GULF WAR ILLNESS

Gulf War illness associated with abnormal auditory P1 event-related potential: Evidence of impaired cholinergic processing replicated in a national sample.

Tillman GD[1], Spence JS[2], Briggs RW[3], Haley RW[2], Hart J Jr[4], Kraut MA[5].

Psychiatry Res Neuroimaging. **2018 Nov 10**;283:7-15. doi: 10.1016/j.pscychresns.2018.11.006. PMID: 30453127. [Epub ahead of print]

Our team previously reported event-related potential (ERP) and hyperarousal patterns from a study of one construction battalion of the U.S. Naval Reserve who served during the 1991 Persian Gulf War. We sought to replicate these findings in a sample that was more representative of the entire Gulf War-era veteran population, including male and female participants from four branches of the military. We collected ERP data from 40 veterans meeting Haley criteria for Gulf War syndromes 1-3 and from 22 matched Gulf War veteran controls while they performed an auditory oddball task. Reports of hyperarousal from the ill veterans were significantly greater than those from the control veterans, and P1 amplitudes in Syndromes 2 and 3 were significantly higher than P1 amplitudes in Syndrome 1, replicating our previous findings. Many of the contributors to the generation of the P1 potential are also involved in the regulation of arousal and are modulated by cholinergic and dopaminergic systems-two systems whose dysfunction has been implicated in Gulf War illness. These differences among the three syndrome groups where their means were on either side of controls is a replication of our previous ERP study and is consistent with previous imaging studies of this population.

The Multiple Hit Hypothesis for Gulf War Illness: Self-Reported Chemical/Biological Weapons Exposure and Mild Traumatic Brain Injury.

Janulewicz P[1], Krengel M[2,3], Quinn E[4], Heeren T [5], Toomey R[6], Killiany R[7], Zundel C[8], Ajama J[9], O'Callaghan J[10], Steele L[11], Klimas N[12,13], Sullivan K[14].

Brain Sci. **2018 Nov 13**;8(11). pii: E198. doi: 10.3390/brainsci8110198. PMID: 30428552.

The Gulf War Illness Consortium (GWIC) was designed to identify objective biomarkers of Gulf War Illness (GWI) in 1991 Gulf War veterans. The symptoms of GWI include fatigue, pain, cognitive problems, gastrointestinal, respiratory, and skin problems. Neurotoxicant exposures during deployment, such as pesticides, sarin, and pyridostigmine bromide pills have been identified as contributors to GWI. We have also found an association between mild traumatic brain injury (mTBI) and increased rates of GWI. However, the combined impact of these physical and chemical exposures has not yet been explored in GWI. The objective of this study was to examine both self-reported mTBI and exposure to chemical/biological weapons (CBW) as a multiple or two hit model for increased risk of GWI and other chronic health conditions. The study population included 125 Gulf War (GW) veterans from the Boston GWIC. Exposure to CBW was reported in 47.2% of the study population, and 35.2% reported sustaining a mTBI during the war. Results confirmed that those with both exposures (mTBI and CBW) had higher rates of comorbid chronic health conditions while rates of GWI were equivalent for mTBI and CBW or mTBI alone. The timing of exposure to mTBI was found to be strikingly different between those with GWI and those without it. Correspondingly, 42.3% of GWI cases reported experiencing a mTBI during military service while none of the controls did (p = 0.0002). Rates of mTBI before and after the war did not differ between the cases and controls. In addition, 54% of cases compared to 14.3% of controls (p = <0.001) reported being exposed to CBW during military service. The current study examined the relation of the separate and combined effects of exposure to mTBI and CBW in 1991 GW veterans. The findings from this study suggest that both exposure to mTBI and CBW are associated with the development of GWI and multiple chronic health conditions and that combined exposure appears to lead to higher risk of chronic health effects.

CHRONIC FATIGUE SYNDROME

Brain abnormalities in myalgic encephalomyelitis/chronic fatigue syndrome: Evaluation by diffusional kurtosis imaging and neurite orientation dispersion and density imaging.

Kimura Y[1], Sato N[1], Ota M[2,3], Shigemoto Y[1], Morimoto E[1], Enokizono M[1], Matsuda H[4], Shin I[5], Amano K[6], Ono H[7], Sato W[7], Yamamura T[7].

J Magn Reson Imaging. **2018 Nov 14**. doi: 10.1002/jmri.26247. PMID: 30430664. [Epub ahead of print]

BACKGROUND: Diffusional kurtosis imaging (DKI) and neurite orientation dispersion and density imaging (NODDI) metrics provide more specific information regarding pathological changes than diffusion tensor imaging (DTI).

PURPOSE: To detect microstructural abnormalities in myalgic encephalomyelitis (ME) / chronic fatigue syndrome (CFS) patients by using DKI and NODDI metrics.

