GULF WAR ILLNESS

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

CHRONIC FATIGUE SYNDROME

Cerebral Blood Flow and Heart Rate Variability in Chronic Fatigue Syndrome: A Randomized Cross-Over Study.

Malfliet A[1], Pas R[2], Brouns R[3], De Win J[4], Hatem SM[5], Meeus M[6], Ickmans K[7], van Hooff RJ[3], Nijs J[8].

Pain Physician. **2018 Jan**;21(1):E13-E24.

BACKGROUND: Pain, fatigue, and concentration difficulties are typical features of chronic fatigue syndrome (CFS). The exact underlying mechanisms of these symptoms are still unknown, but available evidence suggests an important role for impaired pain modulation. As evidence also suggests that pain modulation is related to cardiovascular mechanisms, it seems logical to investigate whether cerebral blood flow (CBF) and heart rate variability (HRV) are altered in these patients.

OBJECTIVES: We aimed to investigate the role of the cardiovascular system in pain modulation and symptoms of CFS; the response of CBF and HRV to physical stress and their relation to the change in temporal summation (TS) of pressure pain and self-reported symptoms was evaluated.

STUDY DESIGN: A controlled, randomized cross-over trial.

SETTING: University Hospital Brussels.

METHODS: Twenty CFS patients and 20 sedentary healthy controls were included in this study. In both of the groups, the change in TS of pressure pain, CBF (using transcranial Doppler), and HRV (using finger plethysmography) was examined during physical and emotional stress (to control for potential bias), as well as their association mutually and with self-reported symptoms of pain, fatigue, and concentrations difficulties.

RESULTS: There was no significant interaction or group (F-values ranging from .100 to 1.862, P-values ranging from .754 to .181) effect in CBF or HRV parameters. HRV and CBF did change during physical exercise, but the changes did not differ between patients and controls. While pain scores during TS at the trapezius site reduced in the control group after the physical exercise protocol (P = .037), they did not change in the CFS group (P = .108), suggesting impaired pain modulation. There were no significant correlations between CBF, HRV, TS, and self-reported symptoms (all P-values of correlation analyses > .01).

LIMITATIONS: Although effect sizes were medium to large, the study sample was relatively low. Also, the mild nature of the exercise bout is discussable. Nonetheless, this mild exercise was able to provoke endogenous pain modulation in the control group, which endorsed a proper execution of the cycling exercise. Moreover, mild exercises are more applicable to daily physical activities in CFS patients than vigorous exercises.

CONCLUSION: These results seem to refute the previously suggested alterations of CBF/HRV in CFS patients. These cardiovascular parameters appear not to explain pain before, during, and following exercise.

KEY WORDS: Chronic pain, physical exercise, emotional stress, pain modulation, cardiovascular systems, temporal summation, pain pressure thresholds, transcranial Doppler, plethysmography.

CHRONIC FATIGUE SYNDROME (Continued)

[Chronic fatigue syndrome treated with transcutaneous electrical acupoint stimulation: a randomized controlled trial].

Li J[1], Xie J[2], Pan Z[1], Guo X[1] , Li Y[1], Fu R[1].

Zhongguo Zhen Jiu. **2017 Dec 12**;37(12):1276-9. doi: 10.13703/j.0255-2930.2017.12.006. [Article in Chinese]

OBJECTIVE: To evaluate the clinical therapeutic effects and safety of chronic fatigue syndrome treated with transcutaneous electrical acupoint stimulation (TEAS) on the conception vessel and the governor vessel.

METHODS: Eighty-nine patients of chronic fatigue syndrome were randomized into an observation group (46 cases) and a control group (43 cases). In the observation group, TEAS was applied at Dazhui (GV 14) and Mingmen (GV 4), Shenque (CV 8) and Guanyuan (CV 4) [the current intensity: (14±2) mA]. In the control group, the simulated TEAS was applied at the same acupoints as the observation group (the current intensity: 1 mA). The treatment was given for 30 min, once a day, 5 times a week and the treatment of 4 weeks was as 1 session in the two groups. One session of treatment was required. Before treatment and at the end of 1 session of treatment, the fatigue severity scale (FSS) was adopted to evaluate the fatigue symptoms and the somatic and psychological health report (SPHERE) was adopted to evaluate the potential symptoms and observe the safety of TEAS therapy.

