

GULF WAR ILLNESS

[Report of Autonomic Symptoms in a Clinical Sample of Veterans with Gulf War Illness.](#)

[Fox A](#)¹, [Helmer D](#)¹, [Tseng CL](#)¹, [Patrick-DeLuca L](#)¹, [Osinubi O](#)¹.

Mil Med. 2018 Mar 1;183(3-4):e179-e185. doi: 10.1093/milmed/usx052. PMID: 29514346.

Introduction: Previous studies suggest that autonomic dysfunction may be an underlying factor in Gulf War Illness. This study examined self-reported symptoms of autonomic dysfunction and their relationship with physical functioning among veterans with Gulf War Illness.

Materials and Methods: We abstracted medical records of Gulf War Veterans clinically evaluated at the New Jersey War Related Illness and Injury Study Center between 2010 and 2016. The outcome measure was the Veteran version of the Short Form Health Survey (VR-36) physical functioning scale. Autonomic function was assessed using a composite variable constructed from the chart abstraction to mimic the Composite Autonomic Symptom Scale (COMPASS-31).

Results: Seventy-six veterans were included in the final analysis. The autonomic symptom burden score was 45 (± 14). Increased autonomic symptom burden, greater mental health burden (PTSD/depression), and greater body mass index were individually associated with poorer physical functioning. A general linear regression containing these variables revealed that patients with both PTSD and depression ($b = -15.2$, $p = 0.03$) or either PTSD or depression ($b = -22.7$, $p < 0.01$) had lower physical functioning than those without; the other variables became not significant (body mass index: $p = 0.07$; autonomic function: $p = 0.89$).

Conclusion: The average autonomic function score indicated significant burden in Gulf War Veterans, consistent with published research. We did not detect an independent association between autonomic symptom burden and physical functioning, likely due to the non-specific nature of the measure used to capture autonomic symptoms or the stronger association between mental health conditions and physical functioning. Future work utilizing valid and standardized instruments to clinically evaluate autonomic function is warranted.

CHRONIC FATIGUE SYNDROME

[Does the microbiome and virome contribute to myalgic encephalomyelitis/chronic fatigue syndrome?](#)

[Newberry F](#)^{1,2}, [Hsieh SY](#)^{3,2}, [Wileman T](#)^{3,2}, [Carding SR](#)^{3,2}.

Clin Sci (Lond). 2018 Mar 9;132(5):523-542. doi: 10.1042/CS20171330. PMID: 29523751. Print 2018 Mar 15.

Myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) (ME/CFS) is a disabling and debilitating disease of unknown aetiology. It is a heterogeneous disease characterized by various inflammatory, immune, viral, neurological and endocrine symptoms. Several microbiome studies have described alterations in the bacterial component of the microbiome (dysbiosis) consistent with a possible role in disease development. However, in focusing on the bacterial components of the microbiome, these studies have neglected the viral constituent known as the virome. Viruses, particularly those infecting bacteria (bacteriophages), have the potential to alter the function and structure of the microbiome via gene transfer and host lysis. Viral-induced microbiome changes can directly and indirectly influence host health and disease. The contribution of viruses towards disease pathogenesis is therefore an important area for research in ME/CFS. Recent advancements in sequencing technology and bioinformatics now allow more comprehensive and inclusive investigations of human microbiomes. However, as the number of microbiome studies increases, the need for greater consistency in study design and analysis also increases. Comparisons between different ME/CFS microbiome studies are difficult because of differences in patient selection and diagnosis criteria, sample processing, genome sequencing and downstream bioinformatics analysis. It is therefore important that microbiome studies adopt robust, reproducible and consistent study design to enable more reliable and valid comparisons and conclusions to be made between studies. This article provides a comprehensive review of the current evidence supporting microbiome alterations in ME/CFS patients. Additionally, the pitfalls and challenges associated with microbiome studies are discussed.

CHRONIC FATIGUE SYNDROME (Continued)

[ASIA, chronic fatigue syndrome, and selective low dose neurotoxicity of aluminum adjuvants.](#)

[Crépeaux G](#)¹, [Gherardi RK](#)², [Authier FJ](#)².

[See Elsevier ClinicalKey for full text of Editorial with references.]

J Allergy Clin Immunol Pract. **2018 Mar - Apr**;6(2):707. doi: 10.1016/j.jaip.2017.10.039. PMID: 29525002.

Editorial comment on: Ameratunga, et al. [Evidence Refuting the Existence of Autoimmune/Autoinflammatory Syndrome Induced by Adjuvants \(ASIA\)](#). J Allergy Clin Immunol Pract. **2017 Sep 6**. pii: S2213-2198 [Listed in the Gulf War Illness section of RAC Research Alerts for Sep. 05 to 09, 2017.]

In their recent paper, Ameratunga et al have considered the autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA) to be inexistent. We have questioned long-term aluminum adjuvants safety since the understanding that some adult vaccine recipients cannot clear out aluminum hydroxide particles from their immune cells as assessed by very long persistence of a lesion called macrophagic myofasciitis (MMF) at the site of previous immunizations. These patients typically present with diffuse myalgias, chronic fatigue, characteristic cognitive dysfunction, and positron emission tomography with fluorodesoxyglucose scanner abnormalities, forming a syndrome used as a paradigm of ASIA by Prof. Y. Shoenfeld. On the basis of a thorough investigation of 348 symptomatic patients with MMF and recent experimental findings from our lab, we would like to raise some important points.

(1) According to Ameratunga et al, diagnostic criteria for ASIA are too large and vague. This is not very surprising because delineation of ASIA primarily aimed to encompass and conceptually unify a wide spectrum of medical conditions observed in individuals exposed to immunologic adjuvants. These criteria now require validation/refinement by a panel of international experts. We emphasize that the subset of patients with MMF typically meet the validated Oxford 1991 and CDC 1994 international criteria for chronic fatigue syndrome.