STUDY TYPE: Prospective.

POPULATION: Twenty ME/CFS patients and 23 healthy controls were recruited.

FIELD STRENGTH/SEQUENCE: Three-b value DWI (b-values = 0, 1000, and 2000 sec/mm^2) and 3D T_1 -weighted images were at 3.0T.

ASSESSMENT: Mean kurtosis (MK), neurite density index (NDI), orientation dispersion index (ODI), fractional anisotropy (FA), and mean diffusivity (MD) were calculated.

STATISTICAL TESTING: The two-sample t-test analysis in SPM12 software was used to compare the differences between ME/CFS and control groups.

RESULTS: In the ME/CFS patients, we observed significant FA decreases in the genu of the corpus callosum and the anterior limb of the right internal capsule ($P < 0.05$), but no significant difference in MD ($P = 0.164$); there were also significant MK decreases in the right frontal area, anterior cingulate gyrus, superior longitudinal fasciculus (SLF), and left parietal area ($P < 0.05$). Significant NDI decreases were observed in the right posterior cingulate gyrus, SLF, and left frontal area of the ME/CFS patients ($P < 0.05$). Significant ODI decreases were seen in the bilateral occipital areas, right superior temporal gyrus, the anterior limb of internal capsule, and the posterior cingulate gyrus ($P < 0.05$), and significant ODI increases were revealed in the bilateral occipital and right temporal areas ($P < 0.05$).

DATA CONCLUSION: Right SLF abnormalities may be a diagnostic marker for ME/CFS.

LEVEL OF EVIDENCE: 1 Technical Efficacy: Stage 2 J. Magn. Reson. Imaging 2018.

Effects of activity pacing in patients with chronic conditions associated with fatigue complaints: a meta-analysis.

Abonie US[1], Sandercock GRH[1], Heesterbeek M[1], Hettinga FJ[1].

Disabil Rehabil. **2018 Nov 18**:1-10. doi: 10.1080/09638288.2018.1504994. PMID: 30449204. [Epub ahead of print]

A meta-analysis was conducted to (1) determine the effect of activity pacing interventions on fatigue, physical functioning and physical activity among patients with chronic conditions associated with fatigue complaints, and to (2) examine potential moderator effects of trial characteristics (components of intervention and amount of patient-provider contact). Six studies were included in the meta-analysis. Relevant content of the studies was extracted and rated on methodological quality. Random-effects modeling was used to pool data across studies. Medium (standardized mean difference =0.50) and marginal (standardized mean difference =0.34) effects were found for fatigue at post-treatment and follow-up respectively. Inconsequential effects were found for physical functioning and activity (standardized mean difference =0.08-0.30) at both assessment points. Subgroup analyses revealed components of intervention and amount of patient-provider contact were not the source of variance. Minimal patient-provider contact had an effect on fatigue comparable in magnitude to more intensive contact. This meta-analysis of activity pacing in patients with fatigue complaints suggests that activity pacing might have sustained beneficial effects on fatigue management, in particular on fatigue reduction. The divergence in effects for all outcomes suggests that alternative ways such as tailoring advice to individual's behavior toward physical activity may be more successful. Implications for rehabilitation: In a relatively small sample this meta-analysis shows fatigue severity improved after activity pacing interventions and provides a basis to integrate activity pacing in activity stimulation programs for persons with chronic conditions. Activity pacing can feasibly be implemented within standard health care to manage fatigue and physical activity behaviors in persons with chronic conditions.

HEADACHE and MIGRAINE

Migraine with visual aura a risk factor for incident atrial fibrillation: A cohort study.

Sen S[1], Androulakis XM[2], Duda V[2], Alonso A[2], Chen LY[2], Soliman EZ[2], Magnani J[2], Trivedi T[2], Merchant AT[2], Gottesman RF[2], Rosamond WD[2].

Neurology. **2018 Nov 14**. pii: 10.1212/WNL.0000000000006650. doi: 10.1212/WNL.0000000000006650. PMID: 30429278. [Epub ahead of print]

OBJECTIVE: Migraine with visual aura is associated with cardioembolic stroke risk. The aim of this study was to test association between migraine with visual aura and atrial fibrillation (AF), in the Atherosclerosis Risk in Communities study.

METHODS: In the Atherosclerosis Risk in Communities study, a longitudinal, community-based cohort study, participants were interviewed for migraine history in 1993-1995 and were followed for incident AF through 2013. AF was adjudicated using ECGs, discharge codes, and death certificates. Multivariable Cox proportional hazards models were used to study the relation between migraine and its subtypes with incident AF, compared with controls without headaches. Mediation analysis was conducted to test whether AF was a mediator of migraine with visual aura-associated stroke risk.

