GULF WAR ILLNESS

Depressed prostaglandins and leukotrienes in veterans with Gulf War illness.

Golomb BA[1], Koslik HJ[1], Christians U[2], Ritchie J[1], Wilson P[3], Elkins N[3], Klawitter J[2], Klawitter J[2], Smith D[4], Repine JE[3].

J Environ Sci Health B. **2019 Apr 29**:1-17. doi: 10.1080/03601234.2019.1596001. PMID: 31033394. [Epub ahead of print]

BACKGROUND: There is need to understand biological markers and mechanisms in Gulf War illness (GWI).

GOAL: To examine whether and how eicosanoids - prostaglandins and leukotrienes - are altered in veterans with GWI.

METHODS: Seventy participants including 37 GWI and 33 healthy controls, shared exposure information, and had plasma eicosanoids assessed - prostaglandin F2 alpha (pgf2α), prostaglandin D2 (pgd2), leukotriene B4 (lb4) among others. Values were compared for GWI versus controls. Eicosanoid intercorrelations were compared in cases vs. controls. For the most significantly altered eicosanoid in GWI, exposure and symptom relations were assessed.

RESULTS: Prostaglandins and leukotrienes were depressed in GWI, strongest for pgf2α, then lb4. Eicosanoid intercorrelations differed in GWI vs. controls. Fuel-solvent, pesticide, radioactive chemicals and metal exposures related negatively to pgf2α; as, in GWI, did chemical attack and vaccines. Multivariate predictors included fuels-solvents and radioactive chemicals (negative); tetanus vaccine and herbicides (positive). Fuels-solvents and radioactive chemicals predicted lower pgf2α in cases, controls, and all participants controlled for case status. Lower pgf2α related to GWI "Kansas criteria" domains of pain, respiratory, and (borderline significantly) skin symptoms.

CONCLUSION: Multiple eicosanoids are depressed in GWI, particularly pgf2α and lb4. Prior fuel-solvent exposures, radioactive chemicals, and (in GWI cases) vaccines were linked to lower pgf2α.

CHRONIC FATIGUE SYNDROME

Validation of impaired Transient Receptor Potential Melastatin 3 ion channel activity in natural killer cells from Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis patients.

Cabanas H[1,2,3], Muraki K[4,5], Balinas C[6,7,5], Eaton-Fitch N[6,7,5], Staines D[6,7,5], Marshall-Gradisnik S[6,7,5].

Mol Med. **2019 Apr 23**;25(1):14. doi: 10.1186/s10020-019-0083-4. PMID: 31014226.

BACKGROUND: Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis (CFS/ME) is a complex multifactorial disorder of unknown cause having multi-system manifestations. Although the aetiology of CFS/ME remains elusive, immunological dysfunction and more particularly reduced cytotoxic activity in natural killer (NK) cells is the most consistent laboratory finding. The Transient Receptor Potential (TRP) superfamily of cation channels play a pivotal role in the pathophysiology of immune diseases and are therefore potential therapeutic targets. We have previously identified single nucleotide polymorphisms in TRP genes in peripheral NK cells from CFS/ME patients. We have also described biochemical pathway changes and calcium signaling perturbations in NK cells from CFS/ME patients. Notably, we have previously reported a decrease of TRP cation channel subfamily melastatin member 3 (TRPM3) function in NK cells isolated from CFS/ME patients compared with healthy controls after modulation with pregnenolone sulfate and ononetin using a patch-clamp technique. In the present study, we aim to confirm the previous results describing an impaired TRPM3 activity in a new cohort of CFS/ME patients using a whole cell patch-clamp technique after modulation with reversible TRPM3 agonists, pregnenolone sulfate and nifedipine, and an effective TRPM3 antagonist, ononetin. Indeed, no formal research has commented on using pregnenolone sulfate or nifedipine to treat CFS/ME patients while there is evidence that clinicians prescribe calcium channel blockers to improve different symptoms.

