GULF WAR ILLNESS

Post-exertional malaise in veterans with gulf war illness.

Lindheimer JB[1], Stegner AJ[1], Wylie GC[2], Klein-Adams JC[3], Almassi NE[1], Ninneman JV[1], VanRiper SM[1], Dougherty RJ[4], Falvo MJ[5], Cook DB[6].

Int J Psychophysiol. **2019 Nov 28**. pii: S0167-8760(19)30549-5. doi: 10.1016/j.ijpsycho.2019.11.008. PMID: 31786249. [Epub]

Post-exertional malaise (PEM) is a potentially debilitating aspect of Gulf War Illness (GWI) that has received limited research attention. The purpose of the present investigation was to determine symptom severity changes following exercise in Veterans with GWI compared to control Veterans without GWI (CO). Sixty-seven Veterans (n = 39 GWI; n = 28 CO) underwent a 30-minute submaximal exercise challenge at 70% of heart rate reserve. Symptom measurements (e.g. fatigue, pain) occurred pre-, immediately post-, and 24-hour post-exercise. Self-reported physical and mental health, and physiological and perceptual responses to exercise were compared between groups using descriptive statistics, independent samples t-tests and repeated measures Analysis of Variance (RM-ANOVA). Post-exertional malaise was modeled using Group by Time (2 × 3) doubly-multivariate, RM-MANOVAs for (1) mood, (2) pain and (3) GWI-related symptoms, respectively (α = 0.05). Data were analyzed for the full sample of Veterans with GWI (n = 39) compared to CO (n = 28) and a subsample of Veterans (n = 18) who endorsed "feeling unwell after physical exercise or exertion" ("PEM endorsers") during screening. Veterans with GWI reported significantly lower physical and mental health. Groups exercised at similar relative exercise intensities, but GWI perceived exercise as more painful and fatiguing. Group-by-Time interactions were not significant for the entire sample for the three PEM models, however limiting the GWI sample to "PEM endorsers" resulted in significant interactions for Pain- and GWI-related PEM models. These results indicate that not all GVs with GWI experience PEM 24 h after exercise, and that more research is needed to determine the extent that exercise worsens symptoms in GWI.

CHRONIC FATIGUE SYNDROME

A laboratory approach for characterizing chronic fatigue: what does metabolomics tell us?

Erasmus E[1], Mason S[2], van Reenen M[2], Steffens FE[3], Vorster BC[2], Reinecke CJ[2].

Metabolomics. **2019 Nov 27**;15(12):158. doi: 10.1007/s11306-019-1620-4. PMID: 31776682.

INTRODUCTION: Manifestations of fatigue range from chronic fatigue up to a severe syndrome and myalgic encephalomyelitis. Fatigue grossly affects the functional status and quality of life of affected individuals, prompting the World Health Organization to recognize it as a chronic non-communicable condition.

OBJECTIVES: Here, we explore the potential of urinary metabolite information to complement clinical criteria of fatigue, providing an avenue towards an objective measure of fatigue in patients presenting with the full spectrum of fatigue levels.

METHODS: The experimental group consisted of 578 chronic fatigue female patients. The measurement design was composed of (1) existing clinical fatigue scales, (2) a hepatic detoxification challenge test, and (3) untargeted proton nuclear magnetic resonance (^{1}H-NMR) procedure to generate metabolomics data. Data analysed via an in-house Matlab script that combines functions from a Statistics and a PLS Toolbox.

RESULTS: Multivariate analysis of the original 459 profiled ^{1}H-NMR bins for the low (control) and high (patient) fatigue groups indicated complete separation following the detoxification experimental challenge. Important bins identified from the ^{1}H-NMR spectra provided quantitative metabolite information on the detoxification challenge for the fatigue groups.

CONCLUSIONS: Untargeted ^{1}H-NMR metabolomics proved its applicability as a global profiling tool to reveal the impact of toxicological interventions in chronic fatigue patients. No clear potential biomarker emerged from this study, but the quantitative profile of the phase II biotransformation products provide a practical visible effect directing to up-regulation of crucial phase II enzyme systems in the high fatigue group in response to a high xenobiotic-load.

HEADACHE and MIGRAINE

An Overview of Systematic Reviews of Randomized Controlled Trials on Acupuncture Treating Migraine.

Zhang XT[1], Li XY[1], Zhao C[2], Hu YY[1], Lin YY[1], Chen HQ[1], Shi ZF[1], Zhang XY[1], Shang HC[1], Tian GH[1].

Pain Res Manag. **2019 Oct 29**;2019:5930627. doi: 10.1155/2019/5930627. PMCID: PMC6875188. PMID: 31781318.