RESULTS: Of 11,939 participants assessed for headache and without prior AF or stroke, 426 reported migraines with visual aura, 1,090 migraine without visual aura, 1,018 nonmigraine headache, and 9,405 no headache. Over a 20-year follow-up period, incident AF was noted in 232 (15%) of 1,516 with migraine and 1,623 (17%) of 9,405 without headache. After adjustment for multiple confounders, migraine with visual aura was associated with increased risk of AF compared to no headache (hazard ratio 1.30, 95% confidence interval 1.03-1.62) as well as when compared to migraine without visual aura (hazard ratio 1.39, 95% confidence interval 1.05-1.83). The data suggest that AF may be a potential mediator of migraine with visual aura-stroke risk.

CONCLUSIONS:

Migraine with aura was associated with increased risk of incident AF. This may potentially lead to ischemic strokes.

Lasmiditan is an effective acute treatment for migraine: A phase 3 randomized study.

Kuca B[1], Silberstein SD[1], Wietecha L[2], Berg PH[1], Dozier G[1], Lipton RB[1]; COL MIG-301 Study Group. Collaborators (98)

Neurology. **2018 Nov 16**. pii: 10.1212/WNL.0000000000006641. doi: 10.1212/WNL.0000000000006641. PMID: 30446595.

OBJECTIVE: To assess the efficacy and safety of lasmiditan in the acute treatment of migraine.

METHODS: Adult patients with migraine were randomized (1:1:1) to a double-blind dose of oral lasmiditan 200 mg, lasmiditan 100 mg, or placebo and were asked to treat their next migraine attack within 4 hours of onset. Over 48 hours after dosing, patients used an electronic diary to record headache pain and the presence of nausea, phonophobia, and photophobia, one of which was designated their most bothersome symptom (MBS).

RESULTS: Of the 1,856 patients who treated an attack, 77.9% had ≥1 cardiovascular risk factors in addition to migraine. Compared with placebo, more patients dosed with lasmiditan 200 mg were free of headache pain at 2 hours after dosing (32.2% vs 15.3%; odds ratio [OR] 2.6, 95% confidence interval [CI] 2.0-3.6, $p< 0.001$), similar to those dosed with lasmiditan 100 mg (28.2%; OR 2.2, 95% CI 1.6-3.0, $p< 0.001$). Furthermore, compared with those dosed with placebo, more patients dosed with lasmiditan 200 mg (40.7% vs 29.5%; OR 1.6, 95% CI 1.3-2.1, $p< 0.001$) and lasmiditan 100 mg (40.9%; OR 1.7, 95% CI, 1.3-2.2, $p< 0.001$) were free of their MBS at 2 hours after dosing. Adverse events were mostly mild or moderate in intensity.

CONCLUSIONS: Lasmiditan dosed at 200 and 100 mg was efficacious and well tolerated in the treatment of acute migraine among patients with a high level of cardiovascular risk factors.

CLINICALTRIALSGOV IDENTIFIER: NCT02439320.

CLASSIFICATION OF EVIDENCE: This study provides Class I evidence that for adult patients with migraine, lasmiditan increases the proportion of subjects who are headache pain free at 2 hours after treating a migraine attack.

HEADACHE and MIGRAINE (Continued)

Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study.

Detke HC[1], Goadsby PJ[2], Wang S[2], Friedman DI[2], Selzler KJ[2], Aurora SK[2].

Neurology. **2018 Nov 16**. pii: 10.1212/WNL.0000000000006640. doi: 10.1212/WNL.0000000000006640. PMID: 30446596.

OBJECTIVE: To evaluate the efficacy and safety of galcanezumab, a humanized monoclonal antibody that selectively binds to calcitonin gene-related peptide, in the preventive treatment of chronic migraine.

METHODS: A phase 3, randomized, double-blind, placebo-controlled study of LY2951742 in patients with chronic migraine (Evaluation of Galcanezumab in the Prevention of Chronic Migraine [REGAIN]) was a phase 3 study with a 3-month double-blind, placebo-controlled treatment phase and a 9-month open-label extension. Eligible patients 18 to 65 years of age with chronic migraine were randomized 2:1:1 to monthly subcutaneous injections of placebo (n = 558), galcanezumab 120 mg (with a 240-mg loading dose, n = 278), or galcanezumab 240 mg (n = 277). The primary endpoint was the overall mean change from baseline in the number of monthly migraine headache days (MHDs) during the 3-month double-blind treatment phase.

