

GULF WAR ILLNESS

[Gulf War agents pyridostigmine bromide and permethrin cause hypersensitive nociception that is restored after vagus nerve stimulation.](#)

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Neurotoxicology. **2018 Sep 29**;69:93-96. doi: 10.1016/j.neuro.2018.09.007. PMID: 30273628 [Epub ahead of print]

Gulf war illness (GWI) is a chronic multi-symptom disease that afflicts 25-33% of troops that were deployed in the 1990-1991 Gulf War. GWI symptoms include cognitive, behavioral and emotional deficits, as well as migraines and pain. It is possible that exposure to Gulf War agents and prophylactics contributed to the reported symptomatology. Pyridostigmine bromide (PB) and permethrin (PER) were given to protect from nerve gas attacks and insect vector born disease, respectively. Previous studies have demonstrated that 10 days of exposure to these chemicals can cause symptoms analogous to those observed in GWI, including impairment of long-term memory in mice. Other studies using this model have shown chronic neuroinflammation, and chronic neuroinflammation can lead to altered nociceptive sensitivity. At 10-weeks after the 10-day PB and PER exposure paradigm, we observed lowered nociceptive threshold on the Von Frey test that was no longer evident at 28 weeks and 38 weeks post-exposure. We further determined that vagus nerve stimulation, initiated at 38 weeks after exposure, restores the lowered nociceptive sensitivity. Therefore, stimulating the vagus nerve appears to influence nociception. Future studies are need to elucidate possible mechanisms of this effect.

CHRONIC FATIGUE SYNDROME

[Emotional Regulation in Women with Chronic Fatigue Syndrome and Depression: Internal Representations and Adaptive Defenses.](#)

[Bram AD](#), [Gottschalk KA](#), [Leeds WM](#).

J Am Psychoanal Assoc. **2018 Aug**;66(4):701-741. doi: 10.1177/0003065118798043. PMID: 30249136.

Chronic fatigue syndrome (CFS) presents challenges in differential diagnosis and treatment. Complicating diagnosis is that its symptoms overlap with those of depression. This study applies psychoanalytic concepts to understand emotional regulation (ER) in women with CFS and/or depression. One hundred eighty-six women were assigned to four groups and compared: (a) CFS plus high er depression (CFS-HD); (b) CFS plus lower depression (CFS-LD); (c) depressive disorder (DD); and (d) healthy controls (HC). ER was operationalized by measures of capacity to form internal representations and adaptive defenses. The study's premise was that difficulties metabolizing emotions psychologically would be associated with their greater somatic expression. Some support was found for the hypothesis that CFS participants would exhibit more impairment in representing emotions and in adaptive defenses compared to the DD and HC groups, but this held only for the CFS-HD group. Although CFS-LD participants were expected to be more purely somatizing than the CFS-HD group, they instead showed more sophisticated capacities for ER than that group and recalled less distressing early relationships, revealing more resilience. Still, however, we found support for somatization in some CFS sufferers: Within both the CFS-HD and the CFS-LD groups, weaknesses in representing emotions and in defensive functioning were associated with more severe physical symptoms. Clinically, the heterogeneity of CFS and those who suffer from it indicates the need for individual assessment and depression treatment.

CHRONIC FATIGUE SYNDROME (Continued)

[Chronic fatigue is highly prevalent in survivors of autologous stem cell transplantation and associated with IL-6, neuroticism, cardiorespiratory fitness, and obesity.](#)

[Smeland KB](#)¹, [Loge JH](#)^{2,3}, [Aass HCD](#)⁴, [Aspelin T](#)⁴, [Bersvendsen H](#)⁵, [Bolstad N](#)⁴, [Fagerli UM](#)^{6,7}, [Falk RS](#)⁸, [Fluge Ø](#)⁹, [Fosså A](#)¹⁰, [Holte H](#)¹⁰, [Lund MB](#)^{2,11}, [Murbræch K](#)¹², [Reinertsen KV](#)¹³, [Stenehjem JS](#)¹⁴, [Kiserud CE](#)¹³.