RESULTS: At the end of treatment, FSS score and SPHERE score in the control group were not different significantly as compared with those before treatment (both $P>0.05$). FSS score and SPHERE score in the observation group were reduced significantly as compared with those before treatment (both $P<0.01$). FSS score and SPHERE score in the observation group were reduced apparently as compared with those in the control group (both $P<0.001$). In the entire process of treatment with TEAS, no any adverse reaction occurred.

CONCLUSION: TEAS on the conception vessel and the governor vessel relieves fatigue symptoms and the potential symptoms in the patients of chronic fatigue syndrome. It is a safe therapy.

Elevated brain natriuretic peptide levels in chronic fatigue syndrome associate with cardiac dysfunction: a case control study.

Tomas C[1], Finkelmeyer A[1,2], Hodgson T[2], MacLachlan L[1], MacGowan GA[1,3], Blamire AM[1,2], Newton JL[1,4].

Open Heart. **2017 Dec 27**;4(2):e000697. doi: 10.1136/openhrt-2017-000697. PMCID: PMC5761285. eCollection 2017.

Objectives: To explore levels of the brain natriuretic peptide (BNP) and how these associate with the cardiac abnormalities recently identified in chronic fatigue syndrome (CFS).

Methods: Cardiac magnetic resonance examinations were performed using 3T Philips Intera Achieva scanner (Best, Netherlands) in CFS (Fukuda) participants and sedentary controls matched group wise for age and sex. BNP was also measured by using an enzyme immunoassay in plasma from 42 patients with CFS and 10 controls.

Results: BNP levels were significantly higher in the CFS cohort compared with the matched controls (P=0.013). When we compared cardiac volumes (end-diastolic and end-systolic) between those with high BNP levels (BNP >400 pg/mL) and low BNP (<400 pg/mL), there were significantly lower cardiac volumes in those with the higher BNP levels in both end-systolic and end-diastolic volumes (P=0.05). There were no relationships between fatigue severity, length of disease and BNP levels (P=0.2) suggesting that our findings are unlikely to be related to deconditioning.

Conclusion: This study confirms an association between reduced cardiac volumes and BNP in CFS. Lack of relationship between length of disease suggests that findings are not secondary to deconditioning. Further studies are needed to explore the utility of BNP to act as a stratification paradigm in CFS that directs targeted treatments.

Trail registration number: Registered with NIHR Portfolio CLRN ID 97805.

HEADACHE and MIGRAINE

Clinical spectrum of hemiplegic migraine and chances of finding a pathogenic mutation.

Pelzer N[1], Haan J[1], Stam AH[1], Vijfhuizen LS[1], Koelewijn SC[1], Smagge A[1], de Vries B[1], Ferrari MD[1], van den Maagdenberg AMJM[1], Terwindt GM [2].

Neurology. **2018 Jan 17**. pii: 10.1212/WNL.0000000000004966. doi: 10.1212/WNL.0000000000004966. [Epub ahead of print]

OBJECTIVE: To investigate whether the clinical characteristics of patients with hemiplegic migraine with and without autosomal dominant mutations in *CACNA1A*, *ATP1A2*, or *SCN1A* differ, and whether the disease may be caused by mutations in other genes.

METHODS: We compared the clinical characteristics of 208 patients with familial (n = 199) or sporadic (n = 9) hemiplegic migraine due to a mutation in *CACNA1A*, *ATP1A2*, or *SCN1A* with those of 73 patients with familial (n = 49) or sporadic (n = 24) hemiplegic migraine without a mutation in these genes. In addition, 47 patients (familial: n = 33; sporadic: n = 14) without mutations in *CACNA1A*, *ATP1A2*, or *SCN1A* were scanned for mutations in novel genes using whole exome sequencing.

RESULTS: Patients with mutations in *CACNA1A*, *ATP1A2*, or *SCN1A* had a lower age at disease onset, larger numbers of affected family members, and more often attacks (1) triggered by mild head trauma, (2) with extensive motor weakness, and (3) with brainstem features, confusion, and brain edema. Mental retardation and progressive ataxia were exclusively found in patients with a mutation. Whole exome sequencing failed to identify pathogenic mutations in new genes.

