GULF WAR ILLNESS

No Updates this Week for Gulf War Illness or Chronic Multisymptom Illness.

CHRONIC FATIGUE SYNDROME

A systematic review of cytokines in chronic fatigue syndrome/myalgic encephalomyelitis/ systemic exertion intolerance disease (CFS/ME/SEID).

Corbitt M[1], Eaton-Fitch N[2,3,4], Staines D[2,3,4], Cabanas H[2,3,4], Marshall-Gradisnik S[2,3,4].

BMC Neurol. **2019 Aug 24**;19(1):207. doi: 10.1186/s12883-019-1433-0. PMID: 31445522.

BACKGROUND: Cytokines in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis/Systemic Exertion Intolerance Disease (CFS/ME/SEID) patients compared with healthy controls have been extensively studied. However, the evidence regarding whether a baseline difference between CFS/ME/SEID patients and the normal population remains unclear. The aim of this study was to conduct a systematic review of the literature regarding cytokines in CFS/ME/SEID and whether there is a significant difference in cytokine levels between this patient group and the normal population.

METHODS: Pubmed, Scopus, Medline (EBSCOHost), and EMBASE databases were searched to source relevant studies for CFS/ME/SEID. The review included any studies examining cytokines in CFS/ME/SEID patients compared with healthy controls. Results of the literature search were summarised according to aspects of their study design and outcome measures, namely, cytokines. Quality assessment was also completed to summarise the level of evidence available.

RESULTS: A total of 16,702 publications were returned using our search terms. After screening of papers according to our inclusion and exclusion criteria, 15 studies were included in the review. All the included studies were observational case control studies. Ten of the studies identified measured serum cytokines in CFS/ME/SEID patients, and four measured cytokines in other physiological fluids of CFS/ME/SEID patients. The overall quality assessment revealed most papers included in this systematic review to be consistent.

CONCLUSIONS: Despite the availability of moderate quality studies, the findings of this review are inconclusive as to whether cytokines play any definitive role in CFS/ME/SEID, and consequently, they would not serve as reliable biomarkers. Therefore, in light of these results, it is recommended that further efforts toward a diagnostic test and treatment for CFS/ME/SEID continue to be developed in a range of research fields.

HEADACHE and MIGRAINE

Acupuncture versus propranolol in migraine prophylaxis: an indirect treatment comparison meta-analysis.

Chen YY[1], Li J[2], Chen M[3], Yue L[1], She TW[1], Zheng H[4].

J Neurol. **2019 Aug 21**. doi: 10.1007/s00415-019-09510-x. PMID: 31435770. [Epub ahead of print]

BACKGROUND: Propranolol is recommended as first-line treatment for preventing migraine attacks; acupuncture has not been compared with propranolol in a head-to-head trial.

OBJECTIVE: To compare acupuncture with propranolol using indirect treatment comparison meta-analysis.

METHOD: We searched MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL). Randomized controlled trials comparing acupuncture or propranolol with sham acupuncture, placebo, waiting-list control or usual care were included. We extracted information from the included trials using a standardized extraction form. The primary outcome was migraine episodes. The secondary outcomes included migraine days, migraine frequency, and adverse events.

RESULTS: We included 19 RCTs (n = 3656) after screening 1078 articles. The analysis showed that acupuncture had a significant advantage over propranolol in reducing migraine episodes over a 4-week period (SMD - 0.74, 95% CI - 1.04 to - 0.44). Acupuncture also had a significant advantage over waiting-list control in decreasing migraine frequency (SMD - 1.57, 95% CI - 2.08 to - 1.06). Acupuncture caused fewer adverse events than propranolol (RR 0.82, 95% CI 0.11-5.94).

CONCLUSIONS: Acupuncture had a better effect than propranolol in reducing migraine episodes in indirect comparison. The result should be confirmed in subsequent head-to-head studies. Registration: PROSPERO CRD42018108585.

HEADACHE and MIGRAINE (Continued)

Interim results of a prospective, randomized, open-label, Phase 3 study of the long-term safety and efficacy of lasmiditan for acute treatment of migraine (the GLADIATOR study).