RESULTS: Mean number of monthly MHDs at baseline was 19.4 for the total sample. Both galcanezumab dose groups demonstrated greater overall mean reduction in the number of monthly MHDs compared to placebo (placebo -2.7, galcanezumab 120 mg -4.8, galcanezumab 240 mg -4.6) ($p < 0.001$ for each dose compared to placebo). There were no clinically meaningful differences between galcanezumab doses and placebo on any safety or tolerability outcome except for a higher incidence of treatment-emergent injection-site reaction ($p < 0.01$), injection-site erythema ($p < 0.001$), injection-site pruritus ($p < 0.01$), and sinusitis ($p < 0.05$) in the galcanezumab 240-mg group relative to placebo.

CONCLUSIONS: Both doses of galcanezumab were superior to placebo in reducing the number of monthly MHDs. Galcanezumab appears efficacious, safe, and well tolerated for the preventive treatment of chronic migraine.

CLINICALTRIALSGOV IDENTIFIER: NCT02614261.

CLASSIFICATION OF EVIDENCE: This interventional study provides Class I evidence that galcanezumab is superior to placebo in the reduction of the number of monthly MHDs.

Efficacy of Co Q10 as Supplementation for Migraine: A Meta-Analysis.

Zeng Z[1], Li Y[2], Lu S[3], Huang W[4], Di W[5].

Acta Neurol Scand. **2018 Nov 14**. doi: 10.1111/ane.13051. PMID: 30428123. [Epub ahead of print]

OBJECTIVES: Migraine ranks among the most frequent neurological disorders globally. Co-enzyme Q10 (CoQ10) is a nutritional agent that might play a preventative role in migraine. This meta-analysis aimed to investigate the effects of CoQ10 as a supplemental agent in migraine.

SUBJECTS AND METHODS: Web of Science, PubMed and Cochrane Library were searched for potential articles that assessed the effects of CoQ10 on migraine. Data were extracted by two independent reviewers and analyzed with Revman 5.2 software.

RESULTS: We included 5 studies with 346 patients (120 pediatric and 226 adult subjects) in the meta-analysis. CoQ10 was comparable with placebo with respect to migraine attacks/month (P = 0.08) and migraine severity/day (P = 0.08). However, CoQ10 was more effective than placebo in reducing migraine days/month (P <0.00001) and migraine duration (P = 0.009).

CONCLUSION: This is the first study to demonstrate the effects of CoQ10 supplementation on migraine. The results support the use of CoQ10 as a potent therapeutic agent with respect to migraine duration and migraine days per month. Nonetheless, more studies are needed to support the conclusions. This article is protected by copyright. All rights reserved.

HEADACHE and MIGRAINE (Continued)

The Effect of Beginning Treatment With Fremanezumab on Headache and Associated Symptoms in the Randomized Phase 2 Study of High Frequency Episodic Migraine: Post-Hoc Analyses on the First 3 Weeks of Treatment.

Silberstein SD[1], Rapoport AM[2], Loupe PS[3], Aycardi E[4], McDonald M[5], Yang R[5], Bigal ME[6].

Headache. **2018 Nov 18**. doi: 10.1111/head.13446. PMID: 30450545. [Epub ahead of print]

BACKGROUND: Migraine has a substantial impact on daily living, affecting productivity and quality of life for patients and their families. Patients frequently discontinue preventive medications in part because of a delay in headache and symptom relief due to the long dose titration procedures necessary for some migraine preventives.

OBJECTIVE: To evaluate the efficacy of fremanezumab, a selective monoclonal CGRP ligand antibody, during the first 3 weeks of therapy in patients with high-frequency episodic migraine (HFEM) to relieve migraine headaches and associated symptoms and to reduce use of acute migraine medications.

METHODS: In a multicenter, randomized, double-blind, placebo-controlled, phase 2 study, patients with HFEM who met inclusion criteria and were 80% compliant with daily headache diary entry were randomized and treated once every 28 days for 3 months with either placebo or fremanezumab 225 or 675 mg. Compared to placebo, both doses of fremanezumab significantly reduced the primary endpoint of the HFEM study, change in the number of migraine days in month 3 relative to baseline. Herein, we performed post-hoc analyses to assess the efficacy of each dose during the first 3 weeks of treatment to reduce migraine headache parameters, associated migraine symptoms, and the consumption of acute migraine medications.