CONCLUSIONS: Most patients with hemiplegic migraine without a mutation in *CACNA1A*, *ATP1A2*, or *SCN1A* display a mild phenotype that is more akin to that of common (nonhemiplegic) migraine. A major fourth autosomal dominant gene for hemiplegic migraine remains to be identified. Our observations might guide physicians in selecting patients for mutation screening and in providing adequate genetic counseling.

Serum apolipoprotein E may be a novel biomarker of migraine.

Yuasa N[1], Nagata E[2], Fujii N[2], Ito M[3], Tsukamoto H[3], Takizawa S[2].

PLoS One. **2018 Jan 22**;13(1):e0190620. doi: 10.1371/journal.pone.0190620. eCollection 2018.

Migraine attacks alter various molecules that might be related to the pathophysiology of migraine, such as serotonin, calcitonin gene-related peptide, and nitric oxide. The underlying pathophysiology of migraine is as yet unclear. We explored key proteins related to the pathogenesis of migraine here. Serum was collected from two patients with migraine with aura (MA) and seven patients with migraine without aura (MO) during attack-free periods and migraine attacks. Samples were analyzed using 2-dimensional gel electrophoresis. Nineteen protein spots were altered between the attack-free versus migraine attack periods. Mass spectrometric analysis was performed to identify the proteins within each of the 19 altered spots. Thirty-six proteins were significantly altered in samples collected during attack-free periods versus migraine attacks. The protein with the statistically most significant MASCOT/Mowse score (268±112) among lipoproteins was apolipoprotein (ApoE). In the MA and MO groups, ApoE protein levels were significantly higher during migraine attack than during the attack-free period ($p<0.05$). ApoE protein levels were also significantly increased in the MA group during the attack-free period compared to healthy controls and patients with tension type headaches ($p<0.01$). Migraine alters ApoE levels, especially in MA. ApoE might play an important role in the pathophysiology of migraine, and may act as a diagnostic biomarker of migraine.

HEADACHE and MIGRAINE (Continued)

Headache following head injury: a population-based longitudinal cohort study (HUNT).

Nordhaug LH[1], Hagen K[2,3], Vik A[2,4], Stovner LJ[2,3], Follestad T[5], Pedersen T[6], Gravdahl GB[3], Linde M[2,3].

J Headache Pain. **2018 Jan 22**;19(1):8. doi: 10.1186/s10194-018-0838-2.

BACKGROUND: Headache is the most frequent symptom following head injury, but long-term follow-up of headache after head injury entails methodological challenges. In a population-based cohort study, we explored whether subjects hospitalized due to a head injury more often developed a new headache or experienced exacerbation of previously reported headache compared to the surrounding population.

METHODS: This population-based historical cohort study included headache data from two large epidemiological surveys performed with an 11-year interval. This was linked with data from hospital records on exposure to head injury occurring between the health surveys. Participants in the surveys who had not been hospitalized because of a head injury comprised the control group. The head injuries were classified according to the Head Injury Severity Scale (HISS). Multinomial logistic regression was performed to investigate the association between head injury and new headache or exacerbation of pre-existing headache in a population with known pre-injury headache status, controlling for potential confounders.

RESULTS: The exposed group consisted of 294 individuals and the control group of 25,662 individuals. In multivariate analyses, adjusting for age, sex, anxiety, depression, education level, smoking and alcohol use, mild head injury increased the risk of new onset headache suffering (OR 1.74, 95% CI 1.05-2.87), stable headache suffering (OR 1.70, 95% CI 1.15-2.50) and exacerbation of previously reported headache (OR 1.93, 95% CI 1.24-3.02). The reference category was participants without headache in both surveys.

CONCLUSION: Individuals hospitalized due to a head injury were more likely to have new onset and worsening of pre-existing headache and persistent headache, compared to the surrounding general population. The results support the entity of the ICHD-3 beta diagnosis "persistent headache attributed to traumatic injury to the head".

Increased pain sensitivity in migraine and tension-type headache coexistent with low back pain: A cross-sectional population study.

Ashina S[1,2], Lipton RB[3,4,5], Bendtsen L[2], Hajiyeva N[2], Buse DC[3,5], Lyngberg AC[6], Jensen R[2].

Eur J Pain. **2018 Jan 19**. doi: 10.1002/ejp.1176. [Epub ahead of print]

BACKGROUND: Low back pain is common in the general population and in individuals with primary headaches. We assessed the relative frequency of self-reported back pain in persons with and without primary headaches and examined pain sensitivity.