Brandes JL[1], Klise S[2], Krege JH[2], Case M[2], Khanna R[3], Vasudeva R[2], Raskin J[2], Pearlman EM[2], Kudrow D[4].

Cephalalgia. **2019 Aug 21**:333102419864132. doi: 10.1177/0333102419864132. PMID: 31433669. [Epub ahead of print]

OBJECTIVES: To address the need for long-term lasmiditan data, the GLADIATOR study evaluated the safety (primary) and efficacy (secondary) of lasmiditan for the intermittent, acute treatment of migraine attacks for up to 1 year.

METHODS: In this prospective, randomized, open-label, Phase 3 study, patients who had completed either of two single-attack studies were offered the opportunity to be randomized 1:1 to lasmiditan 100 mg or 200 mg. Patients were asked to use lasmiditan as the first treatment for each new migraine attack of at least moderate severity. Assessments occurred at baseline and at prespecified time increments up to 48 hours after each dose of study drug using an electronic diary, and safety was assessed throughout the study. Migraine Disability Assessment (MIDAS) was assessed at each visit.

RESULTS: As of the cut-off date for this interim analysis (6 March 2018), 1978 patients had received ≥ 1 lasmiditan dose and treated 19,058 migraine attacks. Overall, treatment-emergent adverse events (TEAEs) were similar to those in the single-attack studies and included dizziness (18.6%), somnolence (8.5%), and paresthesia (6.8%). The frequency of TEAEs generally decreased with subsequent attacks. No treatment-related serious adverse events and no cardiovascular TEAEs potentially due to vasoconstriction were observed. For both lasmiditan doses, efficacy measures were generally consistent over study quarters and treated attacks. Overall, across all treated attacks at 2 hours post-dose, pain freedom was observed in 26.9% of the attacks treated with lasmiditan 100 mg and 32.4% of the attacks treated with lasmiditan 200 mg. MIDAS total scores decreased over time.

CONCLUSIONS: The interim results of this long-term study showed intermittent lasmiditan (100 mg and 200 mg) to be generally well tolerated and efficacious for the acute treatment of migraine over a 1-year period. Trial registration number: NCT02565186.

Weather, ambient air pollution, and risk of migraine headache onset among patients with migraine.

Li W[1], Bertisch SM[2], Mostofsky E[3], Buettner C[4], Mittleman MA[5].

Environ Int. **2019 Aug 22**;132:105100. doi: 10.1016/j.envint.2019.105100. PMID: 31446321. [Epub ahead of print]

OBJECTIVE: Migraine is a common recurrent headache disorder affecting 14% American adults. Although weather and air pollution are often reported by patients with migraine as precipitating factors, previous studies have had mixed results.

METHODS: We prospectively collected migraine headache onset data using electronic questionnaires from 98 adults with episodic migraine in the Greater Boston area (2016-2017). Each participant was followed for an average of 45 days for a total of 4406 days of observation. Temperature, relative humidity, and barometric pressure data were obtained from local weather station. Daily average fine particulate matter, daily maximum 1-hour sulfur dioxide, daily maximum 1-hour nitrogen dioxide, daily maximum 8-hour ozone, and daily maximum 8-hour carbon monoxide from local air pollution monitors. We conducted a repeated measures analysis using fixed effects logistic regression models. In the models we adjusted for day of week, a natural cubic spline term of day of the year with 4 degrees of freedom, and a participant identifier. We additionally adjusted for linear terms of temperature and relative humidity in the air pollution analyses. We also applied logistic regression models with generalized estimating equation (GEE) and autoregressive correlation structure in the sensitivity analysis.

RESULTS: The mean age was 35 years and 88% were women. Mean temperature was 56.9 °F, relative humidity 67.3%, and fine particulate matter 7.3 μg/m^3. Higher relative humidity was associated with higher odds of migraine headache, but the association was only observed in warm season (April-September). Higher levels of daily maximum 8-hour ozone and daily maximum 8-hour carbon monoxide appeared to be associated with higher odds of migraine headache onset in cold season (October-March). Although the associations for ozone and relative humidity were attenuated and no longer statistically significant in the overall GEE analysis, the differing associations by season remained.

