GULF WAR ILLNESS

Oleoylethanolamide treatment reduces neurobehavioral deficits and brain pathology in a mouse model of Gulf War Illness.

Joshi U[1,2,3], Evans JE[4,5], Joseph R[4,5], Emmerich T[4,5], Saltiel N[4,5], Lungmus C[4,5], Oberlin S[4], Langlois H[4,5], Ojo J[4,6], Mouzon B[4,6,5], Paris D[4,6,5], Mullan M[4,6,5], Jin C[4], Klimas N[7,8], Sullivan K[9], Crawford F[4,6,5], Abdullah L[4,6,5].

Sci Rep. **2018 Aug 27**;8(1):12921. doi: 10.1038/s41598-018-31242-7. PMCID: PMC6110778.

There are nearly 250,000 Gulf War (GW) veterans who suffer from Gulf War Illness (GWI), a multi-symptom condition that remains untreatable. The main objective was to determine if targeting peroxisomal function could be of therapeutic value in GWI. We performed a pilot study that showed accumulation of very long chain fatty acids (VLCFA), which are metabolized in peroxisomes, in plasma from veterans with GWI. We then examined if targeting peroxisomal β-oxidation with oleoylethanolamide (OEA) restores these lipids to the normal levels and mitigates neuroinflammation and neurobehavioral deficits in a well-established mouse model of GWI. In GWI mice, treatment with OEA corresponded with cognitive benefits and reduced fatigue and disinhibition-like behavior in GWI mice. Biochemical and molecular analysis of the brain tissue showed reduced astroglia and microglia staining, decreased levels of chemokines and cytokines, and decreased NFκB phosphorylation. Treatment with OEA reduced accumulation of peroxisome specific VLCFA in the brains of GWI mice. These studies further support the translational value of targeting peroxisomes. We expect that OEA may be a potential therapy for treating neurobehavioral symptoms and the underlying lipid dysfunction and neuroinflammation associated with GWI. Oleoylethanolamide is available as a dietary supplement, making it appealing for human translational studies.

CHRONIC FATIGUE SYNDROME

New ME/CFS Web Content for Healthcare Providers

The Centers for Disease Control and Prevention (CDC), Thursday, **July 12, 2018.** Media Advisory.

The Centers for Disease Control and Prevention (CDC) today released an updated website (https://www.cdc.gov/me-cfs/healthcare-providers/index.html) for healthcare providers about myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). The new site is designed specifically with clinicians in mind and offers information about how physicians can better assess and help their patients manage the illness. CDC's new ME/CFS web content includes information about how ME/CFS presents and its clinical course, the diagnostic criteria released in 2015 by the Institute of Medicine (now National Academy of Medicine), and how healthcare providers can approach medical care for people who have been diagnosed with ME/CFS. The new web content is part of an effort to increase awareness among healthcare providers about this condition.

An estimated 836,000 to 2.5 million Americans suffer from ME/CFS, a serious, long-term illness that can severely impair their abilities to live normal lives. Many people struggle with symptoms for years before receiving a diagnosis and there is no definitive diagnostic test. One of the reasons that people with ME/CFS are not diagnosed is a lack of awareness and understanding about ME/CFS among healthcare providers. Most medical schools in the United States do not have ME/CFS as part of their physician training. Less than one-third of medical school curricula and less than half of medical textbooks in the U.S. include information about ME/CFS.

The new website notes that anyone can get ME/CFS. While most common in people between 40 and 60 years old, the illness affects children, adolescents, and adults of all ages. More education for doctors, nurses, and other healthcare providers is urgently needed, so they are prepared to provide timely diagnosis and appropriate care for patients with ME/CFS.

Besides information for healthcare providers, the updated ME/CFS website includes resources for patients, families, and schools. The site also features patients' personal accounts of living with ME/CFS in the recently added section, Voice of the Patient (https://www.cdc.gov/me-cfs/patient-stories/index.html).

CHRONIC FATIGUE SYNDROME (Continued)

Oxidative Stress is a Convincing Contributor to Idiopathic Chronic Fatigue.

Lee JS[1], Kim HG[1], Lee DS[2], Son CG[3].

Sci Rep. **2018 Aug 27**;8(1):12890. doi: 10.1038/s41598-018-31270-3. PMCID: PMC6110864. PMID: 30150620.