(2) Much less convincing is what Ameratunga et al present as “strong human data refuting the existence of ASIA caused by aluminum-containing vaccine adjuvants.” First, they report on a series of 28 patients with lupus who had no exacerbations after hepatitis B immunization. What can be concluded from this small series? None of the patients with MMF followed in our center or described in the literature had systemic lupus erythematosus, and the chronic fatigue syndrome they suffer from is not an autoimmune disease. Second, they refer to a Danish survey showing decreased, instead of increased, incidence of autoimmune disease in patients undergoing allergen-specific immunotherapy with aluminum-containing compounds. Again, chronic fatigue syndrome is not an autoimmune disease and, therefore, was not included in the list of 16 autoimmune diseases considered in the study they refer to. Moreover, Ameratunga et al pointed out that “100 times the dose of aluminum contained in 3 hepatitis vaccinations” was intradermally injected to the patients. This is the exact contrary of a massive argument against aluminum hydroxide toxicity because the dose-response curve of aluminum hydroxide neurotoxicity indicates that low doses of the adjuvant are selectively associated with aluminum translocation to brain and neurobehavioral changes 6 months after injections in mice. In contrast, the highest doses, forming large adjuvant aggregates remaining trapped at the periphery, were nontoxic. Thus the dose does not “make the poison” in case of aluminum adjuvants. In addition, whether or not systemic diffusion of particles may be significantly influenced by the route of administration, for example, intramuscular versus intradermal injections, is currently unknown.

In conclusion, assertions based on indirect arguments cannot satisfactorily replace epidemiological studies specifically designed to assess aluminum-containing vaccines' long-term safety that are notoriously lacking in both adults and children.⁷

HEADACHE and MIGRAINE

[Lifestyle factors and risk of migraine and tension-type headache. Follow-up data from the Nord-Trøndelag Health Surveys 1995-1997 and 2006-2008.](#)

[Hagen K](#)^{1,2}, [Åsberg AN](#)¹, [Stovner L](#)^{1,2}, [Linde M](#)^{1,2}, [Zwart JA](#)^{3,4,5}, [Winsvold BS](#)^{3,4}, [Heuch I](#)⁵.

Cephalalgia. **2018 Jan 1**:333102418764888. doi: 10.1177/0333102418764888. PMID: 29517305. [Epub ahead of print]

Aims The aim of this population-based historical cohort study was to investigate the influence of lifestyle factors on the risk of developing migraine or tension-type headache (TTH). **Methods** Data from the Nord-Trøndelag Health Study performed in 1995-1997 and 2006-2008 was used. A total of 15,276 participants without headache at baseline were included. A Poisson regression was used to evaluate the associations between lifestyle factors and risk ratios (RRs) of migraine and TTH 11 years later. Precision of the estimates was assessed by 95% confidence interval (CIs). **Results** Increased risk of migraine (RR 1.30, 95% CI 1.11-1.52) was found in smokers (past or current) compared to those who had never smoked. Hard physical exercise 1-2 hours per week reduced the risk of migraine (OR 0.71, 95% CI 0.54-0.94) compared to inactivity, and the risk of migraine was also lower among those who consumed alcohol (RR 0.73, 95% CI 0.57-0.94) compared to abstainers. No association was found between smoking, physical activity, alcohol use and risk of TTH. **Conclusions** The main finding was that current and previous smoking was associated with increased risk of migraine, but not of TTH.

HEADACHE and MIGRAINE (Continued)

[Flunarizine in migraine-related headache prevention: Results from 200 patients treated in the UK.](#)

[Karsan N](#)^{1,2}, [Paletorpe D](#)^{1,2}, [Rattanawong W](#)^{1,2}, [Marin JC](#)^{1,2}, [Bhola R](#)^{1,2}, [Goadsby PJ](#)^{1,2}.

Eur J Neurol. 2018 Mar 7. doi: 10.1111/ene.13621. PMID: 29512871. [Epub ahead of print]

BACKGROUND: For over 20 years, as a group we have been using flunarizine in primary headache disorders. Flunarizine is widely used in Europe, but not licensed in the UK. In September 2014, the National Institute for Clinical Excellence (NICE) published supportive guidelines for flunarizine use in migraine, based on randomised controlled evidence that it is as effective as propranolol and topiramate in adults.

METHODS: We reviewed a cohort of adult patients (n=200) treated with flunarizine from our practice. These patients' clinical information: diagnosis, dose, efficacy, side effects and duration of treatment, was collected.

RESULTS: The most common indication for flunarizine use was chronic migraine, followed by migraine with aura, sporadic hemiplegic migraine and familial hemiplegic migraine and new daily persistent headache with migrainous features. Flunarizine is generally effective; with only 24% (n = 47) of patients reporting no clinical effect. The commonest dose used was 10 mg per day. Duration of treatment information was available for 39% (n = 78). Of these patients 64% (n = 50) continued treatment for more than one year. Doses up to 15 mg were generally well tolerated, with only 10.5% (n = 21) of patients stopping treatment due to adverse effects. The most common adverse events were tiredness, mood change and weight gain.

CONCLUSION: The data provide supportive evidence from tertiary headache practice in the UK for the use of flunarizine in migraine. The data encourage development of future guidance regarding flunarizine use in headache centres in countries where its use is not routine. This article is protected by copyright. All rights reserved.

[The Prevalence and Impact of Migraine and Severe Headache in the United States: Figures and Trends From Government Health Studies.](#)

[Burch R](#)¹, [Rizzoli P](#)¹, [Loder E](#)¹.

Headache. 2018 Mar 12. doi: 10.1111/head.13281. PMID: 29527677. [Epub ahead of print]

BACKGROUND AND OBJECTIVES: In this targeted systematic review, we aimed to identify up-to-date prevalence estimates of migraine and severe headache in adults from population-based US government surveys. Our goal was to assess the stability of prevalence estimates over time, and to identify additional information pertinent to the burden and treatment of migraine and other severe headache conditions.