Bone Marrow Transplant. **2018 Sep 27**. doi: 10.1038/s41409-018-0342-y. PMID: 30262906. [Epub ahead of print]

Chronic fatigue (CF, defined as elevated fatigue levels for ≥ 6 months) is a common and distressing late effect [1], affecting 25–30% of long-term lymphoma survivors (LSs) [2, 3], compared with 11% in a national representative population [2]. One might hypothesize that CF would be more prevalent after high-dose therapy with autologous stem cell transplantation (HDT-ASCT). However, a prevalence of CF of 28% was found among 40 LSs 3 years after HDT-ASCT, comparable to what is found after conventional chemotherapy [4].

The etiology of CF in LSs is multifactorial, influenced by demographic, somatic, and psychological factors [1]. The underlying pathophysiology is incompletely understood, but is suggested to involve dysregulation of proinflammatory cytokines [1]. An association between fatigue and raised levels of cytokines, such as interleukin (IL)-6, IL-1 receptor antagonist (IL-1RA), IL-1 β , and tumor necrosis factor- α (TNF- α) has been demonstrated, especially in breast cancer survivors [1]. The literature is, however, limited for LSs, with only a few small studies, mainly on mixed hematological diagnoses, that give inconsistent results [5–7]. To our knowledge, no previous study has investigated cytokines in relation to CF in longterm LSs specifically.

On this background, we assessed the prevalence of CF in a national cohort of adult LSs treated with HDT-ASCT, and investigated associations between CF and disease/treatment characteristics, psychological factors and objectively measured somatic variables, including cardiorespiratory fitness and selected cytokines.

[See full text, figures, and references at the following link: [Bone Marrow Transplantation](#)]

HEADACHE and MIGRAINE

[Involvement of the Tetraspanin 2 \(TSPAN2\) Gene in Migraine: A Case-Control Study in Han Chinese.](#)

[Fang J](#)¹, [Yuan X](#)², [An X](#)¹, [Qu H](#)¹, [Wang C](#)¹, [Hong G](#)¹, [Zheng L](#)³, [Yi K](#)⁴, [Chen S](#)⁵, [Wang X](#)⁶, [Ma Q](#)^{1,3}.

Front Neurol. **2018 Sep** 11;9:714. doi: 10.3389/fneur.2018.00714. PMCID: PMC6143784. PMID: 30258394. eCollection 2018.

Tetraspanin 2 (TSPAN2) belongs to the tetraspanin superfamily. Previous studies have identified significant associations of the *TSPAN2* single nucleotide polymorphisms (SNPs) rs12134493 and rs2078371 with migraine in Western populations; however, these associations need to be confirmed in the Chinese Han population. In addition, we carried out further studies to see whether *TSPAN2* is associated with susceptibility to migraine to provide new clinical evidence. A case-control study (425 patients with migraine and 425 healthy controls) in a Chinese Han population was performed to evaluate the associations between migraine and *TSPAN2* via a genotype-phenotype analysis between *TSPAN2* and clinical symptoms. The SNP rs2078371 was found to be significantly associated with migraines especially in migraines without aura (MO) and in female patients. Meta-analysis revealed that the A allele of rs12134493 was significantly associated with migraines (OR = 1.14, $P = 0.0001$). Our findings suggested that *TSPAN2* is a potential susceptibility factor for migraines. To confirm our results, a large-scale Chinese Han population study should be conducted. Considering that these two SNPs have not been definitively shown to affect *TSPAN2* or to regulate nearby genes in this genomic region, the biological function and molecular mechanism of *TSPAN2* in migraine should be further explored.

HEADACHE and MIGRAINE (Continued)**[Using a Genetic Risk Score Approach to Predict Headache Response to Triptans in Migraine Without Aura.](#)**

[Cargnin S](#)¹, [Viana M](#)², [Sances G](#)², [Cantello R](#)³, [Tassorelli C](#)^{2,4}, [Terrazzino S](#)¹.