RESULTS: The sample consisted of 297 study participants. Compared to placebo, decreases in migraine days were seen during the first week of therapy for both fremanezumab doses with least square mean (LSM) differences between fremanezumab 225 mg and placebo of -0.93 (95% CI: -1.36, -0.49) and between 675 mg dose and placebo of -1.02 (95% CI: -1.46, -0.58), both P < .0001. This benefit was maintained through the second week of therapy for the 225 and 675 mg doses, respectively, (-0.76 (95% CI: -1.11, -0.40) P < .0001, -.79 (95% CI: -1.15, -0.44) P < .0001) and the third week of therapy (-0.64 (95% CI: -0.97, -0.30) P = .0003 and -0.64 (95% CI: -0.98, -0.30) P = .0003). Likewise in the first week, patients recorded reductions in associated migraine symptoms such as nausea, vomiting, photophobia, and phonophobia, which continued through weeks 2 and 3. There were also reductions in days with acute medication use to treat migraine for the 225 and 675 mg fremanezumab doses compared to placebo. In the first week, LSM differences between 225 mg and placebo were -1.02 (95% CI: -1.39, -0.64) and between 675 mg and placebo were -1.06 (95% CI: -1.39, -0.64) P < .0001); for the second and third weeks (-1.01 (95% CI: -1.14, -0.55) P < .0001; -.90 (95% CI: -1.04, -0.44) P < .0001; -.91 (95% CI: -0.92, -0.34) P < .0001; and -.83 (95% CI: -0.84, -0.26) P = .0002), respectively.

CONCLUSION: Fremanezumab treatment resulted in a rapid preventive response in patients with HFEM, with reductions seen in several headache parameters and migraine symptoms within the first week after therapy initiation and continuing during the second and third weeks. Patients also were able to rapidly reduce their use of acute medications to treat migraine attacks. The trial is registered at Clinicaltrials.gov as NCT02025556.

CHRONIC PAIN

Living with disabling chronic pain: results from a face-to-face cross-sectional population-based study.

Cabrera-León A[1,2,3,4], Cantero-Braojos MÁ[5], Garcia-Fernandez L[6], Guerra de Hoyos JA[7].

BMJ Open. **2018 Nov 12**;8(11):e020913. doi: 10.1136/bmjopen-2017-020913. PMID: 30420342.

OBJECTIVES: To estimate the prevalence of disabling chronic pain (DCP) in Spanish adults, to analyse its characteristics, to determine its multimorbidity and to identify its associated factors.

SETTINGS: 2011 Andalusian Health Survey, a cross-sectional population survey based on face-to-face home interviews.

PARTICIPANTS: 6507 people aged 16 years or older and living in Andalusia, Spain.

OUTCOMES: The response variable was disabling chronic pain. Multivariate multinomial logistic regression models were used to analyse the association of factors with disabling chronic pain. The sample design was considered throughout the statistical analysis.

RESULTS: The prevalence of disabling chronic pain in the Spanish adult population was 11.36% (95% CI 11.23 to 11.49), while that of non-disabling chronic pain was 5.67% (95% CI 5.57 to 5.77). Disabling chronic pain was associated with high multimorbidity (especially in women (51%) and in the elderly (70%) with three or more additional chronic diseases), as well as with disadvantaged social status (such as female gender (OR=2.12), advanced age ($OR_{10\text{-year increase}}$=1.28), unemployment (OR=1.33), manual work (OR=1.26), low income (OR=1.14) and reduced emotional social support (OR=1.04)). Other influential factors were tobacco consumption (OR=1.42), sleeping ≤7 hours (OR=1.2)], environmental or work conditions (OR=1.16) and quality of life (OR_{mental}=1.21, $OR_{physical}$=2.37).

CONCLUSIONS: The population with disabling chronic pain was associated with multimorbidity, vulnerable social status and an impaired quality of life. In contrast, the population with non-disabling chronic pain showed almost no differences when compared with the population without chronic pain. The association between DCP and mental disorders highlights the need for psychosocial services in the management of chronic pain.

Genome-wide association reveals contribution of MRAS to painful temporomandibular disorder in males.

Smith SB[1], Parisien M[2], Bair E[3,1], Belfer I[2], Chabot-Doré AJ[2], Gris P[2], Khoury S[2], Tansley S[2,3], Torosyan Y[4], Zaykin DV[5], Bernhardt O[6], de Oliveira Serrano P[7], Gracely RH[3], Jain D[8], Järvelin MR[9,10,11,12], Kaste LM[13], Kerr KF[8], Kocher T[14], Lähdesmäki R[15,16], Laniado N[17], Laurie CC[8], Laurie CA[8], Männikkö M[10,18], Meloto CB[2], Nackley AG[1], Nelson SC[8], Pesonen P[15], Ribeiro-Dasilva MC[19], Rizzatti-Barbosa CM[7], Sanders AE[3,20], Schwahn C[21], Sipilä K[22,23,15,24], Sofer T[25,26], Teumer A[27], Mogil JS[2,6], Fillingim RB[28], Greenspan JD[29], Ohrbach R[30], Slade GD[3,18,31], Maixner W[1], Diatchenko L[2].