The linkage between oxidative stress and idiopathic chronic fatigue (ICF) has not been explored in detail. This study thoroughly compared the serum levels of biomarkers for oxidative stress and antioxidants from 103 subjects with ICF (20 men and 83 women) to those of 82 healthy volunteers (27 men and 55 women). Oxidative parameters, which included reactive oxygen species (ROS), malondialdehyde (MDA) and F2-isoprotan, and tumor necrosis factor-alpha (TNF-α) were significantly elevated, while antioxidant parameters, which included total antioxidant activity (TAC), catalase, superoxide dismutase, SOD and GSH activity, were decreased compared to those of healthy subjects (by approximately 1.2- to 2.3-fold, $p < 0.05$ or 0.01). Our results confirmed that oxidative stress is a key contributor in the pathophysiology of ICF, and firstly explored the features of oxidative stress parameters in ICF subjects compared to a healthy population.

Chronic fatigue syndrome and the somatic expression of emotional distress: Applying the concept of illusory mental health to address the controversy.

Bram AD[1,2,3], Gottschalk KA[4], Leeds WM[3,5].

J Clin Psychol. **2018 Aug 28**. doi: 10.1002/jclp.22692. PMID: 30152867. [Epub ahead of print]

OBJECTIVE: The process of somatization in chronic fatigue syndrome (CFS) was investigated using the concept of illusory mental health (IMH). IMH involves self-reporting low emotional distress alongside performance-based assessment of distress.

METHOD: We studied IHM and physical symptoms in 175 women across four groups: (a) CFS plus depression; (b) CFS with no depression (CFS-ND); (c) depressive disorder without CFS; and (d) healthy controls (HC). IMH was assessed using a self-report measure plus the performance-based Early Memory Index (EMI).

RESULTS: CFS-NDs were no more likely to have IMH compared with HCs. Among the CFS-NDs, IMH was associated with more physical symptoms. For CFS-NDs, EMI added meaningfully beyond self-reported mental health in predicting physical symptoms.

CONCLUSION: Findings refute reducing CFS to somatization, but there is a subgroup of CFS whose lacking access to emotional distress is associated with heightened physical symptomatology.

HEADACHE and MIGRAINE

Accelerating Clinical Research Using Headache Common Data Elements.

Oshinsky ML[1], Tanveer S[2], Hershey A[3].

Headache. **27 Aug 2018**;58(7):928-930. doi: 10.1111/head.13352. PMID: 30152159. E-pub: 2018 Jul

The National Institute of Neurological Disorders and Stroke (NINDS) Headache Version 2.0 Common Data Elements (CDEs) are a free resource available for researchers to include in clinical trials and research studies to improve data quality and comparison across studies. In the era of big data, it is becoming increasingly important to facilitate collaboration between researchers and tools for interoperability. By working together and toward a common goal, the headache scientific community will be able to disseminate evidence-based information to health care providers and patients suffering from headache and migraine.

The goals of the Headache Version 2.0 CDEs project is to: (1) increase the efficiency and effectiveness of headache clinical research and in turn, clinical treatment; (2) improve data quality; (3) facilitate data sharing; (4) effectively gather information into significant metadata results; (5) appreciably reduce study start-up time; (6) and aid new clinical investigators by providing easily available study data collection forms.

[See article full text in the Wiley Online Library for the journal Headache.]

HEADACHE and MIGRAINE (Continued)

Deployment-related Traumatic Brain Injury and Risk of New Episodes of Care for Back Pain in Veterans.

Suri P[1], Stolzmann K[2], Williams R[3], Pogoda TK[4].

J Pain. **2018 Aug 30**. pii: S1526-5900(18)30490-5. doi: 10.1016/j.jpain.2018.08.002. PMID: 30172707. [Epub ahead of print]

Traumatic brain injury (TBI) may be a predisposing factor to pain syndromes other than headache. We conducted a longitudinal cohort study among Veterans evaluated for TBI in the Department of Veterans Affairs (VA). Among 36,880 Veterans at baseline, 55% reported back pain. TBI history was classified by trained clinicians according to VA-Department of Defense criteria. 14,223 Veterans without back pain were followed for up to 6 years for new (incident) episodes of VA care for back pain. We estimated adjusted odds ratios (aORs), adjusted hazard ratios (aHRs) and 95% confidence intervals (CI), accounting for covariates. Deployment-related mild TBI was significantly associated with self-reported back pain in cross-sectional analyses (aOR 1.27, 95% CI 1.21-1.35), but not with incident episodes of VA care for back pain in longitudinal analysis (aHR 1.07, 95% CI 0.99-1.17). Deployment-related moderate/severe TBI was significantly associated with self-reported back pain in cross-sectional (aOR 1.74, 95% CI 1.58-1.91), and longitudinal analyses (aHR 1.20, 95% CI 1.05-1.38; p=.01). These findings indicate that deployment-related moderate/severe TBI confers increased back pain risk, but do not support a causal effect of deployment-related mild TBI on back pain.