J Clin Pharmacol. 2018 Sep 26. doi: 10.1002/jcph.1320. PMID: 30256423. [Epub ahead of print]

A large meta-analysis of genome-wide association studies has recently identified a number of risk loci for migraine without aura (MwoA). In this study, we tested the hypothesis that a genetic risk score based on single-nucleotide polymorphisms (SNPs), previously reported to be associated with MwoA at genome-wide significance, may influence headache response to triptans in patients with migraine without aura. Genotyping of rs9349379, rs2078371, rs6478241, rs11172113, rs1024905, and rs6724624 was conducted with a real-time PCR allelic discrimination assay in 172 MwoA patients, of whom 36.6% were inconsistent responders to triptans. Each genetic risk score model was constructed as an unweighted score, calculated by adding the number of risk alleles for MwoA across each SNP at selected loci. The association with headache response to triptans was evaluated by logistic regression analysis adjusted for triptan, and the P values were corrected for the false discovery rate. The genetic risk score including susceptibility risk alleles at TRPM8 rs6724624 and FGF6 rs1024905 was found to be inversely associated with risk of inconsistent response to triptans (OR, 0.62; 95%CI, 0.43-0.89; false discovery rate q value, 0.045). In addition, adding this genetic risk score to the triptan-adjusted logistic regression model significantly improved (P = .037) the discrimination accuracy, from 0.57 (95%CI, 0.50-0.65) to 0.64 (95%CI, 0.57-0.72). A modest but significant effect on risk of inconsistent response to triptans was identified for a genetic risk score model composed of 2 known risk alleles for MwoA, suggesting its potential utility in predicting headache response to triptan therapy.

[White matter tract microstructure of the mPFC-amygdala predicts interindividual differences in placebo response related to treatment in migraine patients.](#)

[Liu J](#)^{1,2}, [Mu J](#)^{1,2}, [Chen T](#)^{1,2}, [Zhang M](#)³, [Tian J](#)^{1,2}.

Hum Brain Mapp. 2018 Sep 5. doi: 10.1002/hbm.24372. PMID: 30256491. [Epub ahead of print]

To investigate whether interindividual variability of white matter (WM) tract microstructure of the medial prefrontal cortex (mPFC)-amygdala circuit could predict 8-week placebo treatment outcomes in patients with migraine without aura (MO) using diffusion tensor imaging (DTI) with a tractography atlas-based analysis algorithm and a linear support vector machine algorithm. This study received institutional review board approval, and all subjects gave informed consent. One hundred and twenty-four MO had an 8-week sham acupuncture treatment. Patients were subdivided into recovering (MOr, >50% improvement in migraine attack frequency after treatment) and persisting (MOp, <50% reduction in number of migraine days). Neuroimaging was collected via magnetic resonance imaging (MRI) in all subjects. Patients were imaged during the interictal phase of migraine (at least 72 hr after, and not within 24 hr of a migraine) before the treatment. WM microstructures were quantified along the selected fiber pathway and were used to evaluate the discrimination performance for classifying MOr and MOp. The combined features of diffusion measures from vertices along the pathways of the mPFC-amygdala accurately discriminated MOr from MOp migraineurs with an accuracy of 84.0% (p < .005, permutation test). The most discriminative WM features that contributed to the classification were located in the external capsule and ACC/mPFC. Our findings suggested that the variability of placebo treatment outcomes in migraineurs could be predicted from priori diffusion measures along the fiber pathways of the mPFC-amygdala, which may demonstrate a potential of WM neuroimaging features as imaging markers for identifying placebo responders in migraine patients.