CONCLUSIONS: We found that higher relative humidity was associated with higher odds of migraine headache onset in warm season, and traffic-related gaseous pollutants may be associated with higher odds of migraine headache onset in cold season.

HEADACHE and MIGRAINE (Continued)

Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial.

Ferrari MD[1], Diener HC[2], Ning X[3], Galic M[4], Cohen JM[3], Yang R[3], Mueller M[4], Ahn AH[3], Schwartz YC[5], Grozinski-Wolff M[3], Janka L[3], Ashina M[6].

Lancet. **2019 Aug 16**. pii: S0140-6736(19)31946-4. doi: 10.1016/S0140-6736(19)31946-4. PMID: 31427046. [Epub ahead of print]

BACKGROUND: Antibodies targeting calcitonin gene-related peptide (CGRP) or its receptor have shown efficacy in the prevention of migraine attacks. We investigated the efficacy and tolerability of fremanezumab, a fully humanised CGRP antibody, in patients with migraine who had previously not responded to two to four classes of migraine preventive medications.

METHODS: The randomised, double-blind, placebo-controlled, parallel-group, phase 3b FOCUS trial was done at 104 sites (including hospitals, medical centres, research institutes, and group practice clinics) across Belgium, the Czech Republic, Denmark, Finland, France, Germany, Italy, the Netherlands, Poland, Spain, Sweden, Switzerland, the UK, and the USA. We enrolled participants aged 18-70 years with episodic or chronic migraine who had documented failure to two to four classes of migraine preventive medications in the past 10 years. Failure was defined as no clinically meaningful improvement after at least 3 months of therapy at a stable dose, as per the treating physician's judgment; discontinuation because of adverse events that made treatment intolerable; or treatment contraindicated or unsuitable for the preventive treatment of migraine for the patient. Participants were randomly assigned (1:1:1) by electronic interactive response technology to subcutaneously administered quarterly fremanezumab (month 1, 675 mg; months 2 and 3: placebo), monthly fremanezumab (month 1: 225 mg in episodic migraine and 675 mg in chronic migraine; months 2 and 3: 225 mg in both migraine subgroups), or matched monthly placebo for 12 weeks. The primary outcome was mean change from baseline in the monthly average number of migraine days during the 12-week treatment period. This trial is registered with ClinicalTrials.gov, number NCT03308968, and is now completed.

FINDINGS: Between Nov 10, 2017, and July 6, 2018, 838 participants with episodic (329 [39%]) or chronic (509 [61%]) migraine were randomly assigned to placebo (n=279), quarterly fremanezumab (n=276), or monthly fremanezumab (n=283). Reductions from baseline in monthly average migraine days over 12 weeks were greater versus placebo (least-squares mean [LSM] change -0·6 [SE 0·3]) with quarterly fremanezumab (LSM change -3·7 [0·3]; LSM difference vs placebo -3·1 [95% CI -3·8 to -2·4]; p<0·0001) and with monthly fremanezumab (LSM change -4·1 [0·34]; LSM difference vs placebo -3·5 [-4·2 to -2·8]; p<0·0001). Adverse events were similar for placebo and fremanezumab. Serious adverse events were reported in four (1%) of 277 participants with placebo, two (<1%) of 276 with quarterly fremanezumab, and four (1%) of 285 with monthly fremanezumab.

INTERPRETATION: Fremanezumab was effective and well tolerated in patients with difficult-to-treat migraine who had previously not responded to up to four classes of migraine preventive medications.

FUNDING: Teva Pharmaceuticals.

CHRONIC PAIN

Subtle changes of gray matter volume in fibromyalgia reflect chronic musculoskeletal pain rather than disease-specific effects.

Sundermann B[1], Dehghan Nayyeri M[1,2], Pfleiderer B[1], Stahlberg K[3], Jünke L[3], Baie L[3], Dieckmann R[4], Liem D[4], Happe T[5], Burgmer M[3].