PERSPECTIVE: Findings from this longitudinal study of Veterans indicate that deployment-related moderate/severe TBI confers increased back pain risk, but do not support a causal effect of deployment-related mild TBI on back pain.

Symptoms of Autonomic Dysfunction Among Those With Persistent Posttraumatic Headache Attributed to Mild Traumatic Brain Injury: A Comparison to Migraine and Healthy Controls.

Howard L[1], Dumkrieger G[1], Chong CD[1], Ross K[2], Berisha V[3], Schwedt TJ[1].

Headache. **2018 Aug 29**. doi: 10.1111/head.13396. PMID: 30156267. [Epub ahead of print]

BACKGROUND: Most persistent posttraumatic headaches (PPTH) have a phenotype that meets diagnostic criteria for migraine or probable migraine. Although symptoms of autonomic dysfunction have been well described among those with migraine, the presence and relative severity of such symptoms among those with PPTH have yet to be reported.

OBJECTIVE: The objective of this study was to assess and compare symptoms of autonomic dysfunction among those with PPTH attributed to mild traumatic brain injury (mTBI) vs migraine vs healthy controls using Composite Autonomic Symptom Score 31 (COMPASS-31) questionnaire scores.

METHODS: Individuals with PPTH (n = 56) (87.5% of whom had a migraine/probable migraine phenotype), migraine (n = 30), and healthy controls (n = 36) were prospectively assessed in this cross-sectional cohort study using the COMPASS-31 questionnaire. Total COMPASS-31 scores and individual domain scores (bladder, gastrointestinal, orthostatic intolerance, pupillomotor, secretomotor, vasomotor) were compared between subject groups.

RESULTS: COMPASS-31 mean total weighted score was 37.22 ± 15.44 in the PPTH group, 27.15 ± 14.37 in the migraine group, and 11.67 ± 8.98 for healthy controls. COMPASS-31 mean weighted total scores were significantly higher in those with PPTH vs migraine (P = .014), for PPTH vs healthy controls (P = .001), and for migraine vs healthy controls (P = .001). Those with PPTH had numerically higher scores for all COMPASS-31 domains compared to those with migraine, and the domain scores were significantly higher for orthostatic intolerance (PPTH = 4.80 ± 2.47 vs migraine = 3.33 ± 2.31, P = .027) and bladder (PPTH = 1.14 ± 1.45 vs migraine = 0.47 ± 0.73, P = .020). Among individuals with PPTH, post hoc correlations indicated a positive association between number of total lifetime TBIs with total weighted COMPASS-31 scores (rho = 0.32, P = .020), between years lived with headache and vasomotor domain subscores (rho = 0.27; P = .044), and between headache frequency with vasomotor domain subscores (rho = 0.27; P = .041).

CONCLUSIONS: Symptoms of autonomic dysfunction were greatest among those with PPTH compared to migraine and healthy controls. Among individuals with PPTH, number of lifetime TBIs was associated with greater symptoms of autonomic dysfunction, while greater headache burden was associated with higher vasomotor domain autonomic dysfunction subscores, potentially indicating that PPTH patients with higher disease burden have an increased risk for having autonomic dysfunction. Symptoms of autonomic dysfunction should be ascertained during the clinical management of patients with PPTH and might be a characteristic that helps differentiate PPTH from migraine.

HEADACHE and MIGRAINE (Continued)

Restless legs syndrome is associated with headache-related disabilities in patients with migraine: a prospective 7-year follow-up study.

Suzuki K[1], Suzuki S[1], Haruyama Y[2], Kobashi G[2], Shiina T[1], Hirata K[1].

Eur J Neurol. **2018 Aug 31**. doi: 10.1111/ene.13796. PMID: 30169898. [Epub ahead of print]

BACKGROUND: No prospective study has evaluated the impact of restless legs syndrome (RLS) on clinical factors in migraine patients.