METHODS: Whole-cell patch-clamp technique was used to measure TRPM3 activity in isolated NK cells from twelve age- and sex-matched healthy controls and CFS/ME patients, after activation with pregnenolone sulfate and nifedipine and inhibition with ononetin.

RESULTS: We confirmed a significant reduction in amplitude of TRPM3 currents after pregnenolone sulfate stimulation in isolated NK cells from another cohort of CFS/ME patients compared with healthy controls. The pregnenolone sulfate-evoked ionic currents through TRPM3 channels were again significantly modulated by ononetin in isolated NK cells from healthy controls compared with CFS/ME patients. In addition, we used nifedipine, another reversible TRPM3 agonist to support the previous findings and found similar results confirming a significant loss of the TRPM3 channel activity in CFS/ME patients.

CONCLUSIONS: Impaired TRPM3 activity was validated in NK cells isolated from CFS/ME patients using different pharmacological tools and whole-cell patch-clamp technique as the gold standard for ion channel research. This investigation further helps to establish TRPM3 channels as a prognostic marker and/ or a potential therapeutic target for CFS/ME.

HEADACHE and MIGRAINE

Onset of efficacy and duration of response of galcanezumab for the prevention of episodic migraine: a post-hoc analysis.

Goadsby PJ[1], Dodick DW[2], Martinez JM[3], Ferguson MB[3], Oakes TM[3], Zhang Q[4], Skljarevski V[3], Aurora SK[3].

J Neurol Neurosurg Psychiatry. **2019 Aug**;90(8):939-944. doi: 10.1136/jnnp-2018-320242. PMID: 31004075 Epub 2019 Apr 19.

BACKGROUND AND OBJECTIVE: As new migraine prevention treatments are developed, the onset of a preventive effect, how long it is maintained and whether patients initially non-responsive develop clinically meaningful responses with continued treatment can be assessed.

METHODS: Analyses were conducted post-hoc of a double-blind, placebo-controlled, phase II-a study in patients with episodic migraine receiving galcanezumab 150 mg or placebo biweekly for 12 weeks (*Lancet Neurol* 13:885, 2014). The number of migraine headache days per week, and onset of efficacy measured as the first week galacanezumab separated from placebo were determined. Patients with ≥50%, ≥75% and 100% reduction in migraine headache days from baseline at months 1, 2 and 3 were calculated and defined as sustained responses. Non-responders (<50% response) at month 1 or 2 who then showed ≥50%, ≥75% and 100% response at later time-points were calculated.

RESULTS: Patients were randomised to galcanezumab (n=107) or placebo (n=110). A significant (p=0.018) change of -0.89±0.11 (galcanezumab) vs -0.53±0.11 (placebo) migraine headache days indicated onset at week 1. Forty-seven per cent of galcanezumab and 25% of placebo patients responding at month 1 maintained response through months 2 and 3. Of non-responders at month 1, 27% on galcanezumab and 20% on placebo responded on months 2 and 3, and 50% of galcanezumab non-responders in months 1 and 2 responded on month 3, vs 24% on placebo.

CONCLUSIONS: The onset of efficacy of galcanezumab is within 1 week in a majority of patients, and patients receiving galcanezumab are twice more likely to maintain responses than placebo patients. Early non-responders may respond by month 2 or month 3.

TRIAL REGISTRATION NUMBER: **NCT01625988**.

CHRONIC PAIN

Complementary and Integrated Health Approaches: What Do Veterans Use and Want.

Taylor SL[1,2], Hoggatt KJ[3,4], Kligler B[5].

J Gen Intern Med. **2019 Apr 22**. doi: 10.1007/s11606-019-04862-6. PMID: 31011973. [Epub ahead of print]

OBJECTIVES: Non-pharmacological treatment options for common conditions such as chronic pain, anxiety, and depression are being given increased consideration in healthcare, especially given the recent emphasis to address the opioid crisis. One set of non-pharmacological treatment options are evidence-based complementary and integrative health (CIH) approaches, such as yoga, acupuncture, and meditation. The Veterans Health Administration (VHA), the nation's largest healthcare system, has been at the forefront of implementing CIH approaches, given their patients' high prevalence of pain, anxiety, and depression. We aimed to conduct the first national survey of veterans' interest in and use of CIH approaches.

