GULF WAR ILLNESS

Protective Effect of Human Leukocyte Antigen (HLA) Allele DRB1*13:02 on Age-Related Brain Gray Matter Volume Reduction in Healthy Women.

James LM[1], Christova P[2], Lewis SM[3], Engdahl BE[4], Georgopoulos A[5], Georgopoulos AP[6].

EBioMedicine. **2018 Feb 8**. pii: S2352-3964(18)30054-9. doi: 10.1016/j.ebiom.2018.02.005. PMID: 29452862. [Epub ahead of print].

BACKGROUND: Reduction of brain volume (brain atrophy) during healthy brain aging is well documented and dependent on genetic, lifestyle and environmental factors. Here we investigated the possible dependence of brain gray matter volume reduction in the absence of the Human Leukocyte Antigen (HLA) allele DRB1*13:02 which prevents brain atrophy in Gulf War Illness (James et al., 2017).

METHODS: Seventy-one cognitively healthy women (32-69years old) underwent a structural Magnetic Resonance Imaging (sMRI) scan to measure the volumes of total gray matter, cerebrocortical gray matter, and subcortical gray matter. Participants were assigned to two groups, depending on whether they lacked the DRB1*13:02 allele (No DRB1*13:02 group, N=60) or carried the DRB1*13:02 allele (N=11). We assessed the change of brain gray matter volume with age in each group by performing a linear regression where the brain volume (adjusted for total intracranial volume) was the dependent variable and age was the independent variable.

FINDINGS: In the No DRB1*13:02 group, the volumes of total gray matter, cerebrocortical gray matter, and subcortical gray matter were reduced highly significantly. In contrast, none of these volumes showed a statistically significant reduction with age in the DRB1*13:02 group.

INTERPRETATION: These findings document the protective effect of DRB1*13:02 on age-dependent reduction of brain gray matter in healthy individuals. Since the role of this allele is to connect to matching epitopes of external antigens for the subsequent production of antibodies and elimination of the offending antigen, we hypothesize that its protective effect may be due to the successful elimination of such antigens to which we are exposed during the lifespan, antigens that otherwise would persist causing gradual brain atrophy. In addition, we consider a possible beneficial role of DRB1*13:02 attributed to its binding to cathepsin S, a known harmful substance in brain aging (Wendt et al., 2008). Of course, other factors covarying with the presence of DRB1*13:02 could be involved.

CHRONIC FATIGUE SYNDROME

Value of Circulating Cytokine Profiling During Submaximal Exercise Testing in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.

Moneghetti KJ[1,2,3], Skhiri M[4], Contrepois K[5], Kobayashi Y[5,6], Maecker H[7], Davis M[7], Snyder M[5], Haddad F[5,6], Montoya JG[8,9].

Sci Rep. **2018 Feb 9**;8(1):2779. doi: 10.1038/s41598-018-20941-w. PMID: 29426834.

Myalgic Encephalomyelitis or Chronic Fatigue Syndrome (ME/CFS) is a heterogeneous syndrome in which patients often experience severe fatigue and malaise following exertion. Immune and cardiovascular dysfunction have been postulated to play a role in the pathophysiology. We therefore, examined whether cytokine profiling or cardiovascular testing following exercise would differentiate patients with ME/CFS. Twenty-four ME/CFS patients were matched to 24 sedentary controls and underwent cardiovascular and circulating immune profiling. Cardiovascular analysis included echocardiography, cardiopulmonary exercise and endothelial function testing. Cytokine and growth factor profiles were analyzed using a 51-plex Luminex bead kit at baseline and 18 hours following exercise. Cardiac structure and exercise capacity were similar between groups. Sparse partial least square discriminant analyses of cytokine profiles 18 hours post exercise offered the most reliable discrimination between ME/CFS and controls (κ = 0.62(0.34,0.84)). The most discriminatory cytokines post exercise were CD40L, platelet activator inhibitor, interleukin 1-β, interferon-α and CXCL1. In conclusion, cytokine profiling following exercise may help differentiate patients with ME/CFS from sedentary controls.