HEADACHE and MIGRAINE (Continued)

[Guideline on the use of onabotulinumtoxinA in chronic migraine: a consensus statement from the European Headache Federation.](#)

[Bendtsen L](#)¹, [Sacco S](#)², [Ashina M](#)³, [Mitsikostas D](#)⁴, [Ahmed F](#)⁵, [Pozo-Rosich P](#)^{6,7}, [Martelletti P](#)⁸.

J Headache Pain. 2018 Sep 26;19(1):91. doi: 10.1186/s10194-018-0921-8. PMID: 30259200.

OnabotulinumtoxinA is being increasingly used in the management of chronic migraine (CM). Treatment with onabotulinumtoxinA poses challenges compared with traditional therapy with orally administered preventatives. The European Headache Federation identified an expert group that was asked to develop the present guideline to provide recommendations for the use of onabotulinumtoxinA in CM. The expert group recommend onabotulinumtoxinA as an effective and well-tolerated treatment of CM. Patients should preferably have tried two to three other migraine prophylactics before start of onabotulinumtoxinA. Patients with medication overuse should be withdrawn from the overused medication before initiation of onabotulinumtoxinA if feasible, if not onabotulinumtoxinA can be initiated from the start or before withdrawal. OnabotulinumtoxinA should be administered according to the PREEMPT injection protocol, i.e. injecting 155 U-195 U to 31-39 sites every 12-weeks. We recommend that patients are defined as non-responders, if they have less than 30% reduction in headache days per month during treatment with onabotulinumtoxinA. However other factors such as headache intensity, disability and patient preferences should also be considered when evaluating response. Treatment should be stopped, if the patient does not respond to the first two to three treatment cycles. Response to continued treatment with onabotulinumtoxinA should be evaluated by comparing the 4 weeks before with the 4 weeks after each treatment cycle. It is recommended that treatment is stopped in patients with a reduction to less than 10 headache days per month for 3 months and that patients are re-evaluated 4-5 months after stopping onabotulinumtoxinA to make sure that the patient has not returned to CM. Questions regarding efficacy and tolerability of onabotulinumtoxinA could be answered on the basis of scientific evidence. The other recommendations were mainly based on expert opinion. Future research on the treatment of CM with onabotulinumtoxinA may further improve the management of this highly disabling disorder.

CHRONIC PAIN

[Effects of Pain, Insomnia, and Depression on Psychoactive Medication Supply in Older Adults With Osteoarthritis.](#)

[Liu M](#)^{1,2,3}, [McCurry SM](#)^{4,5}, [Belza B](#)², [Buchanan DT](#)², [Dobra A](#)^{2,6,7}, [Von Korff M](#)⁸, [Vitiello MV](#)^{2,5}.

Med Care. 2018 Sep 25. doi: 10.1097/MLR.0000000000000982. PMID: 30256279. [Epub ahead of print]

BACKGROUND: Determinants of prescribing psychoactive medications for symptom management in older adults remain underexamined despite known risks and cautions concerning these medications.

OBJECTIVE: To examine independent and combined effects of pain, concurrent insomnia and depression symptoms on psychoactive medications supplied to older adults with osteoarthritis (OA).

RESEARCH DESIGN: Survey data on pain, insomnia, and depression obtained from OA patients screened for a randomized controlled trial were used to identify predictors of psychoactive medication supply [opioids, sedatives, tricyclic antidepressants (TCAs), and non-TCAs] over a 4-year period.

SUBJECTS: Group Health Cooperative patients with a diagnosis of OA (N=2976).

MEASURES: Survey data on pain (Graded Chronic Pain Scale), insomnia (Insomnia Severity Index), and depression (Patient Health Questionnaire-8); and medications supply assessed from electronic medical records.