METHODS: Using a large national convenience sample of veterans who regularly use the VHA, we conducted the first national survey of veterans' interest in, frequency of and reasons for use of, and satisfaction with 26 CIH approaches (n = 3346, 37% response rate) in July 2017.

RESULTS: In the past year, 52% used any CIH approach, with 44% using massage therapy, 37% using chiropractic, 34% using mindfulness, 24% using other meditation, and 25% using yoga. For nine CIH approaches, pain and stress reduction/relaxation were the two most frequent reasons veterans gave for using them. Overall, 84% said they were interested in trying/learning more about at least one CIH approach, with about half being interested in six individual CIH approaches (e.g., massage therapy, chiropractic, acupuncture, acupressure, reflexology, and progressive relaxation). Veterans appeared to be much more likely to use each CIH approach outside the VHA vs. within the VHA.

CONCLUSIONS: Veterans report relatively high past-year use of CIH approaches and many more report interest in CIH approaches. To address this gap between patients' level of interest in and use of CIH approaches, primary care providers might want to discuss evidence-based CIH options to their patients for relevant health conditions, given most CIH approaches are safe.

CHRONIC PAIN (Continued)

Delivering Cognitive Behavioral Therapy for Insomnia in Military Personnel and Veterans.

Kelly MR[1], Robbins R[2], Martin JL[3].

Sleep Med Clin. **2019 Jun**;14(2):199-208. doi: 10.1016/j.jsmc.2019.01.003. PMID: 31029187. Epub 2019 Mar 29.

Insomnia is commonly reported by military populations, especially those with comorbid mental and physical health conditions. Co-occurring conditions result in an altered presentation of insomnia symptoms, and complicate provision of cognitive-behavioral therapy for insomnia (CBT-I), requiring supplementary assessment or modifications to traditional techniques. CBT-I has consistently demonstrated positive outcomes for active-duty service members and veterans, even in the context of significant comorbidities such as post-traumatic stress disorder, depression, sleep apnea, and chronic pain. Despite its promise, studies of CBT-I in some populations, including women and individuals with substance use disorders, remain relatively understudied in active-duty and veteran populations.

Setting Expectations, Following Orders, Safety, and Standardization: Clinicians' Strategies to Guide Difficult Conversations About Opioid Prescribing.

Wyse JJ[1,2], Ganzini L[3,4], Dobscha SK[3,4], Krebs EE[5,6], Morasco BJ[3,4].

J Gen Intern Med. **2019 Apr 22**. doi: 10.1007/s11606-019-04983-y. PMID: 31011964. [Epub ahead of print]

BACKGROUND: Evidence has continued to accumulate regarding the potential risks of treating chronic pain with long-term opioid therapy (LTOT). Clinical practice guidelines now encourage clinicians to implement practices designed to reduce opioid-related risks. Yet how clinicians implement these guidelines within the context of the patient encounter has received little attention.

OBJECTIVE: This secondary analysis aimed to identify and describe clinicians' strategies for managing prescription opioid misuse and aberrant behaviors among patients prescribed LTOT for chronic pain.

DESIGN: Individual interviews guided by a semi-structured interview protocol probed: (1) methods clinicians utilize to reduce prescription opioid misuse and address aberrant opioid-related behaviors; (2) how clinicians respond to misuse; and (3) resources and constraints faced in managing and treating misuse among their patients.

PARTICIPANTS: Interviews were conducted with 24 physicians and nurse practitioners, representing 22 Veterans Health Administration (VA) facilities across the USA, who had one or more patients in their clinical panels who were prescribed LTOT for the treatment of chronic non-cancer pain.

APPROACH: Qualitative content analysis was the analytic approach utilized. A codebook was developed iteratively following group coding and discussion. All transcripts were coded with the finalized codebook. Quotes pertaining to key themes were retrieved and, following careful review, sorted into themes, which were then further categorized into sub-themes. Quotes that exemplified key sub-themes were selected for inclusion.