Eur J Neurosci. **2019 Aug 26**. doi: 10.1111/ejn.14558. PMID: 31448468. [Epub ahead of print]

Fibromyalgia syndrome (FMS) is a chronic pain syndrome. Neuroimaging studies provided evidence of altered gray matter volume (GMV) in FMS but, similarly, in chronic pain of other origin as well. Therefore, the purpose of this study was to evaluate the disease specificity of GMV alterations in FMS by direct comparison. Structural MRI data of the brain were acquired in 25 females with FMS and two different control groups: 21 healthy subjects and 23 patients with osteoarthritis. Regional GMVs were compared by voxel-based morphometry and additional ROI-analyses. In conclusion we did not identify significant GMV alterations in either FMS or OA patients compared to healthy controls when adopting a conservative statistical approach with multiple comparison correction. However, even under a more liberal approach no FMS-specific GMV changes were found because both pain groups presented increased gray matter volumes in the precentral gyrus and decreased GMV in the angular gyrus/middle occipital gyrus and middle temporal gyrus in comparison to healthy controls. Since no differences between both pain groups could be detected cortical GMV changes in FMS should not be interpreted as FMS-specific but might rather reflect changes in chronic pain in general. This previously held notion is confirmed in this study by direct comparison with a control group consisting of another pain disorder.

CHRONIC PAIN (Continued)

Influence of pain anticipation on brain activity and pain perception in Gulf War Veterans with chronic musculoskeletal pain.

Lindheimer JB[1,2], Stegner AJ[1,2], Ellingson-Sayen LD[3], Van Riper SM[1,2], Dougherty RJ[1,2], Falvo MJ[4,5], Cook DB[1,2].

Psychophysiology. **2019 Aug 20**:e13452. doi: 10.1111/psyp.13452. PMID: 31429944. [Epub ahead of print]

Anticipation of a painful experience can influence brain activity and increase sensitivity to experimental somatosensory stimuli in healthy adults, but this response is poorly understood among individuals with chronic musculoskeletal pain (CMP). Studies of brain and perceptual responses to somatosensory stimuli are used to make inferences about central nervous system dysfunction as a potential mechanism of symptoms. As such, we sought to (a) determine the influence of pain anticipation on pain-relevant brain regions and pain perception, and (b) characterize potential differences in these responses between Gulf War Veterans with CMP and matched healthy control (CO) Veterans. CMP (N = 30) and CO Veterans (N = 31) were randomized to conditions designed to generate expectations that either painful (pain) or nonpainful (no pain) stimuli would be administered. Brain responses to five nonpainful thermal stimuli were measured during fMRI, and each stimulus was rated for pain intensity and unpleasantness. In the pain condition, an incremental linear decrease in activity across stimuli was observed in the posterior cingulate cortex, cingulate cortex, and middle temporal gyrus. Further, in the pain condition, differential responses were observed between CMP and CO Veterans in the middle temporal gyrus. These findings indicate that brain responses to nonpainful thermal stimuli in Veterans with CMP are sensitive to pain anticipation, and we recommend accounting for the influence of pain anticipation in future investigations of central nervous system dysfunction in CMP.

Couple Interventions for Chronic Pain: A Systematic Review.

Smith SM[1], Li R[2], Wolfe H[3], Swanger-Gagne MS[4], Bonham AD[5], Kreher DA[6], Poleshuck EL[6].

Clin J Pain. **2019 Aug 19**. doi: 10.1097/AJP.0000000000000752. PMID: 31433320. [Epub ahead of print]

OBJECTIVE: Couple interventions for chronic pain have been shown to more effectively reduce pain intensity for individuals with chronic pain (ICPs) than individual behavioral interventions or usual care. This systematic review identifies randomized controlled trials (RCTs) of couple interventions to highlight strategies that could be incorporated into psychotherapy with ICPs and their romantic partners.

METHODS: We identified articles reporting RCTs of couple interventions for chronic pain. Three databases were searched (i.e., PubMed, Embase, and PsycInfo), resulting in 18 studies and 22 articles.

RESULTS: Couple interventions resulted in statistically significant improvements in pain intensity compared to other conditions in 8-40% of the studies, as well as in statistically significant improvements on a pain-related outcome compared to other conditions in 31-50% of the studies. Educating couples about pain was the most common strategy (83%). Jointly administered relaxation or meditation skills were included in nearly half of the interventions (48%). Many interventions taught cognitive behavioral skills jointly to couples (39%) or to the ICP with partner encouragement (30%). Teaching couples how to request and provide assistance (30%), as well as encouraging partners to avoid reinforcing pain behaviors (39%), occurred frequently. ICPs and their partners were often asked to set goals (30%).