METHODS: A total of 101 migraine patients who were evaluated for RLS twice at 7-year intervals in a university hospital setting were included in this study. The RLS group was defined as positive for RLS at either baseline or follow-up, and non-RLS group was defined as negative for RLS at both baseline and follow-up. The Migraine Disability Assessment (MIDAS) questionnaire, Beck Depression Inventory (BDI)-II, Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS) were administered to all patients.

RESULTS: The RLS prevalence was 16.8% at baseline and 20.8% at follow-up. Compared to the non-RLS group (n=27), the RLS group (n=74) showed a significantly higher rate of smoking and higher MIDAS and BDI-II scores at 7-year follow-up. A significant reduction in MIDAS and BDI-II scores at 7-year follow-up compared to those at baseline was observed in non-RLS group, but not in RLS group. Non-RLS group showed a significantly lower MIDAS score at 7-year follow-up than RLS group after adjusting for confounding variables such as age, gender, smoking status, ESS scores, and PSQI using analysis of covariance. Persistent RLS group (n=11) - positive for RLS at both baseline and follow-up - showed a significantly higher rate of smoking and increased MIDAS, BDI-II and PSQI scores compared to non-RLS group (n=74) at 7-year follow-up.

CONCLUSIONS: Our prospective study shows that RLS had a significant impact on headache-related disability in migraine patients.

Microglia P2X4 receptor contributes to central sensitization following recurrent nitroglycerin stimulation.

Long T[1], He W[1], Pan Q[1], Zhang S[1], Zhang Y[1], Liu C[1], Liu Q[1], Qin G[2], Chen L[2], Zhou J[3].

J Neuroinflammation. **2018 Aug 30**;15(1):245. doi: 10.1186/s12974-018-1285-3. PMID: 30165876.

BACKGROUND: The mechanism underlying migraine chronification remains unclear. Central sensitization may account for this progression. The microglia P2X4 receptor (P2X4R) plays a pivotal role in the central sensitization of inflammatory and neuropathic pain, but there is no information about P2X4R in migraine. Therefore, the aim of this study was to identify the precise role of microglia P2X4R in chronic migraine (CM).

METHODS: We used an animal model with recurrent intermittent administration of nitroglycerin (NTG), which closely mimics CM. NTG-induced basal and acute mechanical hypersensitivity were evaluated using the von Frey filament test. Then, we detected Iba1 immunoreactivity (Iba1-IR) and P2X4R expression in the trigeminal nucleus caudalis (TNC). To understand the effect of microglia and P2X4R on central sensitization of CM, we examined whether minocycline, an inhibitor of microglia activation, and 5-BDBD, a P2X4R antagonist, altered NTG-induced mechanical hyperalgesia. In addition, we also evaluated the effect of 5-BDBD on c-Fos and calcitonin gene-related peptide (CGRP) expression within the TNC.

RESULTS: Chronic intermittent administration of NTG resulted in acute and chronic basal mechanical hyperalgesia, accompanied with microglia activation and upregulation of P2X4R expression. Minocycline significantly decreased basal pain hypersensitivity but did not alter acute NTG-induced hyperalgesia. Minocycline also reduced microglia activation. 5-BDBD completely blocked the basal and acute hyperalgesia induced by NTG. This effect was associated with a significant inhibition of the NTG-induced increase in c-Fos protein and CGRP release in the TNC.

CONCLUSIONS: Our results indicate that blocking microglia activation may have an effect on the prevention of migraine chronification. Moreover, we speculate that the P2X4R may be implicated in the microglia-neuronal signal in the TNC, which contributes to the central sensitization of CM.

CHRONIC PAIN

Gender Differences in Use of Complementary and Integrative Health by U.S. Military Veterans with Chronic Musculoskeletal Pain.

Evans EA[1], Herman PM[2], Washington DL[3], Lorenz KA[4], Yuan A[5], Upchurch DM[6], Marshall N[7], Hamilton AB[8], Taylor SL[9].

Womens Health Issues. **2018 Aug 30**. pii: S1049-3867(18)30187-7. doi: 10.1016/j.whi.2018.07.003. PMID: 30174254. [Epub ahead of print]

AIMS: The Veterans Health Administration promotes evidence-based complementary and integrative health (CIH) therapies as nonpharmacologic approaches for chronic pain. We aimed to examine CIH use by gender among veterans with chronic musculoskeletal pain, and variations in gender differences by race/ethnicity and age.

