], Chung KK[3,5], Stockinger ZT[2,3], Nessen SC[1], Pusateri AE[1], Akers KS[1,3].

JAMA Surg. **2018 May 30**. doi: 10.1001/jamasurg.2018.1166. PMID: 29847675. [Epub ahead of print]

Importance: Nonbattle injury (NBI) among deployed US service members increases the burden on medical systems and results in high rates of attrition, affecting the available force. The possible causes and trends of NBI in the Iraq and Afghanistan wars have, to date, not been comprehensively described.

Objectives: To describe NBI among service members deployed to Iraq and Afghanistan, quantify absolute numbers of NBIs and proportion of NBIs within the Department of Defense Trauma Registry, and document the characteristics of this injury category.

Design, Setting, and Participants: In this retrospective cohort study, data from the Department of Defense Trauma Registry on 29 958 service members injured in Iraq and Afghanistan from January 1, 2003, through December 31, 2014, were obtained. Injury incidence, patterns, and severity were characterized by battle injury and NBI. Trends in NBI were modeled using time series analysis with autoregressive integrated moving average and the weighted moving average method. Statistical analysis was performed from January 1, 2003, to December 31, 2014.

Main Outcomes and Measures: Primary outcomes were proportion of NBIs and the changes in NBI over time.

Results: Among 29 958 casualties (battle injury and NBI) analyzed, 29 003 were in men and 955 were in women; the median age at injury was 24 years (interquartile range, 21-29 years). Nonbattle injury caused 34.1% of total casualties (n = 10 203) and 11.5% of all deaths (206 of 1788). Rates of NBI were higher among women than among men (63.2% [604 of 955] vs 33.1% [9599 of 29 003]; P < .001) and in Operation New Dawn (71.0% [298 of 420]) and Operation Iraqi Freedom (36.3% [6655 of 18 334]) compared with Operation Enduring Freedom (29.0% [3250 of 11 204]) (P < .001). A higher proportion of NBIs occurred in members of the Air Force (66.3% [539 of 810]) and Navy (48.3% [394 of 815]) than in members of the Army (34.7% [7680 of 22 154]) and Marine Corps (25.7% [1584 of 6169]) (P < .001). Leading mechanisms of NBI included falls (2178 [21.3%]), motor vehicle crashes (1921 [18.8%]), machinery or equipment accidents (1283 [12.6%]), blunt objects (1107 [10.8%]), gunshot wounds (728 [7.1%]), and sports (697 [6.8%]), causing predominantly blunt trauma (7080 [69.4%]). The trend in proportion of NBIs did not decrease over time, remaining at approximately 35% (by weighted moving average) after 2006 and approximately 39% by autoregressive integrated moving average. Assuming stable battlefield conditions, the autoregressive integrated moving average model estimated that the proportion of NBIs from 2015 to 2022 would be approximately 41.0% (95% CI, 37.8%-44.3%).

Conclusions and Relevance: In this study, approximately one-third of injuries during the Iraq and Afghanistan wars resulted from NBI, and the proportion of NBIs was steady for 12 years. Understanding the possible causes of NBI during military operations may be useful to target protective measures and safety interventions, thereby conserving fighting strength on the battlefield.

Adaptive deep brain stimulation for Parkinson's disease using motor cortex sensing.

Swann NC[1], de Hemptinne C, Thompson MC, Miocinovic S, Miller AM, Gilron R, Ostrem JL, Chizeck HJ, Starr PA.

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OBJECTIVE: Contemporary deep brain stimulation (DBS) for Parkinson's disease is delivered continuously, and adjustments based on patient's changing symptoms must be made manually by a trained clinician. Patients may be subjected to energy intensive settings at times when they are not needed, possibly resulting in stimulation-induced adverse effects, such as dyskinesia. One solution is 'adaptive' DBS, in which stimulation is modified in real time based on neural signals that co-vary with the severity of motor signs or of stimulation-induced adverse effects. Here we show the feasibility of adaptive DBS using a fully implanted neural prosthesis.

APPROACH: We demonstrate adaptive deep brain stimulation in two patients with Parkinson's disease using a fully implanted neural prosthesis that is enabled to utilize brain sensing to control stimulation amplitude (Activa PC + S). We used a cortical narrowband gamma (60-90 Hz) oscillation related to dyskinesia to decrease stimulation voltage when gamma oscillatory activity is high (indicating dyskinesia) and increase stimulation voltage when it is low.

MAIN RESULTS: We demonstrate the feasibility of 'adaptive deep brain stimulation' in two patients with Parkinson's disease. In short term in-clinic testing, energy savings were substantial (38%-45%), and therapeutic efficacy was maintained.

SIGNIFICANCE: This is the first demonstration of adaptive DBS in Parkinson's disease using a fully implanted device and neural sensing. Our approach is distinct from other strategies utilizing basal ganglia signals for feedback control.

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