CHRONIC FATIGUE SYNDROME (Continued)

Open-label pilot for treatment targeting gut dysbiosis in myalgic encephalomyelitis/chronic fatigue syndrome: neuropsychological symptoms and sex comparisons.

Wallis A[1], Ball M[2], Butt H[3], Lewis DP[4], McKechnie S[5], Paull P[3], Jaa-Kwee A[5], Bruck D[2].

J Transl Med. **2018 Feb 6**;16(1):24. doi: 10.1186/s12967-018-1392-z. PMID: 29409505.

BACKGROUND: Preliminary evidence suggests that the enteric microbiota may play a role in the expression of neurological symptoms in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Overlapping symptoms with the acute presentation of D-lactic acidosis has prompted the use of antibiotic treatment to target the overgrowth of species within the Streptococcus genus found in commensal enteric microbiota as a possible treatment for neurological symptoms in ME/CFS.

METHODS: An open-label, repeated measures design was used to examine treatment efficacy and enable sex comparisons. Participants included 44 adult ME/CFS patients (27 females) from one specialist medical clinic with Streptococcus viable counts above 3.00×10^5 cfu/g (wet weight of faeces) and with a count greater than 5% of the total count of aerobic microorganisms. The 4-week treatment protocol included alternate weeks of Erythromycin (400 mg of erythromycin as ethyl succinate salt) twice daily and probiotic (D-lactate free multistrain probiotic, 5×10^{10} cfu twice daily). 2 × 2 repeated measures ANOVAs were used to assess sex-time interactions and effects across pre- and post-intervention for microbial, lactate and clinical outcomes. Ancillary non-parametric correlations were conducted to examine interactions between change in microbiota and clinical outcomes.

RESULTS: Large treatment effects were observed for the intention-to-treat sample with a reduction in Streptococcus viable count and improvement on several clinical outcomes including total symptoms, some sleep (less awakenings, greater efficiency and quality) and cognitive symptoms (attention, processing speed, cognitive flexibility, story memory and verbal fluency). Mood, fatigue and urine D:L lactate ratio remained similar across time. Ancillary results infer that shifts in microbiota were associated with more of the variance in clinical changes for males compared with females.

CONCLUSIONS: Results support the notion that specific microorganisms interact with some ME/CFS symptoms and offer promise for the therapeutic potential of targeting gut dysbiosis in this population. Streptococcus spp. are not the primary or sole producers of D-lactate. Further investigation of lactate concentrations are needed to elucidate any role of D-lactate in this population. Concurrent microbial shifts that may be associated with clinical improvement (i.e., increased Bacteroides and Bifidobacterium or decreased Clostridium in males) invite enquiry into alternative strategies for individualised treatment. Trial Registration Australian and New Zealand Clinical Trial Registry (ACTRN12614001077651) 9th October 2014. https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=366933&isReview=true.

HEADACHE and MIGRAINE

One-Day Behavioral Intervention for Distressed Veterans with Migraine: Results of a Multimethod Pilot Study.

Huddleston C[1], Martin L[2,3], Woods K[3], Dindo L[1,3].

Mil Med. **2018 Feb 6**. doi: 10.1093/milmed/usx090. PMID: 29420786. [Epub ahead of print]

Introduction: Migraine, a chronic neurological disorder characterized by episodic severe headache pain and functional impairment, affects approximately 12% of the general US population. Veterans returning from Iraq or Afghanistan have two to four times the incidence of migraine of the general population. Veterans with migraines are more than twice as likely to have comorbid psychiatric conditions as veterans without migraines, with depression and post-traumatic stress disorder being most prevalent. This psychiatric-migraine comorbidity is of major public health significance, as it leads to decreased quality of life, poorer response to migraine and mental health treatment, and overall worse prognosis. Unfortunately, acceptable and effective treatments for these comorbid problems have rarely been investigated. The aims of this study are to examine the acceptability, feasibility, and preliminary efficacy of a 1-d acceptance and commitment therapy (ACT) plus Migraine Education workshop.