METHODS: We conducted a secondary analysis of electronic health records provided by all women (n = 79,537) and men (n = 389,269) veterans age 18 to 54 years with chronic musculoskeletal pain who received Veterans Health Administration-provided care between 2010 and 2013. Using gender-stratified multivariate binary logistic regression, we examined predictors of CIH use, tested a race/ethnicity-by-age interaction term, and conducted pairwise comparisons of predicted probabilities.

RESULTS: Among veterans with chronic musculoskeletal pain, more women than men use CIH (36% vs. 26%), with rates ranging from 25% to 42% among women and 15% to 29% among men, depending on race/ethnicity and age. Among women, patients under age 44 who were Hispanic, White, or patients of other race/ethnicities are similarly likely to use CIH; in contrast, Black women, regardless of age, are least likely to use CIH. Among men, White and Black patients, and especially Black men under age 44, are less likely to use CIH than men of Hispanic or other racial/ethnic identities.

CONCLUSIONS: Women veteran patients with chronic musculoskeletal pain are more likely than men to use CIH therapies, with variations in CIH use rates by race/ethnicity and age. Tailoring CIH therapy engagement efforts to be sensitive to gender, race/ethnicity, and age could reduce differential CIH use and thereby help to diminish existing health disparities among veterans.

A functional riboSNitch in the 3'UTR of *FKBP5* alters microRNA-320a binding efficiency and mediates vulnerability to chronic posttraumatic pain.

Linnstaedt SD[1,2], Riker KD[3], Rueckeis CA[3], Kutchko KM[4], Lackey L[4], McCarthy KR[3], Tsai YH[5], Parker JS[5], Kurz MC[6], Hendry PL[7], Lewandowski C[8], Datner E[9], Pearson C[10], O'Neil B[11,12], Domeier R[13], Kaushik S[14], Laederach A[4], McLean SA[3,2,15].

J Neurosci. **2018 Aug 27**. pii: 3458-17. doi: 10.1523/JNEUROSCI.3458-17.2018. PMID: 30150364. [Epub ahead of print]

Previous studies have shown that common variants of the gene coding for FK506 binding protein 51 (*FKBP5*), a critical regulator of glucocorticoid sensitivity, affect vulnerability to stress-related disorders. In a previous report, *FKBP5* rs1360780 was identified as a functional variant due to its effect on gene methylation. We here report evidence for a novel functional *FKBP5* allele, rs3800373. This study assessed the association between rs3800373 and posttraumatic chronic pain in 1,607 women and men from two ethnically diverse human cohorts. The molecular mechanism through which rs3800373 affects adverse outcomes was established via *in silico, in vivo*, and *in vitro* analyses. The rs3800373 minor allele predicted worse adverse outcomes after trauma exposure, such that individuals with the minor (risk) allele developed more severe posttraumatic chronic musculoskeletal pain. Among these individuals, peritraumatic circulating *FKBP5* expression levels increased as cortisol and glucocorticoid receptor (*NR3C1*) mRNA levels increased, consistent with increased glucocorticoid resistence. Bioinformatic, *in vitro*, and mutational analyses indicate that the rs3800373 minor allele reduces the binding of a stress and pain-associated microRNA, miR-320a, to *FKBP5* via altering *FKBP5* mRNA 3'UTR secondary structure (i.e. is a riboSNitch). This results in relatively greater *FKBP5* translation, unchecked by miR-320a. Overall, these results identify an important gene-miRNA interaction influencing chronic pain risk in vulnerable individuals and suggests that exogenous methods to achieve targeted reduction in post-stress *FKBP5* mRNA expression may constitute useful therapeutic strategies.

Significance statement: *FKBP5* is a critical regulator of the stress response. Previous studies have shown that dysregulation of the expression of this gene plays a role in the pathogenesis of chronic pain development as well as a number of co-morbid neuropsychiatric disorders. In the current study, we identified a functional allele (rs3800373) in the 3'UTR of *FKBP5* that influences vulnerability to chronic post-traumatic pain in two ethnic cohorts. Using multiple complimentary experimental approaches, we show that the *FKBP5* rs3800373 minor allele alters the secondary structure of *FKBP5* mRNA, decreasing the binding of a stress and pain associated microRNA, miR-320a. This results in relatively greater *FKBP5* translation, unchecked by miR-320a, increasing glucocorticoid resistance and increasing vulnerability to post-traumatic pain.

CHRONIC PAIN (Continued)

Opioid Prescribing in the United States Before and After the Centers for Disease Control and Prevention's 2016 Opioid Guideline.

Bohnert ASB[1], Guy GP Jr[2], Losby JL[2].