KEY RESULTS: We detail the challenges clinicians describe in navigating conversations with patients around prescription opioid misuse, which include patient objection as well as clinician ambivalence. We identify verbal heuristics as one strategy clinicians utilize to structure these difficult conversations, and describe four heuristics: setting expectations, following orders, safety, and standardization.

CONCLUSION: Clinicians frequently use verbal heuristics to routinize and increase the efficiency of care management discussions related to opioid prescribing, redirect responsibility, and defuse the potential emotional charge of the encounter.

CHRONIC PAIN (Continued)

Pain Anxiety as a Mechanism Linking Pain Severity and Opioid Misuse and Disability Among Individuals With Chronic Pain.

Rogers AH[1], Bakhshaie J, Zvolensky MJ, Vowles KE.

J Addict Med. **2019 Apr 24**. doi: 10.1097/ADM.0000000000000538. PMID: 31033671. [Epub ahead of print]

OBJECTIVE: Chronic pain affects a significant number of individuals in the United States and is associated with several negative health-related outcomes, including possibility of opioid misuse and disability. The identification of factors associated with both opioid misuse and disability is of critical public health importance, and significant research suggests that pain severity has been shown to be associated with both. Pain-related anxiety has been uniquely associated with both opioid misuse and disability, yet little research has examined pain-related anxiety as a potential mechanism linking pain severity with opioid misuse and disability.

METHOD: Therefore, the current study examined whether pain-related anxiety explains, in part, the relationship between pain severity, opioid misuse, and disability among 396 adults with chronic pain (55.8% female, Mage 36.61, SD 11.40).

RESULTS: Cross-sectional analyses indicated that pain-related anxiety significantly mediated the relationship between pain severity, opioid misuse outcomes, and psychosocial disability, but not physical disability.

CONCLUSIONS: These results build upon the literature indicating the importance of pain-related anxiety in those with chronic pain by suggesting this construct may account, in part, for the relation of pain intensity to opioid misuse and psychosocial disability. Future research should longitudinally examine these associations.

Differences in Long-Term Physical Activity Trajectories among Individuals with Chronic Widespread Pain: A Secondary Analysis of a Randomized Controlled Trial.

Martin KR[1,2], Druce KL[3], Murdoch SE[1], D'Ambruoso L[4], Macfarlane GJ[1,2].

Eur J Pain. **2019 Apr 29**. doi: 10.1002/ejp.1410. PMID: 31034106. PMID: 31034106. [Epub ahead of print]

BACKGROUND: Little is known about long-term physical activity (PA) maintenance in those with chronic widespread pain (CWP) following an exercise intervention. This study examined PA over time to identify the existence and characteristics of subgroups following distinct PA trajectories.

METHODS: Data come from individuals with CWP who took part in a 2x2 factorial randomized controlled trial, receiving either exercise or both exercise and cognitive behavioural therapy treatment. Information, including self-report PA, was collected at baseline recruitment, immediately post-intervention, 3, 24 and 60+ month post-treatment. Analyses were conducted on 196 men and women with ≥3 PA data-points. Group-based itrajectory modelling was used to identify latent PA trajectory groups and baseline characteristics (e.g., demographics, pain, self-rated health, fatigue, coping-strategy use, kinesiophobia) of these groups.

RESULTS: The best fitting model identified was one with three trajectories: "non-engagers" (n=32), "maintainers" (n=144) and "super-maintainers" (n=20). Overall, mean baseline PA levels were significantly different between groups (non-engagers: 1.1; maintainers: 4.6; super-maintainers: 8.6, $p<0.001$) and all other follow-up points. Non-engagers reported, on average, greater BMI, higher disabling chronic pain, poorer self-rated health, physical functioning, as well as greater use of passive coping strategies and lower use of active coping strategies.