RESULTS: In negative binomial models, pain [incidence rate ratio (IRR), 2.8-3.5; P<0.001], insomnia (IRR, 2.0; P<0.001), and depression (IRR, 1.5; P<0.05) each independently predicted opioid supply. Insomnia (IRR, 3.2; P<0.001) and depression (IRR, 3.0; P<0.001) each independently predicted sedative supply. Pain (IRR, 2.1; P<0.05) and insomnia (IRR, 2.0; P<0.05) independently predicted TCA supply, whereas only depression (IRR, 2.2; P<0.001) independently predicted non-TCA supply. Combined effects of pain and insomnia/depression on these medications were additive and increased the rate of medication supply 1.5-7.5 times. Combined effects increased with insomnia or depression severity.

CONCLUSIONS: Concurrent insomnia and depressive symptoms predicted increased supply of opioids, sedatives, and antidepressants after accounting for pain, indicating the importance of sleep and mood disorders as factors increasing supply of these medications.

CHRONIC PAIN (Continued)**[Naldemedine versus placebo for opioid-induced constipation \(COMPOSE-1 and COMPOSE-2\): two multicentre, phase 3, double-blind, randomised, parallel-group trials.](#)**

[Hale M](#)¹, [Wild J](#)², [Reddy J](#)³, [Yamada T](#)³, [Arjona Ferreira JC](#)⁴.

Lancet Gastroenterol Hepatol. **2017 Aug**;2(8):555-564. doi: 10.1016/S2468-1253(17)30105-X. PMID: 28576452. Epub 2017 May 30.

BACKGROUND: Opioid-induced constipation is a frequent side-effect of opioid treatment, and standard interventions have limited or inconsistent efficacy. This study assessed the efficacy and safety of naldemedine, a peripherally acting μ -opioid receptor antagonist, for the treatment of opioid-induced constipation in patients with chronic non-cancer pain.

METHODS: We report two double-blind, randomised, placebo-controlled trials in adults with chronic non-cancer pain and opioid-induced constipation. The first (COMPOSE-1) was done in 68 outpatient sites in seven countries and the second (COMPOSE-2) at 69 outpatient sites in six countries; both studies were done in Europe and the USA. Eligible patients were aged 18-80 years, did not use laxatives, and had a stable opioid regimen for treatment of chronic non-cancer pain with a total daily dose averaging at least 30 mg (morphine equivalent) for at least 1 month before screening. Patients were randomly assigned (1:1) to receive either oral naldemedine 0.2 mg or matching placebo once a day for 12 weeks. Randomisation was stratified by average total daily opioid dose (30-100 mg and >100 mg equivalents of oral morphine sulphate). The primary endpoint was proportion of responders. A responder had at least three spontaneous bowel movements (SBMs) per week with an increase from baseline of at least one SBM per week for at least 9 weeks of the 12-week treatment period including at least three of the last 4 weeks. Efficacy endpoints were analysed by intention to treat and the safety population included all patients who received at least one dose of study drug. These trials have both been completed and are registered with ClinicalTrials.gov, numbers [NCT01965158](#) and [NCT01993940](#).

FINDINGS: In COMPOSE-1, 547 patients were recruited between Aug 29, 2013, and Jan 22, 2015, and were randomly assigned to receive naldemedine (n=274) or placebo (n=273). Patients for COMPOSE-2 were recruited between Nov 4, 2013, and June 9, 2015; 553 patients were randomly assigned to receive naldemedine (n=277) or placebo (n=276). Five patients were enrolled at more than one site, so were excluded from the intention-to-treat population (COMPOSE-1: one per group; COMPOSE-2: one in the naldemedine group, two from the placebo group), with intention-to-treat group sizes of 273 in the naldemedine group and 272 in the placebo group in COMPOSE-1, and 276 in the naldemedine group and 274 in the placebo group in COMPOSE-2. The proportion of responders in both trials was significantly higher with naldemedine than with placebo in COMPOSE-1 (130 responders [47.6%] of 273 in the naldemedine group vs 94 responders [34.6%] of 272 in the placebo group, difference 13.0% [95% CI 4.8-21.3]; p=0.002) and in COMPOSE-2 (145 [52.5%] of 276 vs 92 [33.6%] of 274, difference 18.9% [10.8-27.0]; p<0.0001). Incidence of adverse events with naldemedine was similar to placebo (COMPOSE-1: 132 [49%] of 271 in the naldemedine group vs 123 [45%] of 272 in the placebo group; COMPOSE-2: 136 [50%] of 271 vs 132 [48%] of 274). Treatment-related adverse events were noted in 59 (22%) of 271 patients in the naldemedine group and 45 (17%) of 272 in the placebo group in COMPOSE-1, and in 54 (20%) of 271 patients in the naldemedine group and 31 (11%) of 274 in the placebo group of COMPOSE-2; the between-group differences were largely due to gastrointestinal disorders, which were more common with naldemedine than placebo (COMPOSE-1: 40 [15%] patients in the naldemedine group vs 18 [7%] in the placebo group; COMPOSE-2: 42 [16%] vs 20 [7%]).