METHODS: We searched for the most current publicly available summary statistics from the National Health Interview Survey (NHIS), the National Hospital Ambulatory Medical Care Survey (NHAMCS), and the National Ambulatory Medical Care Survey (NAMCS). We extracted and summarized data from each study over time and as a function of demographic variables.

RESULTS: The prevalence and burden of self-reported migraine and severe headache in the US adult population is high, affecting roughly 1 out of every 6 American and 1 in 5 women over a 3-month period (15.3% overall [95% CI 14.75-15.85], 9.7% of males [95% CI 9.05-10.35] and 20.7% of females [95% CI 19.84-21.56]). The prevalence has been remarkably stable over a period of 19 years. The prevalence of migraine or severe headache in 2015 was highest in American Indian or Alaska Natives (18.4%) compared with whites, blacks, or Hispanics, with the lowest prevalence in Asians (11.3%). There is a higher burden of migraine in those aged 18-44 (17.9%), people who are unemployed (21.4%), those with family income less than \$35,000 per year (19.9%), and the elderly and disabled (16.4%). Headache is consistently the fourth or fifth most common reason for visits to the emergency department, accounting for roughly 3% of all emergency department visits annually. In reproductive aged women, headache is the third leading cause of emergency department visits.

CONCLUSIONS: Severe headache and migraine remain important public health problems that are more common and burdensome for women, particularly women of childbearing age, and other historically disadvantaged segments of the population. These inequities could be exacerbated if new high-cost treatments are inaccessible to those who need them most.

HEADACHE and MIGRAINE (Continued)

[White matter hyperintensities and headache: A population-based imaging study \(HUNT MRI\).](#)

[Honningsvåg LM](#)¹, [Håberg AK](#)^{1,2}, [Hagen K](#)^{1,3}, [Kvistad KA](#)^{1,2}, [Stovner LJ](#)^{1,3}, [Linde M](#)^{1,3}.

Cephalalgia. 2018 Jan 1:333102418764891. doi: 10.1177/0333102418764891. PMID: 29528690. [Epub ahead of print]

Objective To examine the relationship between white matter hyperintensities and headache. **Methods** White matter hyperintensities burden was assessed semi-quantitatively using Fazekas and Scheltens scales, and by manual and automated volumetry of MRI in a sub-study of the general population-based Nord-Trøndelag Health Study (HUNT MRI). Using validated questionnaires, participants were categorized into four cross-sectional headache groups: Headache-free (n = 551), tension-type headache (n = 94), migraine (n = 91), and unclassified headache (n = 126). Prospective questionnaire data was used to further categorize participants into groups according to the evolution of headache during the last 12 years: Stable headache-free, past headache, new onset headache, and persistent headache. White matter hyperintensities burden was compared across headache groups using adjusted multivariate regression models. **Results** Individuals with tension-type headache were more likely to have extensive white matter hyperintensities than headache-free subjects, with this being the case across all methods of white matter hyperintensities assessment (Scheltens scale: Odds ratio, 2.46; 95% CI, 1.44-4.20). Migraine or unclassified headache did not influence the odds of having extensive white matter hyperintensities. Those with new onset headache were more likely to have extensive white matter hyperintensities than those who were stable headache-free (Scheltens scale: Odds ratio, 2.24; 95% CI, 1.13-4.44). **Conclusions** Having tension-type headache or developing headache in middle age was linked to extensive white matter hyperintensities. These results were similar across all methods of assessing white matter hyperintensities. If white matter hyperintensities treatment strategies emerge in the future, this association should be taken into consideration.

CHRONIC PAIN

[Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial.](#)

[Krebs EE](#)^{1,2}, [Gravelly A](#)¹, [Nugent S](#)¹, [Jensen AC](#)¹, [DeRonne B](#)¹, [Goldsmith ES](#)^{1,3}, [Kroenke K](#)^{4,5,6}, [Bair MJ](#)^{4,5,6}, [Noorbaloochi S](#)^{1,2}.

JAMA. 2018 Mar 6;319(9):872-882. doi: 10.1001/jama.2018.0899. PMID: 29509867.

Importance: Limited evidence is available regarding long-term outcomes of opioids compared with nonopioid medications for chronic pain.

Objective: To compare opioid vs nonopioid medications over 12 months on pain-related function, pain intensity, and adverse effects.

Design, Setting, and Participants: Pragmatic, 12-month, randomized trial with masked outcome assessment. Patients were recruited from Veterans Affairs primary care clinics from June 2013 through December 2015; follow-up was completed December 2016. Eligible patients had moderate to severe chronic back pain or hip or knee osteoarthritis pain despite analgesic use. Of 265 patients enrolled, 25 withdrew prior to randomization and 240 were randomized.

Interventions: Both interventions (opioid and nonopioid medication therapy) followed a treat-to-target strategy aiming for improved pain and function. Each intervention had its own prescribing strategy that included multiple medication options in 3 steps. In the opioid group, the first step was immediate-release morphine, oxycodone, or hydrocodone/acetaminophen. For the nonopioid group, the first step was acetaminophen (paracetamol) or a nonsteroidal anti-inflammatory drug. Medications were changed, added, or adjusted within the assigned treatment group according to individual patient response.

Main Outcomes and Measures: The primary outcome was pain-related function (Brief Pain Inventory [BPI] interference scale) over 12 months and the main secondary outcome was pain intensity (BPI severity scale). For both BPI scales (range, 0-10; higher scores = worse function or pain intensity), a 1-point improvement was clinically important. The primary adverse outcome was medication-related symptoms (patient-reported checklist; range, 0-19).