CONCLUSIONS: The majority of individuals with CWP receiving exercise as part of a trial were identified as long-term PA maintainers. Participants with poorer physical health and coping response to symptoms were identified as non-engagers. For optimal symptom management, a stratified approach may enhance initiation and long-term PA maintenance in individuals with CWP.

IRRITABLE BOWEL SYNDROME

Personalized medicine in functional gastrointestinal disorders: Understanding pathogenesis to increase diagnostic and treatment efficacy.

Wang XJ[1], Camilleri M[2].

World J Gastroenterol. **2019 Mar 14**;25(10):1185-1196. doi: 10.3748/wjg.v25.i10.1185. PMCID: PMC6421234. PMID: 30886502.

There is overwhelming evidence that functional gastrointestinal disorders (FGIDs) are associated with specific mechanisms that constitute important targets for personalized treatment. There are specific mechanisms in patients presenting with functional upper gastrointestinal symptoms (UGI Sx). Among patients with UGI Sx, approximately equal proportions (25%) of patients have delayed gastric emptying (GE), reduced gastric accommodation (GA), both impaired GE and GA, or neither, presumably due to increased gastric or duodenal sensitivity. Treatments targeted to the underlying pathophysiology utilize prokinetics, gastric relaxants, or central neuromodulators. Similarly, specific mechanisms in patients presenting with functional lower gastrointestinal symptoms, especially with diarrhea or constipation, are recognized, including at least 30% of patients with functional constipation pelvic floor dyssynergia and 5% has colonic inertia (with neural or interstitial cells of Cajal loss in myenteric plexus); 25% of patients with diarrhea-predominant irritable bowel syndrome (IBSD) has evidence of bile acid diarrhea; and, depending on ethnicity, a varying proportion of patients has disaccharidase deficiency, and less often sucrose-isomaltase deficiency. Among patients with predominant pain or bloating, the role of fermentable oligosaccharides, disaccharides, monosaccharides and polyols should be considered. Personalization is applied through pharmacogenomics related to drug pharmacokinetics, specifically the role of CYP2D6, 2C19 and 3A4 in the use of drugs for treatment of patients with FGIDs. Single mutations or multiple genetic variants are relatively rare, with limited impact to date on the understanding or treatment of FGIDs. The role of mucosal gene expression in FGIDs, particularly in IBS-D, is the subject of ongoing research. In summary, the time for personalization of FGIDs, based on deep phenotyping, is here; pharmacogenomics is relevant in the use of central neuromodulators. There is still unclear impact of the role of genetics in the management of FGIDs.

OTHER RESEARCH OF INTEREST

Metabolomic analysis of male combat veterans with post traumatic stress disorder.

Mellon SH[1], Bersani FS[2], Lindqvist D[2], Hammamieh R[3], Donohue D[3], Dean K[4], Jett M[3], Yehuda R[5], Flory J[5], Reus VI[2], Bierer LM[5], Makotkine I[5], Abu Amara D[6], Henn Haase C[6], Coy M[2], Doyle FJ 3rd[4], Marmar C[6,7], Wolkowitz OM[2].

PLoS One. **2019 Mar 18**;14(3):e0213839. doi: 10.1371/journal.pone.0213839. eCollection 2019. PMCID: PMC6422302. PMID: 30883584.