INTERPRETATION: Naldemedine treatment led to a significantly higher responder rate than did placebo and was generally well tolerated. These results support that naldemedine could be a new option for the treatment of opioid-induced constipation in patients with chronic non-cancer pain.

FUNDING: Shionogi & Co, Ltd.

CHRONIC PAIN (Continued)**[Chronic back pain and its association with quality of life in a large French population survey.](#)**

[Husky MM](#)¹, [Ferdous Farin F](#)², [Compagnone P](#)³, [Fermanian C](#)², [Kovess-Masfety V](#)^{4,5,6}.

Health Qual Life Outcomes. **2018 Sep 26**;16(1):195. doi: 10.1186/s12955-018-1018-4. PMID: 30257670.

BACKGROUND: Chronic back pain is associated with significant burden, yet few epidemiological studies have provided data on chronic back pain, its predictors and correlates in France.

METHODS: Data were drawn from a cross-sectional survey conducted in France (n = 17,249) using computer-assisted telephone interviews. Sample age ranges from 18 to 98 with a mean of 46.39 years (SD = 17.44), and was 56.7% female. Medical conditions were assessed using the CIDI, quality of life was assessed using both the physical and mental component scores of the SF-36.

RESULTS: Overall, 38.3% of adults reported chronic back pain. Female gender, older age, lower education, manual labor occupation, and population density were significantly associated with the distribution of chronic back pain. Chronic back pain was associated with lower scores on all SF-36 mean scores and on the Physical Composite Score and Mental Composite Score controlling for comorbid medical conditions including other types of chronic pain.

CONCLUSION: The study highlights the burden of chronic back pain in the general population and underscores its correlation with quality of life. Such data contribute to raise awareness among clinicians and health policy makers on the necessity of prevention, early diagnosis, proper management and rehabilitation policies in order to minimize the burden associated with chronic pain.

OTHER RESEARCH OF INTEREST**[Genetics of blood lipids among ~300,000 multi-ethnic participants of the Million Veteran Program.](#)**

[Klarin D](#)^{1,2,3}, [Damrauer SM](#)^{4,5}, [Cho K](#)⁶, [Sun YV](#)⁷, [Teslovich TM](#)⁸, [Honerlaw J](#)⁶, [Gagnon DR](#)^{6,9}, [DuVall SL](#)^{10,11}, [Li J](#)^{12,13}, [Peloso GM](#)⁹, [Chaffin M](#)², [Small AM](#)^{4,14}, [Huang J](#)⁶, [Tang H](#)¹⁵, [Lynch JA](#)^{10,16}, [Ho YL](#)⁶, [Liu DJ](#)¹⁷, [Emdin CA](#)^{1,2}, [Li AH](#)⁸, [Huffman JE](#)⁶, [Lee JS](#)^{12,13}, [Natarajan P](#)^{1,2,18}, [Chowdhury R](#)¹⁹, [Saleheen D](#)^{4,20}, [Vujkovic M](#)^{4,20}, [Baras A](#)⁸, [Pyarajan S](#)^{6,21}, [Di Angelantonio E](#)¹⁹, [Neale BM](#)^{2,22,23}, [Naheed A](#)²⁴, [Khera AV](#)^{1,2}, [Danesh J](#)¹⁹, [Chang KM](#)^{4,25}, [Abecasis G](#)²⁶, [Willer C](#)^{27,28,29}, [Dewey FE](#)⁸, [Carey DJ](#)³⁰; [Global Lipids Genetics Consortium](#); [Myocardial Infarction Genetics \(MIGen\) Consortium](#); [Geisinger-Regeneron DiscovEHR Collaboration](#); [VA Million Veteran Program](#), [Concato J](#)^{14,31}, [Gaziano JM](#)^{6,21,32}, [O'Donnell CJ](#)^{6,32}, [Tsao PS](#)^{12,13}, [Kathiresan S](#)^{1,2}, [Rader DJ](#)^{25,32,33,34,35}, [Wilson PWF](#)^{36,37}, [Assimes TL](#)^{38,39}.