Results: Among 240 randomized patients (mean age, 58.3 years; women, 32 [13.0%]), 234 (97.5%) completed the trial. Groups did not significantly differ on pain-related function over 12 months (overall P = .58); mean 12-month BPI interference was 3.4 for the opioid group and 3.3 for the nonopioid group (difference, 0.1 [95% CI, -0.5 to 0.7]). Pain intensity was significantly better in the nonopioid group over 12 months (overall P = .03); mean 12-month BPI severity was 4.0 for the opioid group and 3.5 for the nonopioid group (difference, 0.5 [95% CI, 0.0 to 1.0]). Adverse medication-related symptoms were significantly more common in the opioid group over 12 months (overall P = .03); mean medication-related symptoms at 12 months were 1.8 in the opioid group and 0.9 in the nonopioid group (difference, 0.9 [95% CI, 0.3 to 1.5]).

Conclusions and Relevance: Treatment with opioids was not superior to treatment with nonopioid medications for improving pain-related function over 12 months. Results do not support initiation of opioid therapy for moderate to severe chronic back pain or hip or knee osteoarthritis pain.

Trial Registration: clinicaltrials.gov Identifier: [NCT01583985](#).

CHRONIC PAIN (Continued)**[Chronic Pain, TBI, and PTSD in Military Veterans: a Link to Suicidal Ideation and Violent Impulses?](#)**

[Blakey SM](#)¹, [Wagner HR](#)², [Naylor J](#)², [Branco M](#)², [Lane I](#)³, [Sallee M](#)³, [Kimbrel NA](#)²; [VA Mid-Atlantic MIRECC Workgroup](#), [Elbogen EB](#)².

J Pain. 2018 Mar 8. pii: S1526-5900(18)30092-0. doi: 10.1016/j.jpain.2018.02.012. PMID: 29526669. [Epub ahead of print]

The polytrauma clinical triad refers to the co-occurrence of chronic pain, traumatic brain injury (TBI), and posttraumatic stress disorder (PTSD). Despite research implicating dyadic relationships between these conditions and adverse outcomes, scant research has examined the polytrauma clinical triad's relation to suicide or violence. The present cross-sectional study was designed to examine whether this complex clinical presentation increases risk of suicidal ideation and violent impulses after accounting for other established risk factors. Veterans who served in the military since 9/11/01 (N = 667) who reported chronic pain completed an interview and self-report battery. Bivariate analyses showed that suicidal ideation and violent impulses both correlated with PTSD, TBI+PTSD, pain intensity and interference, drug abuse, and major depressive disorder (MDD). Multiple regression analyses showed that (a) race, chronic pain with PTSD, alcohol abuse, and MDD significantly predicted suicidal ideation, (b) pain interference, chronic pain with TBI, chronic pain with PTSD, chronic pain with TBI+PTSD, drug abuse, and MDD significantly predicted violent impulses, and (c) pain interference was a more critical predictor of suicidal and violent ideation than pain intensity. Implications for risk assessment and treatment are discussed.

PERSPECTIVE: This article presents results from a study examining predictors of suicide and violence risk among a sample of post-9/11 United States Veterans with chronic pain. Healthcare professionals should assess for pain interference, TBI, posttraumatic stress disorder, depression, and alcohol/drug abuse when conducting risk assessments with this population.

[Pharmacoepidemiologic analyses of opioid use among OEF/OIF/OND veterans.](#)

[Hudson TJ](#)¹, [Painter JT](#), [Martin BC](#), [Austen MA](#), [Williams JS](#), [Fortney JC](#), [Sullivan MD](#), [Edlund MJ](#).

Pain. 2017 Jun;158(6):1039-1045. doi: 10.1097/j.pain.0000000000000874. PMID: 28195856.

There is a great deal of concern about opioid use in veterans, particularly those who served in Afghanistan (OEF) and Iraq (OIF and OND). The current study provides a detailed pharmacoepidemiologic analysis of opioid use among OEF/OIF/OND veterans from FY09 to FY12. Data from 3 data repositories from the Veterans Health Administration (VHA) were used to describe demographic, clinical, and medication characteristics associated with opioid use among OEF/OIF/OND veterans and among those with TBI. Logistic regression models were used to identify risks associated with chronic opioid use in FY12. Approximately 23% of all OEF/OIF/OND veterans and 35% of those with TBI received any opioid medications. Most received moderate doses ranging from 26 to 30 mg morphine equivalent dose daily. Median days of opioid use for all OEF/OIF/OND veterans were 30 to 40 days. Factors associated with chronic use in both groups included young age, male sex, white race, being married, and living in rural areas. A diagnosis of PTSD (odds ratio [OR] = 1.22, P < 0.0001), major depressive disorder (OR = 1.14, P < 0.0001), and tobacco use disorder (OR = 1.18, P < 0.0001) were strongly associated with chronic opioid use. Back pain was also strongly associated with chronic use (OR = 2.50, P < 0.0001). As pain severity increased the odds of chronic opioid use also increased: mild pain (OR = 3.76, P < 0.0001), moderate pain (OR = 6.80, P < 0.0001), and severe pain (OR = 8.49, P < 0.0001). Opioid use among OEF/OIF/OND veterans is characterized by moderate doses that are used over relatively long periods of time by a minority of veterans.

CHRONIC PAIN (Continued)**Prevalence of and characteristics associated with insomnia and obstructive sleep apnea among veterans with knee and hip osteoarthritis.**

[Taylor SS¹](#), [Hughes JM²](#), [Coffman CJ^{2,3}](#), [Jeffreys AS²](#), [Ulmer CS^{2,3}](#), [Oddone EZ^{2,3}](#), [Bosworth HB^{2,3}](#), [Yancy WS Jr^{2,3}](#), [Allen KD^{2,4}](#).

BMC Musculoskelet Disord. 2018 Mar 9;19(1):79. doi: 10.1186/s12891-018-1993-y. PMID: 29523117.

BACKGROUND: Few studies have examined patterns of specific sleep problems among individuals with osteoarthritis (OA). The primary objective of this study was to examine prevalence of symptoms of insomnia and obstructive sleep apnea (OSA) among Veterans with OA. Secondary objectives were to assess proportions of individuals with insomnia and OSA symptoms who may have been undiagnosed and to examine Veterans' characteristics associated with insomnia and OSA symptoms.