Posttraumatic stress disorder (PTSD) is associated with impaired major domains of psychology and behavior. Individuals with PTSD also have increased co-morbidity with several serious medical conditions, including autoimmune diseases, cardiovascular disease, and diabetes, raising the possibility that systemic pathology associated with PTSD might be identified by metabolomic analysis of blood. We sought to identify metabolites that are altered in male combat veterans with PTSD. In this case-control study, we compared metabolomic profiles from age-matched male combat trauma-exposed veterans from the Iraq and Afghanistan conflicts with PTSD (n = 52) and without PTSD (n = 51) ('Discovery group'). An additional group of 31 PTSD-positive and 31 PTSD-negative male combat-exposed veterans was used for validation of these findings ('Test group'). Plasma metabolite profiles were measured in all subjects using ultrahigh performance liquid chromatography/tandem mass spectrometry and gas chromatography/mass spectrometry. We identified key differences between PTSD subjects and controls in pathways related to glycolysis and fatty acid uptake and metabolism in the initial 'Discovery group', consistent with mitochondrial alterations or dysfunction, which were also confirmed in the 'Test group'. Other pathways related to urea cycle and amino acid metabolism were different between PTSD subjects and controls in the 'Discovery' but not in the smaller 'Test' group. These metabolic differences were not explained by comorbid major depression, body mass index, blood glucose, hemoglobin A1c, smoking, or use of analgesics, antidepressants, statins, or anti-inflammatories. These data show replicable, wide-ranging changes in the metabolic profile of combat-exposed males with PTSD, with a suggestion of mitochondrial alterations or dysfunction, that may contribute to the behavioral and somatic phenotypes associated with this disease.

OTHER RESEARCH OF INTEREST (Continued)

Efficacy of Integrated Exposure Therapy vs Integrated Coping Skills Therapy for Comorbid Posttraumatic Stress Disorder and Alcohol Use Disorder: A Randomized Clinical Trial.

Norman SB[1,2,3,4], Trim R[1,4], Haller M[1,4], Davis BC[1,5], Myers US[6], Colvonen PJ[1,3,4], Blanes E[1], Lyons R[1,7], Siegel EY[8], Angkaw AC[1,2,4,7], Norman GJ[4], Mayes T[1,4].

JAMA Psychiatry. **2019 Apr 24**. doi: 10.1001/jamapsychiatry.2019.0638. PMCID: PMC6487906. PMID: 31017639. [Epub ahead of print]

Importance: Co-occurrence of posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD) is common and associated with psychiatric and functional problems. Understanding whether exposure therapy is tolerable and efficacious for treating PTSD and AUD is critical to ensure that best practice treatments are available.

Objective: To compare the efficacy of integrated (ie, targeting both PTSD and alcohol use) prolonged exposure (I-PE) therapy with present-centered integrated coping skills (I-CS) therapy, a more commonly available treatment, in reducing PTSD symptoms and alcohol use.

Design, Setting, and Participants: This prospective randomized clinical trial with masked assessments considered 186 veterans seeking Veterans Affairs mental health services. A total of 119 veterans with PTSD and AUD were randomized. Data were collected from February 1, 2013, to May 31, 2017, before treatment, after treatment, and at 3- and 6-month follow-ups. Intention-to-treat analyses were performed.

Interventions: Veterans underwent I-PE (Concurrent Treatment of PTSD and Substance Use Disorder Using Prolonged Exposure) or I-CS (Seeking Safety) therapy.

Main Outcomes and Measures: A priori planned outcomes were PTSD symptoms (Clinician Administered PTSD Scale for DSM-5) and percentage of heavy drinking days (Timeline Follow-Back) before treatment, after treatment, and at 3- and 6-month follow-ups.

Results: A total of 119 veterans (mean [SD] age, 41.6 [12.6] years; 107 [89.9%] male) were randomized. Linear mixture models found that PTSD symptoms decreased in both conditions, with a significantly greater decrease for I-PE treatment compared with I-CS treatment (treatment × time interaction, -2.83; F3,233.1 = 4.92; Cohen d = 0.41; P = .002). The percentage of heavy drinking days improved in both conditions but was not statistically different between I-PE and I-CS treatment (treatment × time interaction, 1.8%; F3,209.9 = 0.18; Cohen d = 0.04; P = .91).

Conclusions and Relevance: The I-PE arm had a greater reduction in PTSD symptoms than the I-CS arm and comparable drinking decreases. The study provides evidence that exposure therapy is more efficacious in treating PTSD than a more commonly available integrated treatment without exposure for comorbid PTSD and AUD.

Trial Registration: ClinicalTrials.gov identifier: **NCT01601067**.

OTHER RESEARCH OF INTEREST (Continued)

Altered overnight levels of pro-inflammatory cytokines in men and women with posttraumatic stress disorder.