METHOD: A population of 796 individuals completed a headache interview based on ICHD criteria and provided data of interest in a self-administered questionnaire. Headache cases were classified into chronic (≥15) (CH) or episodic (<15 headache days/month) (EH). A total of 495 had a pericranial total tenderness score (TTS), and 494 had cephalic and extracephalic pressure pain thresholds (PPTs) assessed.

RESULTS: Adjusted for age, gender, education and poor self-rated health, 1-year relative frequency of back pain was higher in individuals with CH (82.5%) and EH (80.1%) compared to no headache group (65.7%). In persons with back pain, TTS was higher in CH, (26.3 ± 12.1) than in EH, (18.5 ± 10.0; $p < 0.001$) and higher in both groups than in those with no headache, 10.8 ± 8.5 ($p < 0.001$ and $p < 0.001$, respectively). In persons with back pain, temporalis PPT were lower in CH, 169.3 ± 57.8, than in EH, 225.2 ± 98.1, and in no headache group, 244.3 ± 105.4 ($p = 0.02$ and $p = 0.01$, respectively). In persons with back pain, finger PPT were lower in CH, 237.1 ± 106.7, than in EH, 291.3 ± 141.3, or in no headache group, 304.3 ± 137.4 ($p = 0.02$ and $p < 0.001$, respectively).

CONCLUSION: Back pain is highly frequent in individuals with CH, followed by EH and no headache. In persons with CH, back pain is associated with lower cephalic and extracephalic PPTs suggesting central sensitization may be a substrate or consequence of comorbidity.

SIGNIFICANCE: We found that back pain has high relative frequency in individuals with CH followed EH and no headache. Back pain is associated with low cephalic and extracephalic PPTs in individuals with CH. Central sensitization may be a substrate or consequence of this comorbidity of back pain and CH.

HEADACHE and MIGRAINE (Continued)

Comparison of gray matter volume between migraine and "strict-criteria" tension-type headache.

Chen WT[1,2,3,4], Chou KH[5,6], Lee PL[7], Hsiao FJ[5], Niddam DM[5,8], Lai KL[9,10], Fuh JL[9,10,5], Lin CP[5,8,6,7], Wang SJ[9,10,5,8].

J Headache Pain. **2018 Jan 15**;19(1):4. doi: 10.1186/s10194-018-0834-6.

BACKGROUND: Despite evidently distinct symptoms, tension-type headache (TTH) and migraine are highly comorbid and exhibit many similarities in clinical practice. The purpose of this study was to investigate whether both types of headaches are similar in brain morphology.

METHODS: Consecutive patients with TTH and age- and sex-matched patients with migraine and healthy controls were enrolled for brain magnetic resonance imaging examination. Patients with TTH were excluded if they reported any headache features or associated symptoms of migraine. Changes in gray matter (GM) volume associated with headache diagnosis (TTH vs. migraine) and frequency (episodic vs. chronic) were examined using voxel-based morphometry. The correlation with headache profile and the discriminative ability between TTH and migraine were also investigated for these GM changes.

RESULTS: In comparison with controls (n = 43), the patients with TTH (25 episodic and 24 chronic) exhibited a GM volume increase in the anterior cingulate cortex, supramarginal gyrus, temporal pole, lateral occipital cortex, and caudate. The patients with migraine (31 episodic and 25 chronic) conversely exhibited a GM volume decrease in the orbitofrontal cortex. These GM changes did not correlate with any headache profile. A voxel-wise 2 × 2 factorial analysis further revealed the substantial effects of headache types and frequency in the comparison of GM volume between TTH and migraine. Specifically, the migraine group (vs. TTH) had a GM decrease in the superior and middle frontal gyri, cerebellum, dorsal striatum, and precuneus. The chronic group (vs. episodic group) otherwise demonstrated a GM decrease in the bilateral insula and anterior cingulate cortex. In receiver operating characteristic analysis, the GM volumes of the left superior frontal gyrus and right cerebellum V combined had good discriminative ability for distinguishing TTH and migraine (area under the curve = 0.806).

CONCLUSIONS: TTH and migraine are separate headache disorders with different characteristics in relation to GM changes. The major morphological difference between the two types of headaches is the relative GM decrease of the prefrontal and cerebellar regions in migraine, which may reflect a higher allostatic load associated with this disabling headache.