DISCUSSION: This review outlines strategies included in couple interventions for chronic pain which are derived from the cognitive behavioral therapy, acceptance and commitment therapy, and operant-behavioral traditions, but delivered relationally. Therapists working with ICPs and their partners may integrate these strategies into their practice to help couples who are managing chronic pain.

IRRITABLE BOWEL SYNDROME

Lower Gastrointestinal Conditions: Malabsorption Syndromes.

Hogue G[1], Adams R[1].

FP Essent. **2019 Aug**;483:20-24. PMID: 31411845.

Malabsorption syndromes are common in family medicine but may be overlooked because of a wide variation in presentation. Classic symptoms include diarrhea, steatorrhea, weight loss, flatulence, and postprandial abdominal pain. Nongastrointestinal manifestations can include elevated levels of liver function markers, anemia, skin conditions, infertility, and bone disease. Associated conditions include lactose intolerance, celiac disease, and exocrine pancreatic insufficiency. Testing should include screening for anemia. A standard test for lactose intolerance is the hydrogen breath test; however, formal testing typically is not required for diagnosis. The diagnosis of celiac disease depends on serologic testing, histologic findings on duodenal biopsy, or both. Patients should not restrict their diets before testing for malabsorption syndromes. If the initial evaluation is negative for celiac disease, other conditions should be considered, including nonceliac gluten sensitivity, irritable bowel syndrome, and fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) intolerance. Therapies for patients with malabsorption syndromes involve dietary modification. A lactose-restricted diet and use of dairy substitutes are recommended for lactose intolerance. A gluten-free diet is the primary intervention for celiac disease. Pancreatic enzyme replacement therapy and replacement of fat-soluble vitamins are the primary therapies for management of exocrine pancreatic insufficiency.

OTHER RESEARCH OF INTEREST

The prevalence of headaches, pain, and other associated symptoms in different Persian Gulf deployment periods and deployment durations.

Lei K[1], Metzger-Smith V[2], Golshan S[2,3], Javors J[2], Leung A[2,4].

SAGE Open Med. **2019 Aug 26**;7:2050312119871418. doi: 10.1177/2050312119871418. PMCID: PMC6712755. PMID: 31489191. eCollection 2019.

Objectives: This study aims to assess (1) the difference in the prevalence of headaches, pain, and other associated symptoms between Gulf War I (1990-1991) and Post-Gulf War I (1992-2015) veterans who served as active military personnel in the Persian Gulf and (2) how the durations of deployment may affect the prevalence of those symptoms.

Methods: With institutional human subject committee approval, veterans who were accepted to the Gulf War Registry at the VA San Diego Healthcare System between July 2013 and June 2015 ($N = 367$) were included in this retrospective chart review study and grouped according to the Gulf War period they served under or how long they were deployed to the Persian Gulf. Chi-square was used for categorical data analyses and analysis of variance was conducted for continuous outcomes. All analyses were two-tailed, where applicable, with $\alpha = 0.05$ and Bonferroni for pairwise group comparisons.

Results: Veterans who served during Post-Gulf War I or both Gulf War I and Post-Gulf War I exhibited more pain and neurological symptoms than Gulf War I veterans ($p = 0.005$, $p = 0.003$). In addition, veterans who served $\geqslant$12 months reported more overall pain symptoms and analgesic use than those who served less time ($p < 0.001$, $p = 0.024$).

Conclusion: The findings suggest that the length of deployment and Persian Gulf deployment period may play a role in acquiring headaches, pain, and other associated symptoms with increased analgesic consumption.

OTHER RESEARCH OF INTEREST (Continued)

Physical health burden of PTSD, depression, and their comorbidity in the U.S. veteran population: Morbidity, functioning, and disability.

Nichter B[1], Norman S[2], Haller M[3], Pietrzak RH[4].

J Psychosom Res. 2019 Sep;124:109744. doi: 10.1016/j.jpsychores.2019.109744. PMID: 31443821. Epub **2019 Jun 17**.