Nat Genet. **2018 Oct 1**. doi: 10.1038/s41588-018-0222-9. PMID: 30275531 [Epub ahead of print]

The Million Veteran Program (MVP) was established in 2011 as a national research initiative to determine how genetic variation influences the health of US military veterans. Here we genotyped 312,571 MVP participants using a custom biobank array and linked the genetic data to laboratory and clinical phenotypes extracted from electronic health records covering a median of 10.0 years of follow-up. Among 297,626 veterans with at least one blood lipid measurement, including 57,332 black and 24,743 Hispanic participants, we tested up to around 32 million variants for association with lipid levels and identified 118 novel genome-wide significant loci after meta-analysis with data from the Global Lipids Genetics Consortium (total n > 600,000). Through a focus on mutations predicted to result in a loss of gene function and a phenome-wide association study, we propose novel indications for pharmaceutical inhibitors targeting PCSK9 (abdominal aortic aneurysm), ANGPTL4 (type 2 diabetes) and PDE3B (triglycerides and coronary disease).

OTHER RESEARCH OF INTEREST (Continued)**[Intestinal Hyperpermeability in Gulf War Veterans With Chronic Gastrointestinal Symptoms.](#)**

[Zhang B](#)¹, [Verne ML](#)², [Fields JZ](#)¹, [Verne GN](#)¹, [Zhou Q](#)^{1,3}.

J Clin Gastroenterol. 2018 Sep 26. doi: 10.1097/MCG.0000000000001135. PMID: 30260809. [Epub ahead of print]

BACKGROUND: Well over 700,000 United States military personnel participated in the Persian Gulf War in which they developed chronic health disorders of undetermined etiology. Up to 25% of Veterans had persistent and chronic gastrointestinal (GI) symptoms, which they suspected were related to their military service in the Gulf.

AIM: The overall aim of the current study was to evaluate intestinal permeability in previously deployed Gulf War Veterans who developed chronic GI symptoms during their tour in the Persian Gulf.

METHODS: To accomplish this, we evaluated intestinal permeability (IP) using the urinary lactulose/mannitol test. Measurements of intestinal permeability were then correlated with mean ratings of daily abdominal pain, frequency of bowel movements, and consistency of bowel movements on the Bristol Stool Scale in all Veterans.

RESULTS: A total of 73 veterans had documented chronic GI symptoms (diarrhea, abdominal pain) and were included in the study. A total of 29/73 (39%) of veterans has increased IP and had a higher average daily stool frequency ($P<0.05$); increased liquid stools as indicated by a higher Bristol Stool Scale ($P<0.01$); and a higher mean M-VAS abdominal pain rating ($P<0.01$). Pearson correlation coefficients revealed that there was a positive correlation between increased IP and stool frequency, Bristol Stool Scale, and M-VAS abdominal pain rating.