Method: Twenty-five veterans with migraines and co-occurring depression and/or anxiety completed the 1-d ACT plus Migraine Education workshop. Veterans completed assessments of depressive and anxiety symptoms, general functioning, headache-related disability, and ACT-specific skills at baseline and 3 mo after the workshop. Changes from baseline to 3-mo follow-up on the self-report and clinician-rated measures were assessed using the paired t-test and Wilcoxon signed-rank test. Veterans also completed semistructured qualitative interviews documenting their experiences with the workshop 2 wk and 3 mo following the intervention. Qualitative data were analyzed via directed content analysis. Individual codes were aggregated into larger themes agreed upon by consensus.

Results: At 3-mo follow-up, veterans significantly improved in depressive and anxiety symptoms, general functioning, and headache-related disability compared with baseline. Additionally, veterans significantly improved in pain acceptance and engagement in valued life areas. In interviews, veterans indicated that the migraine education helped them feel more knowledgeable about their condition, and this empowered them to better manage their headaches, including talking to their physician about medication adjustments. The ACT component led to greater awareness of the role stress plays in exacerbating pain and ways to manage this stress, including greater acceptance and greater engagement in valued life activities. For some, however, the role of stress in exacerbating migraines needed to be highlighted more. Veterans appreciated being in a group with other veterans with similar health difficulties and wanted this to be incorporated into ongoing care at the Veterans Affairs medical center. The patient education manuals were useful to the veterans, with some referring to them during the months following the workshop.

Conclusion: Findings of this small trial have important implications pending replication in a more rigorously designed large-scale study. A 1-d ACT plus Migraine Education workshop is an acceptable and feasible treatment approach for veterans with migraines and significant distress. Significantly reduced distress and disability, as well as improved coping skills, suggest that veterans were activated to engage more fully in their lives and clinical care. The availability of an effective transdiagnostic intervention that can be completed in 1 d is particularly valuable for veterans who have multiple comorbid conditions and who encounter practical barriers to engaging in the usual prescribed weekly therapy treatments.

HEADACHE and MIGRAINE (Continued)

Increased risk of Parkinson's disease following tension-type headache: a nationwide population-based cohort study.

Yang FC[1], Chen HJ[2], Lee JT[1], Chen SJ[3,4], Sung YF[1], Kao CH[5,6,7], Yang TY[8,9,10].

Oncotarget. **2017 Dec 14**;9(2):2148-2157. doi: 10.18632/oncotarget.23298. PMCID: PMC5788629. PMID: 29416761. eCollection 2018 Jan 5.

Purpose: Previous studies have suggested associations between primary headache and neurodegenerative diseases; however, the relationship between tension-type headache (TTH), which is the most common type of primary headache, and Parkinson's disease (PD) remains controversial. Hence, in this nationwide, population-based, retrospective cohort study, we explored the temporal association between TTH and PD.

Methods: Using claims data in the National Health Insurance Research Database of Taiwan, we evaluated 12,309 subjects aged ≥20 years who were newly diagnosed with TTH from 2000 to 2005. The non-TTH group included 49,236 randomly selected sex- and age-matched patients without TTH. Subjects were followed up until the end of 2011, diagnosis of PD, or death. The incidence of PD was compared between the two groups. A Cox multivariable proportional hazards model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) to estimate the risk of PD.

Results: The overall incidence of PD (per 1,000 person-years) in the TTH and non-TTH groups was 3.01 and 1.68, respectively. After adjustment for sex, age, and comorbidities, the association between TTH and PD remained statistically significant (adjusted HR = 1.37, 95% CI = 1.19-1.57). The TTH group had a higher risk of PD than the non-TTH group did, regardless of subjects' sex, age, and comorbidity status.

Conclusions: These findings demonstrate that patients diagnosed with TTH exhibit an increased risk of PD. Additional studies should investigate the potential shared pathophysiological mechanisms of TTH and PD. Clinicians should be aware that TTH is a potential risk factor for PD.

Prospective memory is dysfunctional in migraine without aura.