[Note: Delayed posting in PubMed—Not previously listed in RAC Research Alerts.]

OBJECTIVE: Although it is well-established that posttraumatic stress disorder (PTSD) and major depressive disorder (MDD) are associated with physical health difficulties among U.S. veterans, the incremental burden of having both disorders relative to either one alone remains largely unknown. The goal of this study was to provide the first population-based characterization of the burden of medical illness associated with PTSD, MDD, and their comorbidity among U.S. veterans.

METHODS: Data were from National Health and Resilience in Veterans Study, a nationally representative survey of U.S. veterans (n = 2732). Analyses (a) examined the magnitude of medical comorbidity and disability associated with PTSD, MDD, and co-occurring PTSD/MDD; and (b) compared physical functioning by PTSD/MDD status.

RESULTS: After adjusting for sociodemographic characteristics and substance use disorders, veterans with comorbid PTSD/MDD were more likely to be diagnosed with heart disease, migraine, fibromyalgia, and rheumatoid arthritis compared to those with MDD-only. Conversely, they were at greater odds of being diagnosed with hypercholesterolemia and hypertension relative to those with PTSD-only. Comorbid PTSD/MDD status was associated with approximately three times greater odds of disability compared to MDD alone. Veterans with co-occurring PTSD/MDD and PTSD-only exhibited worse physical functioning than those with MDD-only.

CONCLUSION: Findings indicate that veterans with co-occurring PTSD/MDD represent a high-risk group for cardiovascular disease and other health problems, and therefore deserve careful attention from healthcare systems. Further research is needed to investigate mechanisms underlying associations between PTSD/MDD and physical health morbidities, as well as whether treatment of PTSD/MDD can reduce risk for comorbid medical conditions.

Barriers to the use of Veterans Affairs health care services among female veterans who served in Iraq and Afghanistan.

Newins AR[1], Wilson SM[2], Hopkins TA[1], Straits-Troster K[2], Kudler H[2], Calhoun PS[2].

Psychol Serv. **2019 Aug**;16(3):484-490. doi: 10.1037/ser0000230. Epub 2018 Feb 8.

[Note: Delayed posting in PubMed—Not previously listed in RAC Research Alerts.]

The study investigated barriers to the utilization of Veterans Affairs (VA) health care services among female veterans who served in served in Iraq and Afghanistan, including reasons for not choosing VA health care, reasons for not seeking mental health treatment, and types of desired VA services. Female respondents to a survey assessing Operation Enduring Freedom/Operation Iraqi Freedom veterans' needs and health (N = 186) completed measures of military history, posttraumatic stress disorder, depression, barriers to VA health care, and preferences for services. Barriers to use of VA health care endorsed by female veterans included receiving care elsewhere and logistical issues. Barriers to utilization of mental health services among female veterans who screened positive for depression or posttraumatic stress disorder included negative treatment biases and concerns about stigma, privacy, and cost. Female veterans endorsed preferences for services related to eligibility education, nonprimary care physical health services, vocational assistance, and a few behavioral/mental health services. Findings highlight the need for ongoing outreach and education regarding eligibility and types of resources for physical and mental health problems experienced by female veterans who served in Iraq and Afghanistan, as well as inform types of VA programming and services desired by female veterans.

OTHER RESEARCH OF INTEREST (Continued)

High-precision plasma β-amyloid 42/40 predicts current and future brain amyloidosis.

Schindler SE[1], Bollinger JG[1], Ovod V[1], Mawuenyega KG[1], Li Y[1], Gordon BA[1], Holtzman DM[1], Morris JC[1], Benzinger TLS[1], Xiong C[1], Fagan AM[1], Bateman RJ[2].

Neurology. **2019 Aug 1**. pii: 10.1212/WNL.0000000000008081. doi: 10.1212/WNL.0000000000008081. PMID: 31371569. [Epub ahead of print]

OBJECTIVE: We examined whether plasma β-amyloid (Aβ)42/Aβ40, as measured by a high-precision assay, accurately diagnosed brain amyloidosis using amyloid PET or CSF p-tau181/Aβ42 as reference standards.