METHODS: Veterans (n = 300) enrolled in a clinical trial completed the Insomnia Severity Index (ISI) and the Berlin Questionnaire (BQ) at baseline; proportions of participants with symptoms consistent with insomnia and OSA were calculated, using standard cut-offs for ISI and BQ. For Veterans with insomnia and OSA symptoms, electronic medical records were searched to identify whether there was a diagnosis code for these conditions. Multivariable linear (ISI) and logistic (BQ) regression models examined associations of the following characteristics with symptoms of insomnia and OSA: age, gender, race, self-reported general health, body mass index (BMI), diagnosis of post-traumatic stress disorder (PTSD), pain severity, depressive symptoms, number of joints with arthritis symptoms and opioid use.

RESULTS: Symptoms consistent with insomnia and OSA were found in 53 and 66% of this sample, respectively. Among participants screening positive for insomnia and OSA, diagnosis codes for these disorders were present in the electronic medical record for 22 and 51%, respectively. Characteristics associated with insomnia were lower age (β (SE) = - 0.09 (0.04), 95% confidence interval [CI] = - 0.16, - 0.02), having a PTSD diagnosis (β (SE) = 1.68 (0.73), CI = 0.25, 3.11), greater pain severity (β (SE) = 0.36 (0.09), CI = 0.17, 0.55), and greater depressive symptoms (β (SE) = 0.84 (0.07), CI = 0.70, 0.98). Characteristics associated with OSA were higher BMI (odds ratio [OR] = 1.13, CI = 1.06, 1.21), greater depressive symptoms (OR = 1.12, CI = 1.05, 1.20), and opioid use (OR = 0.51, CI = 0.26, 0.99).

CONCLUSIONS: Insomnia and OSA symptoms were very common in Veterans with OA, and a substantial proportion of individuals with symptoms may have been undiagnosed. Characteristics associated with insomnia and OSA symptoms were consistent with prior studies.

TRIAL REGISTRATION: [NCT01130740](#) .

Yoga improves quality of life and fall risk-factors in a sample of people with chronic pain and Type 2 Diabetes.

[Schmid AA¹](#), [Atler KE²](#), [Malcolm MP²](#), [Grimm LA²](#), [Klinedinst TC²](#), [Marchant DR³](#), [Marchant TP³](#), [Portz JD⁴](#).

Complement Ther Clin Pract. 2018 Feb 15. pii: S1744-3881(17)30438-3. doi: 10.1016/j.ctcp.2018.01.003. PMID: 29526474. [Epub ahead of print]

OBJECTIVE: Assess pre to-post outcomes for people with chronic pain and Type 2 Diabetes Mellitus (T2DM) randomized to an 8-week yoga intervention or usual care.

METHODS: Participants were included if they self-reported: chronic pain; T2DM; >18 years old; no exercise restrictions or consistent yoga; and consented to the study.

RESULTS: After yoga, there were significant improvements in: Brief Pain Inventory pain interference (49 ± 15.00 vs. 41.25 ± 19.46 , $p = .034$); Fullerton Advanced Balance scale (14.2 ± 14.1 vs. 20.4 ± 13.5 , $p = .03$); upper extremity strength (7.7 ± 6.3 vs. 10.8 ± 6.5 , $p = .02$); lower extremity strength (4.1 ± 3.8 vs. 6.7 ± 4.8 , $p = .02$); and RAND 36 item Health Survey quality of life scores (81.1 ± 7.7 vs. 91.9 ± 8.9 , $p = .04$). Balance scores became significantly worse during the 8 weeks for people randomized to the control (27.1 ± 9.9 vs. 21.7 ± 13.4 , $p = .01$).

CONCLUSION: Data from this small RCT indicates yoga may be therapeutic and may improve multiple outcomes in this seemingly at-risk population.

CLINICAL TRIALS NUMBER: [NCT03010878](#).

CHRONIC PAIN (Continued)**Tai Chi for older adults with chronic multisite pain: a randomized controlled pilot study.**

[You T](#)¹, [Ogawa EF](#)², [Thapa S](#)³, [Cai Y](#)³, [Zhang H](#)⁴, [Nagae S](#)², [Yeh GY](#)^{5,6}, [Wayne PM](#)^{6,7}, [Shi L](#)³, [Leveille SG](#)^{3,5,6}.

Aging Clin Exp Res. **2018 Mar 6**. doi: 10.1007/s40520-018-0922-0. PMID: 29512041. PMID: 29512041. [Epub ahead of print]

BACKGROUND: Chronic pain is associated with poorer cognition and mobility, and fall risk in older adults.

AIMS: To investigate the feasibility of a randomized controlled trial of mind-body exercise (Tai Chi) versus a light physical exercise in older adults with multisite pain.

METHODS: Adults aged ≥ 65 years with multisite pain who reported falling in the past year or current use of an assistive device were recruited from Boston area communities. Participants were randomized to either a Tai Chi or a light physical exercise program, offered twice weekly for 12 weeks. The primary outcomes were feasibility and acceptability. Secondary outcomes included pain characteristics, cognition, physical function, gait mobility, fear of falling, and fall rate.

RESULTS: Of 176 adults screened, 85 were eligible, and 54 consented and were enrolled (average age 75 ± 8 years; 96.30% white; 75.93% female). The dropout rate was 18% for Tai Chi and 12% for light physical exercise. For those completing the study, exercise class attendance rate was 76% for Tai Chi and 82% for light physical exercise. There were no significant group differences in most secondary outcomes. Tai Chi significantly lowered pain severity (4.58 ± 1.73 - 3.73 ± 1.79 , $p < 0.01$) and pain interference (4.20 ± 2.53 to 3.16 ± 2.28 , $p < 0.05$), reduced fear of falling (90.82 ± 9.59 to 96.84 ± 10.67 , $p < 0.05$), and improved several single-task and dual-task gait variables, while light physical exercise did not change these measures.