Santangelo G[1,2], Russo A[3], Tessitore A[3], Garramone F[1], Silvestro M[3], Della Mura MR[1], Marcuccio L[3], Fornaro I[1], Trojano L[1,4], Tedeschi G[2, 3].

Cephalalgia. **2018 Jan 1**:333102418758280. doi: 10.1177/0333102418758280. PMID: 29411639. [Epub ahead of print]

Introduction: Prospective memory is the ability to carry out a delayed intended action, so to maintain and retrieve future plans, goals and activities. Deficits of prospective memory negatively impact on patients and caregivers' everyday living and determine poor adherence to treatment. Since frontal regions are involved in both event- and time-based prospective memory tasks and are impaired in migraine without aura, defects of prospective memory might occur in migraine without aura patients; until now this issue has not been investigated. The aim of the current study was to explore time- versus event-based prospective memory in migraine without aura.

Patients and methods: Ninty-one consecutive migraine without aura patients and 84 healthy subjects were enrolled in the study. They underwent a standardized measure of prospective memory evaluating both time-based and event-based prospective memory, and the Montreal Cognitive Assessment assessing global cognitive status. Moreover, all participants completed the Beck Depression Inventory-II and a self-administered version of the Apathy Evaluation Scale, to assess severity of depressive symptoms and apathy, respectively.

Results: Migraine without aura and healthy subjects did not differ on demographic aspects (i.e. age, education and gender). However, individuals with migraine without aura demonstrated impaired prospective memory performance compared to healthy subjects, with a greater impairment demonstrated for the time-based tasks. Within the migraine without aura group, no significant association was found between prospective memory performance and clinical scores, apathy, and depression.

Conclusions: Individuals with migraine without aura experience particular difficulty executing a future intention; therefore, migraine without aura is associated with dysfunction of prospective memory.

HEADACHE and MIGRAINE (Continued)

Long-term study of the efficacy and safety of OnabotulinumtoxinA for the prevention of chronic migraine: COMPEL study.

Blumenfeld AM[1], Stark RJ[2], Freeman MC[3], Orejudos A[4], Manack Adams A[4].

J Headache Pain. **2018 Feb 5**;19(1):13. doi: 10.1186/s10194-018-0840-8. PMID: 29404713.

BACKGROUND: OnabotulinumtoxinA is approved for the prevention of headache in those with chronic migraine (CM); however, more clinical data on the risk-benefit profile for treatment beyond one year is desirable.

METHODS: The Chronic Migraine OnabotulinuMtoxinA Prolonged Efficacy open Label (COMPEL) Study (ClinicalTrials.gov , NCT01516892) is an international, multicenter, open-label long-term prospective study. Adults with CM received 155 U of onabotulinumtoxinA (31 sites in a fixed-site, fixed-dose paradigm across 7 head/neck muscles) every 12 weeks (±7 days) for 9 treatment cycles (108 weeks). The primary outcome was headache day reductions at 108 weeks; secondary outcomes were headache day reductions at 60 weeks and change in the 6-item Headache Impact Test (HIT-6) score. Safety and tolerability were assessed by reviewing the frequency and nature of adverse events (AEs). AEs were determined at each visit through patient self-report, general non-directed and, for specific AEs, directed questioning, and physical examination. Subgroup analyses for safety and efficacy included, but were not limited to, patients with/without concomitant oral preventive treatment and acute medication overuse at baseline.

RESULTS: Enrolled patients (N = 716) were 18-73 years old and most were female (n = 607, 84.8%). At baseline, patients reported an average 22.0 (SD = 4.8) headache days per month. 52.1% of patients (n = 373) completed the study. By 60 and 108 weeks, a significant reduction in headache days (- 9.2 days and - 10.7 days, respectively, P < 0.0001) was observed. Significant improvements (P < 0.0001) in HIT-6 scores (- 7.1 point change at week 108) were also demonstrated. 131 patients (18.3%) reported ≥1 treatment-emergent adverse events; most frequently reported was neck pain (n = 29, 4.1%). One patient reported a serious treatment-related adverse event (rash). No deaths were reported.