Ann Intern Med. **2018 Aug 28**. doi: 10.7326/M18-1243. PMID: 30167651. [Epub ahead of print]

Background: In response to adverse outcomes from prescription opioids, the Centers for Disease Control and Prevention (CDC) released the Guideline for Prescribing Opioids for Chronic Pain in March 2016.

Objective: To test the hypothesis that the CDC guideline release corresponded to declines in specific opioid prescribing practices.

Design: Interrupted time series analysis of monthly prescribing measures from the IQVIA transactional data warehouse and Real-World Data Longitudinal Prescriptions population-level estimates based on retail pharmacy data. Population size was determined by U.S. Census monthly estimates.

Setting: United States, 2012 to 2017.

Patients: Persons prescribed opioid analgesics.

Measurements: Outcomes included opioid dosage, days supplied, overlapping benzodiazepine prescriptions, and the overall rate of prescribing.

Results: The rate of high-dosage prescriptions (≥90 morphine equivalent milligrams per day) was 683 per 100 000 persons in January 2012 and declined by 3.56 (95% CI, -3.79 to -3.32) per month before March 2016 and by 8.00 (CI, -8.69 to -7.31) afterward. Likewise, the percentage of patients with overlapping opioid and benzodiazepine prescriptions was 21.04% in January 2012 and declined by 0.02% (CI, -0.04% to -0.01%) per month before the CDC guideline release and by 0.08% (CI, -0.08% to -0.07%) per month afterward. The overall opioid prescribing rate was 6577 per 100 000 persons in January 2012 and declined by 23.48 (CI, -26.18 to -20.78) each month before the guideline release and by 56.74 (CI, -65.96 to -47.53) per month afterward.

Limitation: No control population; inability to determine the appropriateness of opioid prescribing.

Conclusion: Several opioid prescribing practices were decreasing before the CDC guideline, but the time of its release was associated with a greater decline. Guidelines may be effective in changing prescribing practices.

Primary Funding Source: CDC.

Lifetime cigarette smoking and chronic widespread and regional pain in later adulthood: evidence from the 1946 British birth cohort study.

Bendayan R[1,2], Cooper R[1], Muthuri SG[1].

BMJ Open. **2018 Aug 29**;8(8):e021896. doi: 10.1136/bmjopen-2018-021896. PMID: 30158227.

OBJECTIVE: To examine whether different lifetime patterns of cigarette smoking are associated with chronic widespread pain (CWP) and chronic regional pain (CRP) at age 68.

DESIGN: Prospective cohort study.

SETTING: England, Scotland and Wales.

PARTICIPANTS: Up to 2347 men and women from the Medical Research Council National Survey of Health and Development, who have been followed up since birth in 1946 and provided sufficient information on cigarette smoking across adulthood to be classified as never smoker, predominantly non-smoker, predominantly smoker or lifelong smoker and pain assessment at age 68.

PRIMARY OUTCOME MEASURES: Pain was self-reported at age 68, and CWP was defined according to American College of Rheumatology criteria. Participants who reported having pain for ≥3 months but who did not meet the CWP definition were classified as having CRP; those who reported pain which had lasted for <3 months were classified as 'other' pain. No pain was the reference group.

RESULTS: Findings from multinomial logistic regression models indicated that compared with never smokers, predominantly non-smokers, predominantly smokers and lifelong smokers all had an increased risk of CWP; relative risk ratios=1.70(95% CI 1.16 to 2.49); 2.10(95% CI 1.34 to 3.28) and 1.88(95% CI 0.99 to 3.57), respectively, after adjusting for sex, own occupational class, educational level, body mass index, leisure time physical activity, alcohol intake, long-standing illness and symptoms of anxiety and depression. No association was observed between smoking history and CRP or other pain.

CONCLUSIONS: These results suggest that exposure to cigarette smoking at any stage in adulthood was associated with higher risk of CWP in later adulthood; highlighting the ongoing importance of smoking prevention programmes. It also suggests that assessment of lifetime smoking behaviour may be more useful in identifying those at greater risk of CWP in later life than assessment of current smoking status.

OTHER RESEARCH OF INTEREST

A bifunctional nociceptin and mu opioid receptor agonist is analgesic without opioid side effects in nonhuman primates.

Ding H[1], Kiguchi N[1,2], Yasuda D[3], Daga PR[3], Polgar WE[3], Lu JJ[3], Czoty PW[1], Kishioka S[2], Zaveri NT[4], Ko MC[5,6].