CHRONIC PAIN

Web-Based Cognitive Behavior Therapy for Chronic Pain Patients with Aberrant Drug-Related Behavior: Outcomes from a Randomized Controlled Trial.

Guarino H[1], Fong C[1], Marsch LA[2], Acosta MC[1], Syckes C[1,3], Moore SK[4], Cruciani RA[5], Portenoy RK[6], Turk DC[7], Rosenblum A[1].

Pain Med. **2018 Jan 13**. doi: 10.1093/pm/pnx334. [Epub ahead of print]

Objective: There is high unmet need for effective behavioral treatments for chronic pain patients at risk for or with demonstrated histories of opioid misuse. Despite growing evidence supporting technology-based delivery of self-management interventions for chronic pain, very few such programs target co-occurring chronic pain and aberrant drug-related behavior. This randomized controlled trial evaluated the effectiveness of a novel, web-based self-management intervention, grounded in cognitive behavior therapy, for chronic pain patients with aberrant drug-related behavior.

Methods: Opioid-treated chronic pain patients at a specialty pain practice who screened positive for aberrant drug-related behavior (N = 110) were randomized to receive treatment as usual plus the web-based program or treatment as usual alone. The primary outcomes of pain severity, pain interference, and aberrant drug-related behavior, and the secondary outcomes of pain catastrophizing and pain-related emergency department visits, were assessed during the 12-week intervention and at one and three months postintervention.

Results: Patients assigned to use the web-based program reported significantly greater reductions in aberrant drug-related behavior, pain catastrophizing, and pain-related emergency department visits-but not pain severity or pain interference-relative to those assigned to treatment as usual. The positive outcomes were observed during the 12-week intervention and for three months postintervention.

Conclusions: A web-based self-management program, when delivered in conjunction with standard specialty pain treatment, was effective in reducing chronic pain patients' aberrant drug-related behavior, pain catastrophizing, and emergency department visits for pain. Technology-based self-management tools may be a promising therapeutic approach for the vulnerable group of chronic pain patients who have problems managing their opioid medication.

CHRONIC PAIN (Continued)

Discrete Modules and Mesoscale Functional Circuits for Thermal Nociception within Primate S1 Cortex.

Yang PF[1,2], Wu R[1,2], Wu TL[1,2], Shi Z[1, 2], Chen LM[3,2].

J Neurosci. **2018 Jan 15**. pii: 2795-17. doi: 10.1523/JNEUROSCI.2795-17.2017. [Epub ahead of print]

This study addresses one long-standing question of whether functional separations are preserved for somatosensory modalities of touch, heat and cold nociception within primate primary somatosensory (S1) cortex. This information is critical for understanding how the nature of pain is represented in the primate brain. Using a combination of submillimeter-resolution fMRI and microelectrode local field potential (LFP) and spike recordings, we identified spatially-segregated cortical zones for processing touch, nociceptive heat and cold stimuli in somatotopically appropriate areas 3a, 3b, 1, and 2 of S1 in male monkeys. The distances between zones were comparable (~ 3.4 mm) across stimulus modalities (heat, cold, and tactile), indicating the existence of uniform, modality-specific modules. Stimulus-evoked LFP maps validated the fMRI maps in areas 3b and 1. Isolation of heat and cold nociceptive neurons from the fMRI zones confirmed the validity of using fMRI to probe nociceptive regions and circuits. Resting state fMRI analysis revealed distinct intrinsic functional circuits among functionally related zones. We discovered distinct modular structures and networks for thermal nociception within S1 cortex, a finding that has significant implications for studying chronic pain syndromes and guiding selection of neuromodulation targets for chronic pain management.

A systematic review and meta-analysis of genetic risk factors for neuropathic pain.

Veluchamy A[1], Hébert HL[1], Meng W[1], Palmer CNA[2], Smith BH[1].