CONCLUSIONS: The COMPEL Study provides additional clinical evidence for the consistency of the efficacy and for the long-term safety and tolerability of onabotulinumtoxinA for the prevention of headache in those with CM who have been treated with onabotulinumtoxinA every 12 weeks over 2 years (9 treatments) with the fixed-site, fixed-dose injection paradigm.

TRIAL REGISTRATION: Trial registration number: NCT01516892 . Name of registry: clinicaltrials.gov . Date of registration: January 20 2012. Date of enrollment of first patient: December 2011.

CHRONIC PAIN

Fibromyalgia and Risk of Dementia-A Nationwide, Population-Based, Cohort Study.

Tzeng NS[1], Chung CH[2], Liu FC[3], Chiu YH[3], Chang HA[1], Yeh CB[4], Huang SY[4], Lu RB[5], Yeh HW[6], Kao YC[7], Chiang WS[8], Tsao CH[9], Wu YF[10], Chou YC[11], Lin FH[11], Chien WC[12].

Am J Med Sci. **2018 Feb**;355(2):153-161. doi: 10.1016/j.amjms.2017.09.002. PMID: 29406043. Epub 2017 Sep 15.

BACKGROUND: Fibromyalgia is a syndrome of chronic pain and other symptoms and is associated with patient discomfort and other diseases. This nationwide matched-cohort population-based study aimed to investigate the association between fibromyalgia and the risk of developing dementia, and to clarify the association between fibromyalgia and dementia.

MATERIALS AND METHODS: A total of 41,612 patients of age ≥50 years with newly diagnosed fibromyalgia between January 1, and December 31, 2000 were selected from the National Health Insurance Research Database of Taiwan, along with 124,836 controls matched for sex and age. After adjusting for any confounding factors, Fine and Gray competing risk analysis was used to compare the risk of developing dementia during the 10 years of follow-up.

RESULTS: Of the study subjects, 1,704 from 41,612 fibromyalgia patients (21.23 per 1,000 person-years) developed dementia when compared to 4,419 from 124,836 controls (18.94 per 1,000 person-years). Fine and Gray competing risk analysis revealed that the study subjects were more likely to develop dementia (hazard ratio: 2.29, 95% CI: 2.16-2.42; P < 0.001). After adjusting for sex, age, monthly income, urbanization level, geographic region of residence and comorbidities the hazard ratio was 2.77 (95% CI: 2.61-2.95, P < 0.001). Fibromyalgia was associated with increased risk of all types of dementia in this study.

CONCLUSIONS: The study subjects with fibromyalgia had a 2.77-fold risk of dementia in comparison to the control group. Therefore, further studies are needed to elucidate the underlying mechanisms of the association between fibromyalgia and the risk of dementia.

CHRONIC PAIN (Continued)

Chronic pain patients can be classified into four groups: Clustering-based discriminant analysis of psychometric data from 4665 patients referred to a multidisciplinary pain centre (a SQRP study).

Bäckryd E[1], Persson EB[2,3], Larsson AI[4], Fischer MR[2,3], Gerdle B[1].

PLoS One. **2018 Feb 8**;13(2):e0192623. doi: 10.1371/journal.pone.0192623. PMID: 29420607. eCollection 2018.

OBJECTIVE: To subgroup chronic pain patients using psychometric data and regress the variables most responsible for subgroup discrimination.

DESIGN: Cross-sectional, registry-based study.

SETTING AND SUBJECTS: Chronic pain patients assessed at a multidisciplinary pain centre between 2008 and 2015.

METHODS: Data from the Swedish quality registry for pain rehabilitation (SQRP) were retrieved and analysed by principal component analysis, hierarchical clustering analysis, and partial least squares-discriminant analysis.