Küffer A[1], Straus LD[2], Prather AA[3], Inslicht SS[4], Richards A[1], Shigenaga JK[1], Madden E[5], Metzler TJ[5], Neylan TC[4], O'Donovan A[4].

Psychoneuroendocrinology. **2019 Apr**;102:114-120. doi: 10.1016/j.psyneuen.2018.12.002. PMCID: PMC6420348. PMID: 30544002. Epub 2018 Dec 5.

BACKGROUND: Posttraumatic stress disorder (PTSD) is associated with disturbed sleep and elevated levels of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). Studies in animals and healthy humans have also shown that disrupted sleep elevates pro-inflammatory cytokines, including IL-6 and TNF-α. A better understanding of overnight cytokine levels and sleep might shed light on possible mechanisms for elevated inflammation in PTSD. Thus, we investigated overnight levels of IL-6 and TNF-α in individuals with and without PTSD while recording sleep polysomnography (PSG).

METHOD: Serum samples were collected from otherwise healthy, medication-free participants with chronic PTSD (n = 44; 50% female; M age = 30.34 ± 8.11) and matched controls (n = 49; 53% female; M age = 30.53 ± 6.57) during laboratory PSG. Levels of IL-6 and TNF-α were measured at hours 0, 2, 4, 6, and 8 after typical sleep onset time using serial serum samples. Plasma IL-6 and TNF-α levels were quantified using enzyme-linked immunosorbent assays.

RESULTS: Growth model analysis indicated a significant group by time interaction for IL-6 (t[247] = -2.92, p = .005) and a significant group by sex by time interaction for TNF-α (t[275] = 2.02, p = .04). PTSD positive men and women initially had higher IL-6 and TNF-α at sleep onset, but not at the end of their sleep cycle. Men with PTSD showed a peak of TNF-α at the end of the sleep cycle, whereas male control subjects demonstrated an inverted U-shaped profile. There were no significant differences in TNF-α levels overnight between women with and without PTSD.

CONCLUSION: To our knowledge, this is the largest study to examine IL-6 overnight in a PTSD sample and the first study to examine overnight TNF-α in PTSD. Overnight IL-6 and TNF-α levels may be altered in individuals with PTSD compared to those without PTSD, and TNF-α trajectories also differed by sex. The current findings highlight the need to consider sex, sleep, time of day, and circadian variation when examining inflammation in PTSD. Additional research in broader study samples will be necessary to clarify associations between disrupted sleep, cytokines, and increased risk for disease in PTSD.

Efficacy and Safety of High-frequency Repetitive Transcranial Magnetic Stimulation for Post-Stroke Depression: A Systematic Review and Meta-Analysis.

Liu C[1], Wang M[1], Liang X[2], Xue J[1], Zhang G[3].

Arch Phys Med Rehabil. **2019 Apr 16**. pii: S0003-9993(19)30242-4. doi: 10.1016/j.apmr.2019.03.012. PMID: 31002813. [Epub ahead of print]

OBJECTIVE: To summarize and systematically review the efficacy and safety of high frequency repetitive transcranial magnetic stimulation (HF-rTMS) for depression in stroke patients.

DATA SOURCES: Six databases (Wanfang, CNKI, PubMed, Embase, Cochrane Library, and Web of Science) were searched from inception until November 15, 2018.

STUDY SELECTION: Seventeen randomized controlled trials were included for meta-analysis.

DATA EXTRACTION: Two independent reviewers selected potentially relevant studies based on the inclusion criteria, extracted data, and evaluated the methodological quality of the eligible trials using the Physiotherapy Evidence Database (PEDro).