Sci Transl Med. **2018 Aug 29**;10(456). pii: eaar3483. doi: 10.1126/scitranslmed.aar3483. PMID: 30158150.

Misuse of prescription opioids, opioid addiction, and overdose underscore the urgent need for developing addiction-free effective medications for treating severe pain. Mu opioid peptide (MOP) receptor agonists provide very effective pain relief. However, severe side effects limit their use in the clinical setting. Agonists of the nociceptin/orphanin FQ peptide (NOP) receptor have been shown to modulate the antinociceptive and reinforcing effects of MOP agonists. We report the discovery and development of a bifunctional NOP/MOP receptor agonist, AT-121, which has partial agonist activity at both NOP and MOP receptors. AT-121 suppressed oxycodone's reinforcing effects and exerted morphine-like analgesic effects in nonhuman primates. AT-121 treatment did not induce side effects commonly associated with opioids, such as respiratory depression, abuse potential, opioid-induced hyperalgesia, and physical dependence. Our results in nonhuman primates suggest that bifunctional NOP/MOP agonists with the appropriate balance of NOP and MOP agonist activity may provide a dual therapeutic action for safe and effective pain relief and treating prescription opioid abuse.

Effects of Threat Context, Trauma History, and Posttraumatic Stress Disorder Status on Physiological Startle Reactivity in Gulf War Veterans.

Niles AN[1,2], Luxenberg A[1,2], Neylan TC[1,2], Inslicht SS[1,2], Richards A[1,2], Metzler TJ[1], Hlavin J[1], Deng J[1,2], O'Donovan A[1,2].

J Trauma Stress. **2018 Aug**;31(4):579-590. doi: 10.1002/jts.22302. PMID: 30058728. Epub 2018 Jul 30.

In the current study, we explored exaggerated physiological startle responses in posttraumatic stress disorder (PTSD) and examined startle reactivity as a biomarker of PTSD in a large veteran sample. We assessed heart rate (HR), skin conductance (SC), and electromyographic (EMG) startle responses to acoustic stimuli under low-, ambiguous-, and high-threat conditions in Gulf War veterans with current (n = 48), past (n = 42), and no history of PTSD (control group; n = 152). We evaluated PTSD status using the Clinician-Administered PTSD Scale and trauma exposure using the Trauma History Questionnaire. Participants with current PTSD had higher HR, ds = 0.28-0.53; SC, d = 0.37; and startle responses than those with past or no history of PTSD. The HR startle response under ambiguous threat best differentiated current PTSD; however, sensitivity and specificity analyses revealed it to be an imprecise indicator of PTSD status, ROC AUC = .66. Participants with high levels of trauma exposure only showed elevated HR and SC startle reactivity if they had current PTSD. Results indicate that startle is particularly elevated in PTSD when safety signals are available but a possibility of danger remains and when trauma exposure is high. However, startle reactivity alone is unlikely to be a sufficient biomarker of PTSD.

Microglial control of astrocytes in response to microbial metabolites.

Rothhammer V[1], Borucki DM[1], Tjon EC[1], Takenaka MC[1], Chao CC[1], Ardura-Fabregat A[2], de Lima KA[1], Gutiérrez-Vázquez C[1], Hewson P[1], Staszewski O[2], Blain M[3], Healy L[3], Neziraj T[1], Borio M[1], Wheeler M[1], Dragin LL[4], Laplaud DA[5], Antel J[3], Alvarez JI[4], Prinz M[2,6], Quintana FJ[7,8].

Nature. **2018 May**;557(7707):724-728. doi: 10.1038/s41586-018-0119-x. PMID: 29769726. Epub 2018 May 16.

Microglia and astrocytes modulate inflammation and neurodegeneration in the central nervous system (CNS)[1-3]. Microglia modulate pro-inflammatory and neurotoxic activities in astrocytes, but the mechanisms involved are not completely understood[4,5]. Here we report that TGFα and VEGF-B produced by microglia regulate the pathogenic activities of astrocytes in the experimental autoimmune encephalomyelitis (EAE) mouse model of multiple sclerosis. Microglia-derived TGFα acts via the ErbB1 receptor in astrocytes to limit their pathogenic activities and EAE development. Conversely, microglial VEGF-B triggers FLT-1 signalling in astrocytes and worsens EAE. VEGF-B and TGFα also participate in the microglial control of human astrocytes. Furthermore, expression of TGFα and VEGF-B in $CD14^+$ cells correlates with the multiple sclerosis lesion stage. Finally, metabolites of dietary tryptophan produced by the commensal flora control microglial activation and TGFα and VEGF-B production, modulating the transcriptional program of astrocytes and CNS inflammation through a mechanism mediated by the aryl hydrocarbon receptor. In summary, we identified positive and negative regulators that mediate the microglial control of astrocytes. Moreover, these findings define a pathway through which microbial metabolites limit pathogenic activities of microglia and astrocytes, and suppress CNS inflammation. This pathway may guide new therapies for multiple sclerosis and other neurological disorders.