Pain. **2018 Nov 13**. doi: 10.1097/j.pain.0000000000001438. PMID: 30431558. [Epub ahead of print]

Painful temporomandibular disorders (TMD) is the leading cause of chronic orofacial pain, but its underlying molecular mechanisms remain obscure. While many environmental factors have been associated with higher risk of developing painful TMD, family and twin studies support a heritable genetic component as well. We performed a GWAS assuming an additive genetic model of TMD in a discovery cohort of 999 cases and 2031 TMD-free controls from the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study. Using logistic models adjusted for sex, age, enrollment site, and race, we identified three distinct loci that were significant in combined or sex-segregated analyses. A single nucleotide polymorphism (SNP) on chromosome 3 (rs13078961) was significantly associated with TMD in males only (odds ratio [OR]=2.9, 95% CI: 2.02-4.27, P=2.2x10). This association was nominally replicated in a meta-analysis of seven independent orofacial pain cohorts including 160,194 participants (OR=1.16, 95% CI: 1.0-1.35, P = 2.3x10). Functional analysis in human dorsal root ganglia (DRG) and blood indicated this variant is an expression quantitative trait locus (eQTL), with the minor allele associated with decreased expression of the nearby muscle RAS oncogene homolog (MRAS) gene (beta = -0.51, P = 2.43x10). Male mice, but not female mice, with a null mutation of Mras displayed persistent mechanical allodynia in a model of inflammatory pain. Genetic and behavioral evidence support a novel mechanism by which genetically-determined MRAS expression moderates the resiliency to chronic pain. This effect is male-specific and may contribute to the lower rates of painful TMD in men.

CHRONIC PAIN (Continued)

Association of Cannabinoid Administration With Experimental Pain in Healthy Adults: A Systematic Review and Meta-analysis.

De Vita MJ[1], Moskal D[1], Maisto SA[1], Ansell EB [1,2].

JAMA Psychiatry. **2018 Nov 1**;75(11):1118-1127. doi: 10.1001/jamapsychiatry.2018.2503. PMID: 30422266.

IMPORTANCE: Cannabinoid drugs are widely used as analgesics, but experimental pain studies have produced mixed findings. The analgesic properties of cannabinoids remain unclear.

OBJECTIVE: To conduct a systematic review and meta-analysis of the association between cannabinoid drug administration and experimental pain outcomes in studies of healthy adults.

DESIGN, SETTING, AND PARTICIPANTS: A systematic search of PubMed, EMBASE, MEDLINE, PsycINFO, and CINAHL was conducted from the inception of each database to September 30, 2017. Studies were eligible for inclusion if they met criteria, including healthy participants and an experimentally controlled administration of any cannabinoid preparation in a quantified dose. Studies that used participants with chronic pain were excluded. Data extracted included study characteristics, cannabinoid types and doses, sex composition, and outcomes. Study quality was assessed using a validity measure previously established in published reviews. Random-effects meta-analyses were used to pool data and generate summary estimates.

MAIN OUTCOMES AND MEASURES: Experimental pain threshold, pain tolerance, pain intensity, pain unpleasantness, and mechanical hyperalgesia.

RESULTS: Eighteen placebo-controlled studies (with 442 participants) were identified. Of the 442 participants, 233 (52.7%) were male and 209 (47.3%) were female. For sample ages, 13 (72%) of the 18 studies reported a mean sample age (26.65 years), 4 (22%) reported a range, and 1 (6%) reported a median value. The search yielded sufficient data to analyze 18 pain threshold comparisons, 22 pain intensity comparisons, 9 pain unpleasantness comparisons, 13 pain tolerance comparisons, and 9 mechanical hyperalgesia comparisons. Cannabinoid administration was associated with small increases in pain threshold (Hedges g = 0.186; 95% CI, 0.054-0.318; P = .006), small to medium increases in pain tolerance (Hedges g = 0.225; 95% CI, 0.015-0.436; P = .04), and a small to medium reduction in the unpleasantness of ongoing experimental pain (Hedges g = 0.288; 95% CI, 0.104-0.472; P = .002). Cannabinoid administration was not reliably associated with a decrease in experimental pain intensity (Hedges g = 0.017; 95% CI, -0.120 to 0.154; P = .81) or mechanical hyperalgesia (Hedges g = 0.093; 95% CI, -0.059 to 0.244; P = .23). The mean quality rating across studies was good.

CONCLUSIONS AND RELEVANCE: Cannabinoid drugs may prevent the onset of pain by producing small increases in pain thresholds but may not reduce the intensity of experimental pain already being experienced; instead, cannabinoids may make experimental pain feel less unpleasant and more tolerable, suggesting an influence on affective processes. Cannabis-induced improvements in pain-related negative affect may underlie the widely held belief that cannabis relieves pain.

OTHER RESEARCH OF INTEREST

Veterans and Agent Orange: Update 11 (2018)

National Academies of Sciences, Engineering, and Medicine.

November 15, 2018. Washington, DC. Report at a Glance: Report highlights (HTML). Summary table (HTML).