METHODS: Using an immunoprecipitation and liquid chromatography-mass spectrometry assay, we measured Aβ42/Aβ40 in plasma and CSF samples from 158 mostly cognitively normal individuals that were collected within 18 months of an amyloid PET scan.

RESULTS: Plasma Aβ42/Aβ40 had a high correspondence with amyloid PET status (receiver operating characteristic area under the curve [AUC] 0.88, 95% confidence interval [CI] 0.82-0.93) and CSF p-tau181/Aβ42 (AUC 0.85, 95% CI 0.79-0.92). The combination of plasma Aβ42/Aβ40, age, and *APOE* ε4 status had a very high correspondence with amyloid PET (AUC 0.94, 95% CI 0.90-0.97). Individuals with a negative amyloid PET scan at baseline and a positive plasma Aβ42/Aβ40 (<0.1218) had a 15-fold greater risk of conversion to amyloid PET-positive compared to individuals with a negative plasma Aβ42/Aβ40 (p = 0.01).

CONCLUSIONS: Plasma Aβ42/Aβ40, especially when combined with age and *APOE* ε4 status, accurately diagnoses brain amyloidosis and can be used to screen cognitively normal individuals for brain amyloidosis. Individuals with a negative amyloid PET scan and positive plasma Aβ42/Aβ40 are at increased risk for converting to amyloid PET-positive. Plasma Aβ42/Aβ40 could be used in prevention trials to screen for individuals likely to be amyloid PET-positive and at risk for Alzheimer disease dementia.

CLASSIFICATION OF EVIDENCE: This study provides Class II evidence that plasma Aβ42/Aβ40 levels accurately determine amyloid PET status in cognitively normal research participants.

A Mechanical Brain Damage Framework Used to Model Abnormal Brain Tau Protein Accumulations of National Football League Players.

Horstemeyer MF[1,2,3], Berthelson PR[4,5], Moore J[6,4], Persons AK[6,4], Dobbins A[7], Prabhu RK[4,5].

Ann Biomed Eng. **2019 Aug 1**. doi: 10.1007/s10439-019-02294-1. PMID: 31372858. [Epub ahead of print]

A mechanics-based brain damage framework is used to model the abnormal accumulation of hyperphosphorylated p-tau associated with chronic traumatic encephalopathy within the brains of deceased National Football League (NFL) players studied at Boston University and to provide a framework for understanding the damage mechanisms. p-tau damage is formulated as the multiplicative decomposition of three independently evolving damage internal state variables (ISVs): nucleation related to number density, growth related to the average area, and coalescence related to the nearest neighbor distance. The ISVs evolve under different rates for three well known mechanical boundary conditions, which in themselves introduce three different rates making a total of nine scenarios, that we postulate are related to brain damage progression: (1) monotonic overloads, (2) cyclic fatigue which corresponds to repetitive impacts, and (3) creep which is correlated to damage accumulation over time. Different NFL player positions are described to capture the different types of damage progression. Skill position players, such as quarterbacks, are expected to exhibit a greater p-tau protein accumulation during low cycle fatigue (higher amplitude impacts with a lesser number), and linemen who exhibit a greater p-tau protein accumulation during high cycle fatigue (lower amplitude impacts with a greater number of impacts). This mechanics-based damage framework presents a foundation for developing a multiscale model for traumatic brain injury that combines mechanics with biology.

OTHER RESEARCH OF INTEREST (Continued)

Mast Cells, Neuroinflammation and Pain in Fibromyalgia Syndrome.

Theoharides TC[1,2,3,4], Tsilioni I[1], Bawazeer M[1,2,5].

Front Cell Neurosci. **2019 Aug 2**;13:353. doi: 10.3389/fncel.2019.00353. PMCID: PMC6687840. PMID: 31427928. eCollection 2019.

Fibromyalgia Syndrome (FMS) is a disorder of chronic, generalized muscular pain, accompanied by sleep disturbances, fatigue and cognitive dysfunction. There is no definitive pathogenesis except for altered central pain pathways. We previously reported increased serum levels of the neuropeptides substance P (SP) and its structural analogue hemokinin-1 (HK-1) together with the pro-inflammatory cytokines IL-6 and TNF in FMS patients as compared to sedentary controls. We hypothesize that thalamic mast cells contribute to inflammation and pain, by releasing neuro-sensitizing molecules that include histamine, IL-1β, IL-6 and TNF, as well as calcitonin-gene related peptide (CGRP), HK-1 and SP. These molecules could either stimulate thalamic nociceptive neurons directly, or via stimulation of microglia in the diencephalon. As a result, inhibiting mast cell stimulation could be used as a novel approach for reducing pain and the symptoms of FMS.