Objectives: To review the evidence of acupuncture for acute and preventive treatment of migraine for further awareness of the effect of acupuncture for migraine.

Design: An overview of systematic reviews and meta-analyses (SR/MAs) for randomized controlled trials.

Material and Methods: We searched PubMed, Embase, the Cochrane Library, China Knowledge Resource Integrated Database, VIP Chinese Journal Full Text Database, WANFANG Data, and China Biology Medicine disc from their establishment to May 27, 2018. SR/MAs of randomized controlled trials comparing the effect of the acupuncture intervention with another treatment control in migraine patients were included.

Results: 428 SRs were identified, and 15 of them were included. Only 4 SR/MAs were assessed by GRADE, which showed certainty of most evidence being low or very low. Assessed by AMSTAR-2, fourteen was critically low rating overall confidence in the results, and 1 was low rating overall confidence in the results. Evidence suggested that acupuncture has a significant advantage of pain improvement, efficacy, and safety relative to blank control, sham acupuncture, or drug treatment, but some of these results are contradictory.

Conclusions: We found that acupuncture on treating migraine has the advantage for pain improvement and safety, but the quality of SR/MAs of acupuncture for migraine remains to be improved.

The Influence of Metoclopramide on Trigeminovascular Nociception: Possible Anti-migraine Mechanism of Action.

Dolgorukova A[1], Osipchuk AV[2], Murzina AA[2], Sokolov AY[3].

Neuroscience. **2019 Nov 27**. pii: S0306-4522(19)30802-4. doi: 10.1016/j.neuroscience.2019.11.026. PMID: 31785356. [Epub]

Metoclopramide widely used as an abortive migraine therapy due to the advantage of having not only antiemetic, but also analgesic properties. Despite the proven clinical efficacy of metoclopramide in acute migraine, the mechanism of its anti-cephalalgic action has not been entirely elucidated. Taking into account the key role of the trigeminovascular system activation in migraine pathophysiology, we aimed to investigate metoclopramide effects on the excitability of central trigeminovascular neurons and neurogenic dural vasodilation using valid electrophysiological and neurovascular models of trigeminovascular nociception. Extracellular recordings of the activity of second-order dura-sensitive neurons were made in the trigeminocervical complex (TCC) of 16 anaesthetised rats. Cumulative metoclopramide infusion (three steps in 30 min intervals, 5 mg/kg i.v. per step, n = 8) significantly and dose-dependently suppressed both ongoing firing of the TCC neurons and their responses to dural electrical stimulation, maximally to 30%[0-49%] (median[Q1-Q3]) and 4%[0-30%] of the initial level, respectively (both $p = 0.001$, compared to saline (n = 8)). By contrast, the neurogenic dural vasodilation studied in a separate group of 12 rats was not significantly affected by cumulative infusion of metoclopramide (5 mg/kg i.v. per step, n = 6) compared to both baseline values and the vehicle group (n = 6) (all $p > 0.05$). These results provide evidence that metoclopramide is unable to affect the peripheral response to trigeminovascular activation, but it does suppress the central response, which is highly predictive of anti-migraine action. Thus, here we show the neurophysiological mechanism underlying the therapeutic efficacy of metoclopramide in migraine.

CHRONIC PAIN

The Interaction Between Chronic Pain and PTSD.

Kind S[1], Otis JD[2,3].

Curr Pain Headache Rep. **2019 Nov 28**;23(12):91. doi: 10.1007/s11916-019-0828-3. PMID: 31781875.

PURPOSE OF REVIEW: Post-traumatic stress disorder (PTSD) and chronic pain often co-occur. Understanding the shared mechanisms, signs to identify PTSD, and treatment options is integral in allowing providers to better serve their patients.

RECENT FINDINGS: Individuals with comorbid PTSD and chronic pain report greater PTSD symptoms, pain, anxiety, depression, disability, and opioid use than those with only one of these conditions. There are several empirically supported therapies for chronic pain, and for PTSD, as well as pilot data for a treatment of comorbid pain and PTSD. The purpose of this paper is to review and synthesize current literature investigating the interaction between chronic pain and PTSD, and provide treatment recommendations for providers treating patients with chronic pain and PTSD.

Mindfulness is associated with sleep quality among patients with fibromyalgia.

Park M[1], Zhang Y[2], Price LL[3,4], Bannuru RR[1,5,6], Wang C[1,6].

Int J Rheum Dis. **2019 Nov 27**. doi: 10.1111/1756-185X.13756. PMID: 31777188. [Epub ahead of print]

AIM: Previous studies suggest higher mindfulness may be associated with better sleep quality in people with chronic pain conditions. However, the relationship between mindfulness and sleep in fibromyalgia patients, who commonly suffer from sleep problems, remains unstudied. We examined the relationship between mindfulness and sleep, and how this relationship may be mediated by depression, anxiety, and pain interference in fibromyalgia patients.