RESULTS: Four subgroups were identified. Group 1 was characterized by low "psychological strain", the best relative situation concerning pain characteristics (intensity and spreading), the lowest frequency of fibromyalgia, as well as by a slightly older age. Group 2 was characterized by high "psychological strain" and by the most negative situation with respect to pain characteristics (intensity and spreading). Group 3 was characterized by high "social distress", the longest pain durations, and a statistically higher frequency of females. The frequency of three neuropathic pain conditions was generally lower in this group. Group 4 was characterized by high psychological strain, low "social distress", and high pain intensity.

CONCLUSIONS: The identification of these four clusters of chronic pain patients could be useful for the development of personalized rehabilitation programs. For example, the identification of a subgroup characterized mainly by high perceived "social distress" raises the question of how to best design interventions for such patients. Differentiating between clinically important subgroups and comparing how these subgroups respond to interventions is arguably an important area for further research.

Comparative Efficacy of Multiple Variables of Mesenchymal Stem Cell Transplantation for the Treatment of Neuropathic Pain in Rats.

Liu L[1], Hua Z[1], Shen J[1], Yin Y[1], Yang J[1], Cheng K[1], Liu A[1], Wang L[1], Cheng J[1].

Mil Med. **2017 Mar**;182(S1):175-184. doi: 10.7205/MILMED-D-16-00096. PMID: 28291470.

OBJECTIVES: The current treatment options for neuropathic pain due to nerve injuries are limited and largely unsatisfactory. Mesenchymal stem cell transplantation (MSC) has shown promise as an emerging therapy for neuropathic pain. However, a number of critical parameters, including the sources of cells, the number of cells, and routes of transplantation, need to be elucidated before it can be tested clinically.

METHODS: MSCs were isolated from rat bone marrow (rBM-MSCs) and adipose tissue (rAD-MSCs) and characterized by flow cytometry and functional differentiation. Rats with chronic constriction injury of the sciatic nerve were transplanted either intravenously or intrathecally with rBM-MSCs or rAD-MSCs in two different doses. The effects were evaluated by using paw withdrawal thresholds in response to noxious stimulation. The MSCs labeled with Dil dye were traced. A total of 75 Sprague-Dawley rats were used for these experiments.

RESULTS: Both intravenous and intrathecal transplantation of MSCs significantly attenuated neuropathic pain. Comparable results were achieved by either rBM-MSCs or rAD-MSCs. No differences were noted between the two doses of cell transplantation. MSCs were found on the surface of the spinal cord and dorsal root ganglia. The animals did not show any signs of toxicity throughout the whole course of the experiments.

CONCLUSIONS: Both intravenous and intrathecal MSC transplantations were safe and efficacious and both rBM-MSCs and rAD-MSCs are suitable for transplantation.

OTHER RESEARCH OF INTEREST

Gandal MJ, Haney JR, Parikshak NN, Leppa V, Ramaswami G, Hartl C, Schork AJ, Appadurai V, Buil A, Werge TM, Liu C, White KP; CommonMind Consortium; PsychENCODE Consortium; iPSYCH-BROAD Working Group, Horvath S, Geschwind DH.

Science. **2018 Feb 9**;359(6376):693-697. doi: 10.1126/science.aad6469. PMID: 29439242.

The predisposition to neuropsychiatric disease involves a complex, polygenic, and pleiotropic genetic architecture. However, little is known about how genetic variants impart brain dysfunction or pathology. We used transcriptomic profiling as a quantitative readout of molecular brain-based phenotypes across five major psychiatric disorders-autism, schizophrenia, bipolar disorder, depression, and alcoholism-compared with matched controls. We identified patterns of shared and distinct gene-expression perturbations across these conditions. The degree of sharing of transcriptional dysregulation is related to polygenic (single-nucleotide polymorphism-based) overlap across disorders, suggesting a substantial causal genetic component. This comprehensive systems-level view of the neurobiological architecture of major neuropsychiatric illness demonstrates pathways of molecular convergence and specificity.

Patterns of zolpidem use among Iraq and Afghanistan veterans: A retrospective cohort analysis.

Shayegani R[1], Song K[2,3], Amuan ME[4], Jaramillo CA[2,3], Eapen BC[2,3], Pugh MJ[2,3,5,6].