From 1962 to 1971, the U.S. military sprayed herbicides over Vietnam to strip the thick jungle canopy that could conceal opposition forces, to destroy crops that those forces might depend on, and to clear tall grasses and bushes from the perimeters of U.S. base camps and outlying fire-support bases. The most-used chemical mixture sprayed was Agent Orange, which at the time of use was contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the most toxic form of dioxin.

Concerns from Vietnam veterans about their own—and their children's—health, as well as emerging evidence on ill effects of exposure to Agent Orange, led Congress to enact the Agent Orange Act of 1991. This legislation directed the U.S. Department of Veterans Affairs (VA) to ask the National Academies of Sciences, Engineering, and Medicine to comprehensively evaluate scientific and medical information regarding the health effects of exposure to Agent Orange, other herbicides used in Vietnam, and the various components of those herbicides, including TCDD. The first report, Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam (VAO), was published in 1994, and Congressionally mandated updates have been published approximately every 2 years since.

This report, Veterans and Agent Orange: Update 11 (2018), presents the committee's analysis of peer-reviewed, scientific reports published between September 30, 2014, and December 31, 2017, about associations between various health outcomes and exposure to TCDD and other chemicals in the herbicides used in Vietnam. The report also takes into account information from the existing evidence base.

OTHER RESEARCH OF INTEREST (Continued)

Inflammation as a predictor of disease course in posttraumatic stress disorder and depression: A prospective analysis from the Mind Your Heart Study.

Eswarappa M[1], Neylan TC[2], Whooley MA[3], Metzler TJ[4], Cohen BE[5].

Brain Behav Immun. **2018 Oct 30**. pii: S0889-1591(18)30764-5. doi: 10.1016/j.bbi.2018.10.012. PMID: 30389462. [Epub ahead of print]

BACKGROUND: Prior research has focused largely on the pro-inflammatory states of PTSD and depression, with few studies evaluating the direction of inflammation's association with these disorders. To clarify whether inflammation plays a role in the development of PTSD or depression, we assessed the predictive value of inflammatory biomarkers on the courses of these conditions in a cohort of Veterans.

METHODS: This research was part of the Mind Your Heart Study, a prospective cohort study designed to examine PTSD-related health outcomes. Between 2008 and 2010, 746 San Francisco area Veterans Administration patients were enrolled. At baseline, inflammatory biomarkers were measured from fasting morning venous blood draws, and cortisol and catecholamine levels were measured from 24-hour urine samples. PTSD was diagnosed using the PTSD Checklist at baseline and annual follow-up. Depression was evaluated using the 9-item Patient Health Questionnaire at baseline and follow-up. Ordinal logistic regression models were used to assess the predictive value of baseline biomarker levels on clinically relevant courses of PTSD and depression categorized and ordered as none, resolved, developed, and chronic.

RESULTS: After adjustment for age and sex, elevated levels of white blood cell count (OR = 1.27(1.10-1.47), p = 0.001), C-reactive protein (OR = 1.20(1.04-1.39), p = 0.02), fibrinogen (OR = 1.19(1.03-1.38), p = 0.02), and ESR (OR = 1.17(1.00-1.36, p = 0.05), and decreased levels of urine cortisol (OR = 0.84(0.71-0.99), p = 0.04) were significant predictors of poorer courses of PTSD. Elevated levels of WBC count (OR = 1.31(1.14-1.50), p < 0.001), CRP (OR = 1.24(1.07-1.43), p = 0.003), fibrinogen (OR = 1.26(1.09-1.46), p = 0.002), and catecholamines (OR = 1.17(1.01-1.36), p = 0.04) were significant predictors of poorer courses of depression. After additionally controlling for physical activity, elevated WBC count (p = 0.002) and decreased levels of urine cortisol (p = 0.05) remained significant predictors of PTSD course, and elevated WBC count (p = 0.001), CRP (p = 0.03), and fibrinogen (p = 0.02) remained significant predictors of depression course. After adjusting for all significant variables, elevated WBC count (p = 0.02) was a significant predictor of a poorer course of PTSD, and elevated WBC count (p = 0.04) and platelet count (p = 0.03) were significant predictors of a poorer course of depression.

CONCLUSIONS: Increased levels of several inflammatory biomarkers were associated with significantly increased odds of clinically worse courses of PTSD and depression. Inflammation may be a target for prevention and treatment of these mental health disorders.

CNS disease-related protein variants as blood-based biomarkers in traumatic brain injury.

Williams SM[1], Peltz C[1], Yaffe K[1], Schulz P[1], Sierks MR[2].

Neurology. **2018 Oct 9**;91(15):702-709. doi: 10.1212/WNL.0000000000006322. PMCID: PMC6177276. PMID: 30297502.