Fatigue, Sleep, and Autoimmune and Related Disorders.

Zielinski MR[1,2], Systrom DM[3,4], Rose NR[5].

Front Immunol. **2019 Aug 6**;10:1827. doi: 10.3389/fimmu.2019.01827. PMCID: PMC6691096. PMID: 31447842. eCollection 2019.

Profound and debilitating fatigue is the most common complaint reported among individuals with autoimmune disease, such as systemic lupus erythematosus, multiple sclerosis, type 1 diabetes, celiac disease, chronic fatigue syndrome, and rheumatoid arthritis. Fatigue is multi-faceted and broadly defined, which makes understanding the cause of its manifestations especially difficult in conditions with diverse pathology including autoimmune diseases. In general, fatigue is defined by debilitating periods of exhaustion that interfere with normal activities. The severity and duration of fatigue episodes vary, but fatigue can cause difficulty for even simple tasks like climbing stairs or crossing the room. The exact mechanisms of fatigue are not well-understood, perhaps due to its broad definition. Nevertheless, physiological processes known to play a role in fatigue include oxygen/nutrient supply, metabolism, mood, motivation, and sleepiness-all which are affected by inflammation. Additionally, an important contributing element to fatigue is the central nervous system-a region impacted either directly or indirectly in numerous autoimmune and related disorders. This review describes how inflammation and the central nervous system contribute to fatigue and suggests potential mechanisms involved in fatigue that are likely exhibited in autoimmune and related diseases.

Safety and Feasibility of Repeated Intrathecal Allogeneic Bone Marrow-Derived Mesenchymal Stromal Cells in Patients with Neurological Diseases.

Pan K[1], Deng L[2], Chen P[1], Peng Q[1], Pan J[1], Wu Y[3], Wang Y[1,4,5].

Stem Cells Int. **2019 Jul 25**;2019:8421281. doi: 10.1155/2019/8421281. PMCID: PMC6683773. PMID: 31428161. eCollection 2019.

Mesenchymal stromal cells (MSCs) have become the most commonly used adult stem cells in regenerative medicine. Preclinical studies have shown that MSCs-based therapy is a potential new treatment approach for neurological diseases. Intrathecal injection has unique feature which allows stem cells to directly migrate to the lesion site in patients with central nervous system (CNS) diseases. In this study, we evaluate the safety and feasibility of intrathecal allogeneic bone marrow-derived MSCs (BM-MSCs) in patients with neurological diseases. This open-label clinical study included 37 patients (14 diseases). Eligible patients underwent a baseline assessment and were intrathecally injected with allogeneic BM-MSCs (1×10^6 cells/kg, 4 consecutive treatments at 1-week intervals). After four infusions, the patients were followed up for at least 6 months. Adverse events, cerebrospinal fluid (CSF) test results, clinical symptoms, physical examination, and haematological and imaging examinations were used to assess the safety and feasibility of the treatment. Also, we performed a systematic review of the safety of all types of intrathecal stem cells and compared our result to previous studies. In our study, the highest adverse event was a slight ache at the injection site (4.11%), followed by fever (3.42%) and mild headache (2.05%). No severe adverse events were reported. After the intrathecal injections, the white blood cell (WBC) counts in the CSF increased in 30 patients and the protein concentration in the CSF exceeded the normal range in 26 patients, while other CSF indicators remained normal. Moreover, these patients had no suspected manifestations of CNS infection. Haematological and imaging examinations showed no abnormal changes after BM-MSCs infusion. Compared with previous studies, the incidence of adverse events was nearly consistent or even lower for headache, fever, nausea, and neck pain. In conclusion, repeated intrathecal allogeneic BM-MSCs are safe, feasible, and promising for the treatment of patients with neurological diseases.

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