PLoS One. **2018 Jan 23**;13(1):e0190022. doi: 10.1371/journal.pone.0190022. PMID: 29360821. PMCID: PMC5779650. eCollection 2018.

BACKGROUND: Although concern exists regarding the adverse effects and rate of zolpidem use, especially long-term use, limited information is available concerning patterns of zolpidem use.

OBJECTIVE: To examine the prevalence and correlates of zolpidem exposure in Iraq and Afghanistan Veterans (IAVs).

METHODS: A retrospective cohort study of zolpidem prescriptions was performed with National Veterans Health Administration (VHA) data. We gathered national VA inpatient, outpatient, and pharmacy data files for IAV's who received VA care between fiscal years (FY) 2013 and 2014. The VA pharmacy database was used to identify the prevalence of long term (>30 days), high-dose zolpidem exposure (>10mg immediate-release; >12.5mg extended-release) and other medications received in FY14. Baseline characteristics (demographics, diagnoses) were identified in FY13. Bivariate and multivariable analyses were used to examine the demographic, clinical, and medication correlates of zolpidem use.

RESULTS: Of 493,683 IAVs who received VHA care in FY 2013 and 2014, 7.6% (n = 37,422) were prescribed zolpidem in FY 2014. Women had lower odds of high-dose zolpidem exposure than men. The majority (77.3%) of IAVs who received zolpidem prescriptions had long-term use with an average days' supply of 189.3 days and a minority (0.9%) had high-dose exposure. In multivariable analyses, factors associated with long-term zolpidem exposure included age greater than 29 years old, PTSD, insomnia, Selim Index, physical 2-3 conditions, opioids, antidepressants, benzodiazepines, atypical antipsychotics, and stimulants. High dose exposure was associated with PTSD, depression, substance use disorder, insomnia, benzodiazepines, atypical antipsychotics, and stimulant prescriptions.

CONCLUSION: The current practices of insomnia pharmacotherapy in IAVs fall short of the clinical guidelines and may reflect high-risk zolpidem prescribing practices that put Iraq and Afghanistan Veterans at risk for adverse effects of zolpidem and poor health outcomes.

OTHER RESEARCH OF INTEREST (Continued)

A role for bacterial urease in gut dysbiosis and Crohn's disease.

Ni J[1], Shen TD[1], Chen EZ[2], Bittinger K[3], Bailey A[4], Roggiani M[5], Sirota-Madi A[6], Friedman ES[1], Chau L[1], Lin A[1], Nissim I[7], Scott J[6], Lauder A[4], Hoffmann C[4], Rivas G[8], Albenberg L[9], Baldassano RN[9], Braun J[10], Xavier RJ[6,10,11], Clish CB[6], Yudkoff M[7], Li H[2], Goulian M[5], Bushman FD[4], Lewis JD[1,2], Wu GD[12].

Sci Transl Med. **2017 Nov 15**;9(416). pii: eaah6888. doi: 10.1126/scitranslmed.aah6888. PMID: 29141885. PMCID: PMC5808452.

Gut dysbiosis during inflammatory bowel disease involves alterations in the gut microbiota associated with inflammation of the host gut. We used a combination of shotgun metagenomic sequencing and metabolomics to analyze fecal samples from pediatric patients with Crohn's disease and found an association between disease severity, gut dysbiosis, and bacterial production of free amino acids. Nitrogen flux studies using ^{15}N in mice showed that activity of bacterial urease, an enzyme that releases ammonia by hydrolysis of host urea, led to the transfer of murine host-derived nitrogen to the gut microbiota where it was used for amino acid synthesis. Inoculation of a conventional murine host (pretreated with antibiotics and polyethylene glycol) with commensal *Escherichia coli* engineered to express urease led to dysbiosis of the gut microbiota, resulting in a predominance of Proteobacteria species. This was associated with a worsening of immune-mediated colitis in these animals. A potential role for altered urease expression and nitrogen flux in the development of gut dysbiosis suggests that bacterial urease may be a potential therapeutic target for inflammatory bowel diseases.

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