OTHER RESEARCH OF INTEREST (Continued)

Differences in Tertiary Glaucoma Care in the Veterans Affairs Health Care System.

Lee AY[1,2], Lee CS[1], Pieters M[3], Maa AY[3,4], Cockerham G[5], Lynch MG[3,4].

JAMA Ophthalmol. **2018 Aug 16**. doi: 10.1001/jamaophthalmol.2018.3463. PMID: 30128546. [Epub ahead of print]

Importance: Glaucoma is a common cause of visual impairment in the Veterans Affairs (VA) health care system, but to our knowledge, no data exist concerning tertiary glaucoma care (ie, laser and filtering surgery).

Objective: To determine whether the rate of tertiary glaucoma care differs among veterans cared for through the 4 different eye care delivery models that are present in the VA: optometry-only clinics, ophthalmology-only clinics, clinics with optometry and ophthalmology functioning as a single integrated clinic with ophthalmology as the lead, and clinics with optometry and ophthalmology functioning as separate clinics.

Design, Setting, and Participants: In this retrospective review of the Veterans Health Administration Support Service Center database, 490 926 veterans with a glaucoma-related diagnosis received care from 136 VA medical centers during fiscal year 2016. Demographic and baseline clinical factors, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, and Current Procedural Terminology codes, and the rates of glaucoma surgery procedures were extracted from the database. The organizational structure of each VA eye clinic was obtained. Univariate and multivariate regression analyses were performed for log percent for laser peripheral iridotomy (LPI), laser trabeculoplasty (LTP), and filtering surgery.

Main Outcomes and Measures: Rates of LPI, LTP, and filtering surgery.

Results: Of the 490 926 veterans with a glaucoma-related diagnosis, 465 842 (94.9%) were male, 309 677 (63.1%) were white, and 203 243 (41.4%) were aged 65 to 74 years. The rate of LPI was 0.30%, 0.28%, 0.67%, and 0.69% in optometry-only clinics, ophthalmology-only clinics, integrated clinics, and separated clinics, respectively ($P < .001$). The rate of LTP was 0.31%, 1.06%, 0.93%, and 0.92% in care delivery models that included optometry-only clinics, ophthalmology-only clinics, integrated clinics, and separated clinics, respectively ($P < .001$). The rate of filtering surgery was 0.32%, 0.51%, 0.69%, and 0.60% in optometry-only clinics, ophthalmology-only clinics, integrated clinics, and separated clinics, respectively ($P < .001$). Multivariate regression analyses showed that these differences remained significantly different even after adjusting for potential confounders.

Conclusions and Relevance: Disparities exist in the use of tertiary glaucoma services within the VA, and different care delivery models may play a role. Outcomes of glaucoma care for the different models of eye care delivery were not analyzed in this study.

Returning Individual Research Results to Participants: Guidance for a New Research Paradigm

Contributors: Health and Medicine Division; Board on Health Sciences Policy; Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories; Jeffrey R. Botkin, Michelle Mancher, Emily R. Busta, and Autumn S. Downey, Editors.

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When is it appropriate to return individual research results to participants? The immense interest in this question has been fostered by the growing movement toward greater transparency and participant engagement in the research enterprise. Yet, the risks of returning individual research results—such as results with unknown validity—and the associated burdens on the research enterprise are competing considerations.

Returning Individual Research Results to Participants reviews the current evidence on the benefits, harms, and costs of returning individual research results, while also considering the ethical, social, operational, and regulatory aspects of the practice. This report includes 12 recommendations directed to various stakeholders—investigators, sponsors, research institutions, institutional review boards (IRBs), regulators, and participants—and are designed to help (1) support decision making regarding the return of results on a study-by-study basis, (2) promote high-quality individual research results, (3) foster participant understanding of individual research results, and (4) revise and harmonize current regulations.

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