CONCLUSIONS: Our study demonstrates that deployed Gulf War Veterans with persistent GI symptoms commonly have increased intestinal permeability that potentiates the severity of abdominal pain, diarrhea, and stool consistency. These new findings in our study are important as they may lead to novel diagnostic biomarkers for returning Gulf War Veterans who suffer from chronic functional gastrointestinal disorders. These advances are also important for an increasing number of veterans who are now serving in the Persian Gulf and are at a high risk of developing these chronic pain disorders.

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[Impact of TBI on caregivers of veterans with TBI: Burden and interventions.](#)

[Malec JF](#)^{1,2,3}, [Van Houtven CH](#)^{4,5}, [Tanielian T](#)⁶, [Atizado A](#)⁷, [Dorn MC](#)⁸.

Brain Inj. 2017;31(9):1235-1245. doi: 10.1080/02699052.2016.1274778.

OBJECTIVES: Describe State-of-the-Art in practice and research in caregiving with individuals, specifically, Veterans with traumatic brain injury (TBI) and the implications for current practice and future research.

SOURCES: Professional literature and personal experience of review panel.

MAIN OUTCOMES: Unpaid caregiving for individuals with TBI is most often provided by a spouse, parent or other blood relative; the majority of caregivers are women. Although caregiving can be rewarding, it also may create financial burden and psychological stress. Depression among family caregivers occurs four times more frequently than in the general population. Positive coping can help reduce the impact of stress, and Department of Veterans Affairs (VA) programmes are available to ease financial burden. Group interventions show promise in reinforcing and improving positive coping for both family caregivers and Veterans with TBI.

CONCLUSIONS: Identifying the specific needs of caregivers and families of Veterans with TBI and other traumatic injuries, including post-traumatic stress syndrome (PTSD), will require further longitudinal research. Currently available group interventions and programmes appear to benefit injured Veterans and their family caregivers financially and psychologically. Increased understanding of characteristics of quality family caregiving and its long term costs and benefits is likely to lead to additional improvements in these interventions and programmes.

OTHER RESEARCH OF INTEREST (Continued)**[Double-Blind Randomized Clinical Trial of Prazosin for Alcohol Use Disorder.](#)**

[Simpson TL](#)¹, [Saxon AJ](#)¹, [Stappenbeck C](#)¹, [Malte CA](#)¹, [Lyons R](#)¹, [Tell D](#)¹, [Millard SP](#)¹, [Raskind M](#)¹.

Am J Psychiatry. 2018 Aug 29;appiajp201817080913. doi: 10.1176/appi.ajp.2018.17080913. PMID: 30153753. [Epub ahead of print]

OBJECTIVE: Current medications for alcohol use disorder do not target brain noradrenergic pathways. Theoretical and preclinical evidence suggests that noradrenergic circuits may be involved in alcohol reinforcement and relapse. After a positive pilot study, the authors tested the α -1 adrenergic receptor antagonist prazosin to treat alcohol use disorder in a larger sample.

METHOD: Ninety-two participants with alcohol use disorder but without posttraumatic stress disorder were randomly assigned to receive prazosin or placebo in a 12-week double-blind study. Medication was titrated to a target dosing schedule of 4 mg in the morning, 4 mg in the afternoon, and 8 mg at bedtime by the end of week 2. The behavioral platform was medical management. Participants provided daily data on alcohol consumption. Generalized linear mixed-effects models were used to examine the impact of prazosin compared with placebo on number of drinks per week, number of drinking days per week, and number of heavy drinking days per week.

RESULTS: Eighty participants completed the titration period and were included in the primary analyses. There was a significant interaction between condition and week for both number of drinks and number of heavy drinking days, such that the rate of drinking and the probability of heavy drinking showed a greater decrease over time for participants in the prazosin condition compared with those in the placebo condition. Participants in the prazosin condition were more likely to report drowsiness and edema than participants in the placebo condition.

CONCLUSIONS: Prazosin holds promise as a harm-reduction pharmacologic treatment for alcohol use disorder and deserves further evaluation by independent research groups.

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