DISCUSSION AND CONCLUSIONS: This study demonstrated the feasibility and acceptability of conducting a larger randomized controlled trial in older adults with multisite pain. Study findings and challenges encountered will inform future research.

Genome-wide methylation analysis of a large population sample shows neurological pathways involvement in chronic widespread musculoskeletal pain.

[Livshits G](#)¹, [Malkin I](#), [Freidin MB](#), [Xia Y](#), [Gao F](#), [Wang J](#), [Spector TD](#), [MacGregor A](#), [Bell JT](#), [Williams FMK](#).

Pain. **2017 Jun**;158(6):1053-1062. doi: 10.1097/j.pain.0000000000000880. PMCID: PMC5427989. PMID: 28221285.

Chronic widespread musculoskeletal pain (CWP), has a considerable heritable component, which remains to be explained. Epigenetic factors may contribute to and account for some of the heritability estimate. We analysed epigenome-wide methylation using MeDIPseq in whole blood DNA from 1708 monozygotic and dizygotic Caucasian twins having CWP prevalence of 19.9%. Longitudinally stable methylation bins (lsBINs), were established by testing repeated measurements conducted ≥ 3 years apart, $n = 292$. DNA methylation variation at lsBINs was tested for association with CWP in a discovery set of 50 monozygotic twin pairs discordant for CWP, and in an independent dataset ($n = 1608$ twins), and the results from the 2 samples were combined using Fisher method. Functional interpretation of the most associated signals was based on functional genomic annotations, gene ontology, and pathway analyses. Of 723,029 signals identified as lsBINs, 26,399 lsBINs demonstrated the same direction of association in both discovery and replication datasets at nominal significance ($P \leq 0.05$). In the combined analysis across 1708 individuals, whereas no lsBINs showed genome-wide significance ($P < 10^{-8}$), 24 signals reached $p \leq 9E^{-5}$, and these included association signals mapping in or near to IL17A, ADIPOR2, and TNFRSF13B. Bioinformatics analyses of the associated methylation bins showed enrichment for neurological pathways in CWP. We estimate that the variance explained by epigenetic factors in CWP is 6%. This, the largest study to date of DNA methylation in CWP, points towards epigenetic modification of neurological pathways in CWP and provides proof of principle of this method in teasing apart the complex risk factors for CWP.

CHRONIC PAIN (Continued)

[Comparative Effectiveness of Treatments for Chronic Low Back Pain: A Multiple Treatment Comparison Analysis.](#)

[Rihn JA](#)¹, [Radcliff K](#), [Norvell DC](#), [Eastlack R](#), [Phillips FM](#), [Berland D](#), [Sherry N](#), [Freedman M](#), [Vaccaro AR](#).

Clin Spine Surg. **2017 Jun**;30(5):204-225. doi: 10.1097/BSD.0000000000000410. PMID: 27831982.

STUDY DESIGN: A systematic review and network meta-analysis.

OBJECTIVE: To determine current treatment options of chronic low back pain (LBP) as defined by randomized controlled trials (RCTs) and to compare effectiveness of those treatments using a mixed-treatment comparison (MTC).

SUMMARY OF BACKGROUND DATA: It is important to provide an evidence-based assessment of the treatment options that exist for LBP.

METHODS: A systematic search of RCTs was conducted in MEDLINE and the Cochrane Collaboration Library from 1990 to 2014. From the selected studies, we extracted preoperative and postoperative ODI and VAS back pain scores, additional surgeries, and complications. Standard and network meta-analytic techniques were used.

RESULTS: Twelve RCTs were included in the analysis: 5 total disk replacement (TDR) versus fusion; 1 TDR versus exercise and cognitive behavioral therapy (CBT); 5 fusion versus exercise and CBT; and 1 fusion versus physical therapy (PT). On the basis of MTC, with respect to ODI change scores, the pooled mean difference favoring fusion over exercise and CBT was 2.0 points (95% CI, -1.2 to 4.8). The pooled mean difference favoring TDR over exercise and CBT was 6.4 points (95% CI, 3.2-9.3). The pooled mean difference favoring fusion over PT was 8.8 points (95% CI, 4.1-13.6). The pooled mean differences favoring TDR over fusion was 4.4 points (95% CI, 2.37-6.63). For PT versus structured exercise with CBT, the pooled mean difference favoring exercise with CBT over PT was 6.8 points (95% CI, 1.5-12.8). For TDR versus PT, the pooled mean difference favoring TDR over PT was 13.2 points (95% CI, 8.0-18.4). Additional surgery rates were similar between treatment options.

CONCLUSIONS: All 4 treatments provided some benefit to patients with chronic LBP. According to the MTC analysis, TDR may be the most effective treatment and PT the least effective treatment for chronic LBP. This review is based on a limited number of RCT studies and does not support any 1 treatment modality for all patients.

OTHER RESEARCH OF INTEREST

[Racial, Ethnic, and Gender Equity in Veteran Satisfaction with Health Care in the Veterans Affairs Health Care System.](#)

[Zickmund SL](#)^{1,2}, [Burkitt KH](#)³, [Gao S](#)³, [Stone RA](#)^{3,4}, [Jones AL](#)^{5,6}, [Hausmann LRM](#)^{3,7}, [Switzer GE](#)^{3,7,8}, [Borrero S](#)^{3,7}, [Rodriguez KL](#)^{3,7}, [Fine MJ](#)^{3,7}.

J Gen Intern Med. **2018 Mar**;33(3):305-331. doi: 10.1007/s11606-017-4221-9. PMCID: PMC5834960. PMID: 29313226.

BACKGROUND: Patient satisfaction is an important dimension of health care quality. The Veterans Health Administration (VA) is committed to providing high-quality care to an increasingly diverse patient population.

OBJECTIVE: To assess Veteran satisfaction with VA health care by race/ethnicity and gender.