METHOD: We performed a cross-sectional analysis of baseline data from a randomized trial in fibromyalgia patients. We measured mindfulness (Five Facet Mindfulness Questionnaire), sleep quality and disturbance (Pittsburgh Sleep Quality Index [PSQI], PROMIS Sleep Disturbance [PROMIS-SD]), pain interference (PROMIS Pain Interference), and anxiety and depression (Hospital Anxiety and Depression Scale). Pearson correlations were used to examine associations among mindfulness and sleep quality and disturbance. Mediation analysis was conducted to assess whether pain interference, depression, and anxiety mediated the relationship between mindfulness and sleep.

RESULTS: A total of 177 patents with fibromyalgia were included (93% female; mean age 52 ± 12 years; body mass index 30 ± 7 kg/m^2 ; 59% White). Higher mindfulness was associated with better sleep quality and less sleep disturbance (PSQI r = -0.23, P = .002; PROMIS-SD r = -.24, P = .002) as well as less pain interference (r = -.31, P < .0001), anxiety (r = -.58, P < .001), and depression (r = -0.54, P < .0001). Pain interference, depression, and anxiety mediated the association between mindfulness and sleep quality and disturbance.

CONCLUSION: Higher mindfulness is associated with better sleep in patients with fibromyalgia, with pain interference, depression, and anxiety mediating this relationship. Longitudinal studies are warranted to examine the potential effect of cultivating mindfulness on sleep in fibromyalgia.

IRRITABLE BOWEL SYNDROME

Targeting the gut microbiota for the treatment of irritable bowel syndrome.

Herndon CC[1], Wang YP[2,3,4], Lu CL[2,3,4].

Kaohsiung J Med Sci. **2019 Nov 29**. doi: 10.1002/kjm2.12154. PMID: 31782606. [Epub ahead of print]

Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder that affects an estimated 11% of people across the world. IBS patients are one of the largest subgroups seen in gastroenterology clinics, exhibit a lesser quality of life, and take greater use of the healthcare system. The exact etiology of IBS remains uncertain. Alterations in the gut microbiome may characterize apotential mechanism in the pathogenesis of IBS. This hypothesis is paralleled by rodent models in which manipulation of the gut microbiota leads to disturbed physiological functions along the brain-gut axis. Recent research in IBS treatments has redirected its focus towards gu microbiome based therapeutics. In this review, we discuss potential roles of enteric bacteria in the pathogenesis of IBS and its comorbidities. We then explore the manipulation of the enteric microbiota by prebiotics, probiotics, antibiotics, dietary changes, and fecal microbiota transfer. We also discuss the positive and negative effects of these therapeutics on IBS symptoms.

OTHER RESEARCH OF INTEREST

Interim Results from the IMPACT Study: Evidence for Prostate-specific Antigen Screening in BRCA2 Mutation Carriers.

98 Authors.

Eur Urol. 2019 Dec;76(6):831-842. doi: 10.1016/j.eururo.2019.08.019. PMCID: PMC6880781. PMID: 31537406. **Epub 2019 Sep 16**.

Comment in: **The IMPACT of BRCA2 in prostate cancer.** [Nat Rev Urol. 2019]

BACKGROUND: Mutations in BRCA2 cause a higher risk of early-onset aggressive prostate cancer (PrCa). The IMPACT study is evaluating targeted PrCa screening using prostate-specific-antigen (PSA) in men with germline BRCA1/2 mutations.

OBJECTIVE: To report the utility of PSA screening, PrCa incidence, positive predictive value of PSA, biopsy, and tumour characteristics after 3 yr of screening, by BRCA status.

DESIGN, SETTING, AND PARTICIPANTS: Men aged 40-69 yr with a germline pathogenic BRCA1/2 mutation and male controls testing negative for a familial BRCA1/2 mutation were recruited. Participants underwent PSA screening for 3 yr, and if PSA > 3.0 ng/ml, men were offered prostate biopsy.

OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: PSA levels, PrCa incidence, and tumour characteristics were evaluated. Statistical analyses included Poisson regression offset by person-year follow-up, chi-square tests for proportion t tests for means, and Kruskal-Wallis for medians.