OBJECTIVE: To utilize a panel of 11 single chain variable fragments (scFvs) that selectively bind disease-related variants of TAR DNA-binding protein (TDP)-43, β-amyloid, tau, and α-synuclein to assess damage following traumatic brain injury (TBI), and determine if the presence of protein variants could account for the increased risk of various neurodegenerative diseases following TBI.

METHODS: We utilized the panel of 11 scFvs in a sensitive ELISA format to analyze sera from 43 older veterans, 25 who had experienced at least 1 TBI incident during their lifetime (~29.4 years after TBI), and 18 controls who did not incur TBI, in a cross-sectional study.

RESULTS: Each of the 11 scFvs individually could significantly distinguish between TBI and control samples, though they did not detect each TBI sample. Comparing the levels of all 11 variants, all 25 TBI cases displayed higher reactivity compared to the controls and receiver operating characteristic analysis revealed 100% sensitivity and specificity. Higher total protein variants levels correlated with TBI severity and with loss of consciousness. Oligomeric tau levels distinguished between single and multiple TBI incidents. While all TBI cases were readily selected with the panel, the binding pattern varied from patient to patient, suggesting subgroups that are at increased risk for different neurodegenerative diseases.

CONCLUSION: The panel of protein variants-specific scFvs can be used to identify blood-based biomarkers indicative of TBI even 20 years or more after the initial TBI. Being able to identify subgroups of biomarker profiles allows for the possibility of individually targeted treatments.

OTHER RESEARCH OF INTEREST (Continued)

PTSD Symptom Severity, but Not Trauma Type, Predicts Mental Health Help-seeking in the Military.

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J Psychiatr Pract. **2018 Sep**;24(5):310-316. doi: 10.1097/PRA.0000000000000331. PMID: 30427817.

OBJECTIVE: Although veterans with posttraumatic stress disorder (PTSD) have been reported to have high rates of inadequate treatment, to our knowledge this is the first study to evaluate associations between each individual PTSD symptom and treatment-seeking, and the first PTSD help-seeking study to evaluate variables across all- rather than specific-types of trauma.

METHODS: This case-control study surveyed a consecutive sample of active duty military outpatients with trauma histories (N=211), comparing those attending voluntary mental health services (help-seeking cases, n=128) or mandatory dental services required for all active duty personnel (general military population controls, n=83). We used logistic regression to estimate associations between help-seeking and demographics, PTSD symptoms, trauma type, suicide attempts, substance use problems, and chronic pain, with each variable adjusted for sex, age, and race.

RESULTS: Significant associations were found between help-seeking and PTSD diagnosis (adjusted odds ratio=4.15, P<0.001) and between help-seeking and severities of PTSD symptoms (total, clusters, all individual symptoms except recklessness; each adjusted odds ratio>1, P<0.05).

CONCLUSIONS: In this clinical sample, a clear positive relationship was found between help-seeking and PTSD symptom severity, but not with trauma type, suicide attempts, substance use problems, or pain, after adjusting for multiple testing. Possible explanations and implications of these findings are discussed.

Microglial calcium release-activated calcium (CRAC) channel inhibition improves outcome from experimental traumatic brain injury and microglia-induced neuronal death.

Mizuma A[1,2], Kim JY[3,4], Kacimi R[5], Stauderman K[6], Dunn M[7], Hebbar S[8], Yenari M[9].

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Store-operated Ca2+ entry (SOCE) mediated by calcium release-activated calcium (CRAC) channels contributes to calcium signaling. The resulting intracellular calcium increases activate calcineurin, which in turn activates immune transcription factor nuclear factor of activated T cells (NFAT). Microglia contain CRAC channels, but little is known whether these channels play a role in acute brain insults. We studied a novel CRAC channel inhibitor to explore the therapeutic potential of this compound in microglia-mediated injury. Cultured microglial BV2 cells were activated by Toll-like receptor agonists or IFNγ. Some cultures were treated with a novel CRAC channel inhibitor (CM-EX-137). Western blots revealed the presence of CRAC channel proteins STIM1 and Orai1 in BV2 cells. CM-EX-137 decreased nitric oxide (NO) release and inducible nitric oxide synthase (iNOS) expression in activated microglia, and reduced agonist-induced intracellular calcium accumulation in microglia, while suppressing inflammatory transcription factors nuclear factor kappa B (NF-kB) and nuclear factor of activated T cells (NFAT). Male C57/BL6 mice exposed to experimental brain trauma (TBI) and treated with CM-EX-137 had decreased lesion size, brain hemorrhage and improved neurological deficits with decreased microglial activation, iNOS and Orai1 and STIM1 levels. We suggest a novel anti-inflammatory approach for treating acute brain injury. Our observations also shed light on new calcium signaling pathways not previously described in brain injury models.

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