DESIGN AND PARTICIPANTS: We conducted semi-structured telephone interviews with gender-specific stratified samples of black, white, and Hispanic Veterans from 25 predominantly minority-serving VA Medical Centers from June 2013 to January 2015.

MAIN MEASURES: Satisfaction with health care was assessed in 16 domains using five-point Likert scales. We compared the proportions of Veterans who were very satisfied, somewhat satisfied, and less than satisfied (i.e., neither satisfied nor dissatisfied, somewhat dissatisfied, or very dissatisfied) in each domain, and used random-effects multinomial regression to estimate racial/ethnic differences by gender and gender differences by race/ethnicity.

KEY RESULTS: Interviews were completed for 1222 of the 1929 Veterans known to be eligible for the interview (63.3%), including 421 white, 389 black, and 396 Hispanic Veterans, 616 of whom were female. Veterans were less likely to be somewhat satisfied or less than satisfied versus very satisfied with care in each of the 16 domains. The highest satisfaction ratings were reported for costs, outpatient facilities, and pharmacy (74-76% very satisfied); the lowest ratings were reported for access, pain management, and mental health care (21-24% less than satisfied). None of the joint tests of racial/ethnic or gender differences in satisfaction (simultaneously comparing all three satisfaction levels) was statistically significant ($p > 0.05$). Pairwise comparisons of specific levels of satisfaction revealed racial/ethnic differences by gender in three domains and gender differences by race/ethnicity in five domains, with no consistent directionality across demographic subgroups.

CONCLUSIONS: Our multisite interviews of a diverse sample of Veterans at primarily minority-serving sites showed generally high levels of health care satisfaction across 16 domains, with few quantitative differences by race/ethnicity or gender.

OTHER RESEARCH OF INTEREST (Continued)**[A Randomized Controlled Trial for Veterans with PTSD and Substance Use Disorder: Creating Change versus Seeking Safe.](#)**

[Najavits LM](#)^{1,2,3}, [Krinsley K](#)¹, [Waring ME](#)^{4,3}, [Gallagher MW](#)⁵, [Skidmore C](#)¹.

Subst Use Misuse. **2018 Feb 20**:1-13. doi: 10.1080/10826084.2018.1432653. PMID: 29461920. [Epub ahead of print]

BACKGROUND: Posttraumatic stress disorder (PTSD) and substance use disorder (SUD) co-occur in military veterans and other populations.

OBJECTIVE: To conduct a randomized controlled trial to compare a new past-focused treatment (Creating Change; CC), to a well-established, evidence-based present-focused treatment for PTSD/SUD (Seeking Safety; SS), on symptoms of both disorders. CC guides patients to process the past through exploration of PTSD/SUD life themes and memories whereas SS focuses on coping skills in the present.

METHODS: Fifty-two male and female veterans with current PTSD/SUD were randomized (n = 26 per treatment) and assessed at baseline, end-of-treatment and 3-month follow-up. They received 17 individual one-hour sessions.

RESULTS: Intent-to-treat analyses indicated that both conditions improved over time, with no difference between conditions, on PTSD, alcohol use, and drug use (our primary outcomes) as well as mental health symptoms, quality of life, self-efficacy, and SUD cognitions. Effect sizes were medium except for alcohol use, which was large.

Change over time reflected improvement from baseline to end-of-treatment, with gains sustained at follow-up, although alcohol use showed continued improvement from end-of-treatment to follow-up. Both treatments evidenced a strong safety profile; and attendance, alliance, and treatment satisfaction were also very strong.

CONCLUSIONS/IMPORTANCE: CC has promise as a PTSD/SUD therapy with strong public health relevance and the potential to fill important gaps in the field. We used minimal exclusionary criteria to obtain a real-world sample, which was severe-predominantly substance-dependent with chronic PTSD and additional psychiatric diagnoses. Future research is warranted, especially on nonveteran samples and treatment mechanisms of action.

[Long-Term Functional Outcomes in Military Service Members and Veterans After Traumatic Brain Injury/Polytrauma Inpatient Rehabilitation.](#)

[Gray M](#)¹, [Chung J](#)¹, [Aguila F](#)¹, [Williams TG](#)², [Teraoka JK](#)³, [Harris OA](#)⁴.

Arch Phys Med Rehabil. **2018 Feb**;99(2S):S33-S39. doi: 10.1016/j.apmr.2017.08.465. PMID: 28866009. Epub 2017 Sep 1.

OBJECTIVE: To determine the effect of the established polytrauma/traumatic brain injury (TBI) infrastructure on immediate posttreatment functional gains, the long-term sustainability of any gains, and participation-related community reintegration outcomes in a baseline cohort of patients 8 years postadmission.

DESIGN: Retrospective review and prospective repeated measures of an inception cohort.

SETTING: Polytrauma rehabilitation center (PRC).

PARTICIPANTS: Patients consecutively admitted to the PRC inpatient rehabilitation unit during its first full fiscal year, 2006 (N=44).

INTERVENTIONS: The PRC infrastructure and formalized rehabilitation for polytrauma/TBI.

MAIN OUTCOME MEASURES: FIM scores at admission, discharge, 3 months, and 8 years postdischarge; participation-related socioeconomic factors reflecting community reintegration 8 years after admission.

RESULTS: Functional gains were statistically significantly increased from admission to discharge. Improvements were maintained at both 3 months postdischarge and 8 years postdischarge. The socioeconomic data collected at 8-year follow-up showed >50% either competitively employed or continuing their education and 100% living in a noninstitutionalized setting.

CONCLUSIONS: This study addresses a concern regarding the long-term functional outcomes of rehabilitation patients treated by the established infrastructure of the Polytrauma System of Care inpatient rehabilitation centers. The results suggest that polytrauma/TBI rehabilitation care using a comprehensive, integrated approach is effective and durable in achieving functional gains and successful community reintegration within our initial PRC cohort. Follow-up of subsequent fiscal year cohorts would add to the validity of these outcome findings.