RESULTS AND LIMITATIONS: A total of 3027 patients (2932 unique individuals) were recruited (919 BRCA1 carriers, 709 BRCA1 noncarriers, 902 BRCA2 carriers, and 497 BRCA2 noncarriers). After 3 yr of screening, 527 men had PSA > 3.0 ng/ml, 357 biopsies were performed, and 112 PrCa cases were diagnosed (31 BRCA1 carriers, 19 BRCA1 noncarriers, 47 BRCA2 carriers, and 15 BRCA2 noncarriers). Higher compliance with biopsy was observed in BRCA2 carriers compared with noncarriers (73% vs 60%). Cancer incidence rate per 1000 person years was higher in BRCA2 carriers than in noncarriers (19.4 vs 12.0; p = 0.03); BRCA2 carriers were diagnosed at a younger age (61 vs 64 yr; p = 0.04) and were more likely to have clinically significant disease than BRCA2 noncarriers (77% vs 40%; p = 0.01). No differences in age or tumour characteristics were detected between BRCA1 carriers and BRCA1 noncarriers. The 4 kallikrein marker model discriminated better (area under the curve [AUC] = 0.73) for clinically significant cancer at biopsy than PSA alone (AUC = 0.65).

CONCLUSIONS: After 3 yr of screening, compared with noncarriers, BRCA2 mutation carriers were associated with a higher incidence of PrCa, younger age of diagnosis, and clinically significant tumours. Therefore, systematic PSA screening is indicated for men with a BRCA2 mutation. Further follow-up is required to assess the role of screening in BRCA1 mutation carriers.

PATIENT SUMMARY: We demonstrate that after 3 yr of prostate-specific antigen (PSA) testing, we detect more serious prostate cancers in men with BRCA2 mutations than in those without these mutations. We recommend that male BRCA2 carriers are offered systematic PSA screening.

OTHER RESEARCH OF INTEREST (Continued)

Robust Stability of Trait-Like Vulnerability or Resilience to Common Types of Sleep Deprivation in a Large Sample of Adults.

Yamazaki EM[1], Goel N[1].

Sleep. **2019 Nov 30**. pii: zsz292. doi: 10.1093/sleep/zsz292. PMID: 31784748. [Epub ahead of print]

STUDY OBJECTIVES: Sleep loss produces large individual differences in neurobehavioral responses, with marked vulnerability or resilience among individuals. Such differences are stable with repeated exposures to acute total sleep deprivation (TSD) or chronic sleep restriction (SR) within short (weeks) and long (years) intervals. Whether trait-like responses are observed to commonly experienced types of sleep loss and across various demographically defined groups remains unknown.

METHODS: 83 adults completed 2 baseline nights (10h-12h time-in-bed, TIB) followed by 5 4h TIB SR nights or 36h TSD. Subjects then received 4 12h TIB recovery nights followed by 5 SR nights or 36h TSD, in counterbalanced order to the first sleep loss sequence. Neurobehavioral tests were completed every 2h during wakefulness.

RESULTS: Subjects who displayed neurobehavioral vulnerability to TSD displayed vulnerability to SR, evidenced by substantial to near perfect intraclass correlation coefficients (ICCs; 78%-91% across measures). Sex, race, age, body mass index (BMI), season and sleep loss order did not impact ICCs significantly. Individuals exhibited significant consistency of responses within, but not between, performance and subjective domains.

CONCLUSIONS: Using the largest, most diverse sample to date, we demonstrate for the first time the remarkable stability of phenotypic neurobehavioral responses to commonly experienced sleep loss types, across demographic variables and different performance and subjective measures. Since sex, race, age, BMI, and season did not affect ICCs, these variables are not useful for determining stability of responses to sleep loss, underscoring the criticality of biological predictors. Our findings inform mathematical models and are relevant for the general population and military and health professions.

Nutritional modulation of the intestinal microbiota; future opportunities for the prevention and treatment of neuroimmune and neuroinflammatory disease.

Lombardi VC[1], De Meirleir KL[2], Subramanian K[3], Nourani SM[4], Dagda RK[5], Delaney SL[6], Palotás A[7].

J Nutr Biochem. **2018 Nov**;61:1-16. doi: 10.1016/j.jnutbio.2018.04.004. PMCID: PMC6195483. PMID: 29886183. Epub 2018 Apr 19.

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The gut-brain axis refers to the bidirectional communication between the enteric nervous system and the central nervous system. Mounting evidence supports the premise that the intestinal microbiota plays a pivotal role in its function and has led to the more common and perhaps more accurate term gut-microbiota-brain axis. Numerous studies have identified associations between an altered microbiome and neuroimmune and neuroinflammatory diseases. In most cases, it is unknown if these associations are cause or effect; notwithstanding, maintaining or restoring homeostasis of the microbiota may represent future opportunities when treating or preventing these diseases. In recent years, several studies have identified the diet as a primary contributing factor in shaping the composition of the gut microbiota and, in turn, the mucosal and systemic immune systems. In this review, we will discuss the potential opportunities and challenges with respect to modifying and shaping the microbiota through diet and nutrition in order to treat or prevent neuroimmune and neuroinflammatory disease.

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