DATA SYNTHESIS: We calculated the combined effect size (standardized mean difference [SMD] and odds ratio [OR]) for the corresponding effects models. Physiotherapy Evidence Database scores ranged from 7 to 8 points (mean = 7.35). The study results indicated that HF-rTMS had significantly positive effects on depression in stroke patients. The effect sizes of the SMD ranged from small to large (SMD = -1.01; 95% confidence interval [95% CI], -1.36 to -0.66; P < .001; I2 = 85%; n = 1053), and the effect sizes of the OR were large (response rates: 58.43% VS 33.59%; OR = 3.31; 95% CI, 2.25 to 4.88; P < .001; I2 = 0%; n = 529; remission rates: 26.59% VS 12.60%; OR = 2.72; 95% CI, 1.69 to 4.38; P < .001; I2 = 0%; n = 529). In terms of treatment side-effects, the HF-rTMS group was more prone to headache than the control group (OR = 3.53; 95% CI, 1.85 to 8.55; P < .001; I2 = 0%; n = 496).

CONCLUSIONS: HF-rTMS is an effective intervention for post-stroke depression, although treatment safety should be further verified via large sample multi-center trials.

OTHER RESEARCH OF INTEREST (Continued)

Effect of a Workplace Wellness Program on Employee Health and Economic Outcomes: A Randomized Clinical Trial.

Song Z[1], Baicker K[2,3].

JAMA. **2019 Apr 16**;321(15):1491-1501. doi: 10.1001/jama.2019.3307. PMCID: PMC6484807. PMID: 30990549.

Comment in: Employer Wellness Programs-A Work in Progress. [JAMA. 2019]

Importance: Employers have increasingly invested in workplace wellness programs to improve employee health and decrease health care costs. However, there is little experimental evidence on the effects of these programs.

Objective: To evaluate a multicomponent workplace wellness program resembling programs offered by US employers.

Design, Setting, and Participants: This clustered randomized trial was implemented at 160 worksites from January 2015 through June 2016. Administrative claims and employment data were gathered continuously through June 30, 2016; data from surveys and biometrics were collected from July 1, 2016, through August 31, 2016.

Interventions: There were 20 randomly selected treatment worksites (4037 employees) and 140 randomly selected control worksites (28 937 employees, including 20 primary control worksites [4106 employees]). Control worksites received no wellness programming. The program comprised 8 modules focused on nutrition, physical activity, stress reduction, and related topics implemented by registered dietitians at the treatment worksites.

Main Outcomes and Measures: Four outcome domains were assessed. Self-reported health and behaviors via surveys (29 outcomes) and clinical measures of health via screenings (10 outcomes) were compared among 20 intervention and 20 primary control sites; health care spending and utilization (38 outcomes) and employment outcomes (3 outcomes) from administrative data were compared among 20 intervention and 140 control sites.

Results: Among 32 974 employees (mean [SD] age, 38.6 [15.2] years; 15 272 [45.9%] women), the mean participation rate in surveys and screenings at intervention sites was 36.2% to 44.6% (n = 4037 employees) and at primary control sites was 34.4% to 43.0% (n = 4106 employees) (mean of 1.3 program modules completed). After 18 months, the rates for 2 self-reported outcomes were higher in the intervention group than in the control group: for engaging in regular exercise (69.8% vs 61.9%; adjusted difference, 8.3 percentage points [95% CI, 3.9-12.8]; adjusted P = .03) and for actively managing weight (69.2% vs 54.7%; adjusted difference, 13.6 percentage points [95% CI, 7.1-20.2]; adjusted P = .02). The program had no significant effects on other prespecified outcomes: 27 self-reported health outcomes and behaviors (including self-reported health, sleep quality, and food choices), 10 clinical markers of health (including cholesterol, blood pressure, and body mass index), 38 medical and pharmaceutical spending and utilization measures, and 3 employment outcomes (absenteeism, job tenure, and job performance).

Conclusions and Relevance: Among employees of a large US warehouse retail company, a workplace wellness program resulted in significantly greater rates of some positive self-reported health behaviors among those exposed compared with employees who were not exposed, but there were no significant differences in clinical measures of health, health care spending and utilization, and employment outcomes after 18 months. Although limited by incomplete data on some outcomes, these findings may temper expectations about the financial return on investment that wellness programs can deliver in the short term.

Trial Registration: ClinicalTrials.gov Identifier: NCT03167658.

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