OTHER RESEARCH OF INTEREST (Continued)

[Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults.](#)

[Sorrells SF^{1,2}](#), [Paredes MF^{1,3}](#), [Cebrian-Silla A⁴](#), [Sandoval K^{1,3}](#), [Qi D⁵](#), [Kelley KW¹](#), [James D¹](#), [Mayer S^{1,3}](#), [Chang J⁶](#), [Auguste KI²](#), [Chang EF²](#), [Gutierrez AJ⁷](#), [Kriegstein AR^{1,3}](#), [Mathern GW^{8,9}](#), [Oldham MC^{1,2}](#), [Huang EJ¹⁰](#), [Garcia-Verdugo JM⁴](#), [Yang Z⁵](#), [Alvarez-Buylla A^{1,2}](#).

Nature. **2018 Mar 15**;555(7696):377-381. doi: 10.1038/nature25975. PMID: 29513649. Epub 2018 Mar 7.

New neurons continue to be generated in the subgranular zone of the dentate gyrus of the adult mammalian hippocampus. This process has been linked to learning and memory, stress and exercise, and is thought to be altered in neurological disease. In humans, some studies have suggested that hundreds of new neurons are added to the adult dentate gyrus every day, whereas other studies find many fewer putative new neurons. Despite these discrepancies, it is generally believed that the adult human hippocampus continues to generate new neurons. Here we show that a defined population of progenitor cells does not coalesce in the subgranular zone during human fetal or postnatal development. We also find that the number of proliferating progenitors and young neurons in the dentate gyrus declines sharply during the first year of life and only a few isolated young neurons are observed by 7 and 13 years of age. In adult patients with epilepsy and healthy adults (18-77 years; n = 17 post-mortem samples from controls; n = 12 surgical resection samples from patients with epilepsy), young neurons were not detected in the dentate gyrus. In the monkey (*Macaca mulatta*) hippocampus, proliferation of neurons in the subgranular zone was found in early postnatal life, but this diminished during juvenile development as neurogenesis decreased. We conclude that recruitment of young neurons to the primate hippocampus decreases rapidly during the first years of life, and that neurogenesis in the dentate gyrus does not continue, or is extremely rare, in adult humans. The early decline in hippocampal neurogenesis raises questions about how the function of the dentate gyrus differs between humans and other species in which adult hippocampal neurogenesis is preserved.

[Association of Dietary Inflammatory Potential With Colorectal Cancer Risk in Men and Women.](#)

[Tabung FK^{1,2}](#), [Liu L^{1,2,3,4,5}](#), [Wang W^{1,2}](#), [Fung TT^{1,6}](#), [Wu K¹](#), [Smith-Warner SA^{1,2}](#), [Cao Y^{1,7}](#), [Hu FB^{1,2,8}](#), [Ogino S^{2,4,9}](#), [Fuchs CS^{4,8,10}](#), [Giovannucci EL^{1,2,8}](#).

JAMA Oncol. **2018 Mar 1**;4(3):366-373. doi: 10.1001/jamaoncol.2017.4844. PMID: 29346484.

Importance: Inflammation is important in colorectal cancer development. Diet modulates inflammation and may thus be a crucial modifiable factor in colorectal cancer prevention.

Objective: To examine whether proinflammatory diets are associated with increased colorectal cancer risk by using an empirical dietary inflammatory pattern (EDIP) score based on a weighted sum of 18 food groups that characterizes dietary inflammatory potential based on circulating levels of inflammation biomarkers.

Design, Settings, and Participants: Cohort study of 46 804 men (Health Professionals Follow-up Study: 1986-2012) and 74 246 women (Nurses' Health Study: 1984-2012) followed for 26 years to examine associations between EDIP scores and colorectal cancer risk using Cox regression. We also examined associations in categories of alcohol intake and body weight. Data analysis began January 17, 2017, and was completed August 9, 2017.

Exposures: EDIP scores calculated from food frequency questionnaires administered every 4 years.

Main Outcomes and Measures: Incident colorectal cancer.

Results: We documented 2699 incident colorectal cancer cases over 2 571 831 person-years of follow-up. Compared with participants in the lowest EDIP quintile (Q) who had a colorectal cancer incidence rate (per 100 000 person-years) of 113 (men) and 80 (women), those in the highest Q had an incidence rate of 151 (men) and 92 (women), leading to an unadjusted rate difference of 38 and 12 more colorectal cancer cases, respectively, among those consuming highly proinflammatory diets. Comparing participants in the highest vs lowest EDIP Qs in multivariable-adjusted analyses, higher EDIP scores were associated with 44% (men: hazard ratio [HR], 1.44; 95% CI, 1.19-1.74; P < .001 for trend), 22% (women: HR, 1.22; 95% CI, 1.02-1.45; P = .007 for trend), and 32% (men and women: pooled HR, 1.32; 95% CI, 1.12-1.55; P < .001 for trend) higher risk of developing colorectal cancer. In both men and women, associations were observed in all anatomic subsites except for the rectum in women. In subgroups (P ≤ .02 for all interactions), associations differed by alcohol intake level, with stronger associations among men (Q5 vs Q1 HR, 1.62; 95% CI, 1.05-2.49; P = .002 for trend) and women (Q5 vs Q1 HR, 1.33; 95% CI, 0.97-1.81; P = .03 for trend) not consuming alcohol; and by body weight, with stronger associations among overweight/obese men (Q5 vs Q1 HR, 1.48; 95% CI, 1.12-1.94; P = .008 for trend) and lean women (Q5 vs Q1 HR, 1.31; 95% CI, 0.99-1.74; P = .01 for trend).

Conclusions and Relevance: Findings suggest that inflammation is a potential mechanism linking dietary patterns and colorectal cancer development. Interventions to reduce the adverse role of proinflammatory diets may be more effective among overweight/obese men and lean women or men and women who do not consume alcohol.