Pain. **2018 Jan 18**. doi: 10.1097/j.pain.0000000000001164. [Epub ahead of print]

Neuropathic pain (NP) is an increasingly common chronic pain state and a major health burden, affecting approximately 7-10% of the general population. Emerging evidence suggests that genetic factors could partially explain individual susceptibility to NP and the estimated heritability in twins is 37%. The aim of this study was to systematically review and summarize the studies in humans that have investigated the influence of genetic factors associated with NP. We conducted a comprehensive literature search and performed meta-analyses of all the potential genetic variants associated with NP. We reviewed 29 full-text articles and identified 28 genes that were significantly associated with NP, mainly involved in neurotransmission, immune response, and metabolism. Genetic variants in HLA genes, COMT, OPRM1, TNFA, IL6, and GCH1, were found to have an association with NP in more than one study. In the meta-analysis, polymorphisms in HLA-DRB1*13 (OR,2.96; CI,1.93-4.56), HLA-DRB1*04 (OR,1.40; CI, 1.02-1.93), HLA-DQB1*03 (OR,2.86; CI,1.57-5.21), HLA-A*33 (OR,2.32; CI,1.42-3.80), and HLA-B*44 (OR,3.17; CI,2.22-4.55) were associated with significantly increased risk of developing NP whereas HLA-A*02 (OR,0.64; CI,0.47-0.87) conferred reduced risk and neither rs1799971 in OPRM1 (OR, 0.55; CI, 0.27-1.11) nor rs4680 in COMT (OR, 0.95; CI, 0.81-1.13) were significantly associated with NP. These findings demonstrate an important and specific contribution of genetic factors to the risk of developing NP. However, large-scale replication studies are required to validate these candidate genes. Our review also highlights the need for genome-wide association studies with consistent case definition to elucidate the genetic architecture underpinning NP.

OTHER RESEARCH OF INTEREST

Therapy on PTSD Symptom Severity in Military Personnel: A Randomized Clinical Trial.

Foa EB[1], McLean CP[1,2], Zang Y[1], Rosenfield D[3], Yadin E[1], Yarvis JS[4], Mintz J[5,6], Young-McCaughan S[5], Borah EV[5,7], Dondanville KA[5], Fina BA[5], Hall-Clark BN[5], Lichner T[1], Litz BT[8,9], Roache J[5], Wright EC[5,10], Peterson AL[5,11,12]; STRONG STAR Consortium.

JAMA. **2018 Jan 23**;319(4):354-364. doi: 10.1001/jama.2017.21242. PMID: 29362795.

Importance: Effective and efficient treatment is needed for posttraumatic stress disorder (PTSD) in active duty military personnel.

Objective: To examine the effects of massed prolonged exposure therapy (massed therapy), spaced prolonged exposure therapy (spaced therapy), present-centered therapy (PCT), and a minimal-contact control (MCC) on PTSD severity.

Design, Setting, and Participants: Randomized clinical trial conducted at Fort Hood, Texas, from January 2011 through July 2016 and enrolling 370 military personnel with PTSD who had returned from Iraq, Afghanistan, or both. Final follow-up was July 11, 2016.

Interventions: Prolonged exposure therapy, cognitive behavioral therapy involving exposure to trauma memories/reminders, administered as massed therapy (n = 110; 10 sessions over 2 weeks) or spaced therapy (n = 109; 10 sessions over 8 weeks); PCT, a non-trauma-focused therapy involving identifying/discussing daily stressors (n = 107; 10 sessions over 8 weeks); or MCC, telephone calls from therapists (n = 40; once weekly for 4 weeks).

Main Outcomes and Measures: Outcomes were assessed before and after treatment and at 2-week, 12-week, and 6-month follow-up. Primary outcome was interviewer-assessed PTSD symptom severity, measured by the PTSD Symptom Scale-Interview (PSS-I; range, 0-51; higher scores indicate greater PTSD severity; MCID, 3.18), used to assess efficacy of massed therapy at 2 weeks posttreatment vs MCC at week 4; noninferiority of massed therapy vs spaced therapy at 2 weeks and 12 weeks posttreatment (noninferiority margin, 50% [2.3 points on PSS-I, with 1-sided α = .05]); and efficacy of spaced therapy vs PCT at posttreatment.

Results: Among 370 randomized participants, data were analyzed for 366 (mean age, 32.7 [SD, 7.3] years; 44 women [12.0%]; mean baseline PSS-I score, 25.49 [6.36]), and 216 (59.0%) completed the study. At 2 weeks posttreatment, mean PSS-I score was 17.62 (mean decrease from baseline, 7.13) for massed therapy and 21.41 (mean decrease, 3.43) for MCC (difference in decrease, 3.70 [95% CI, 0.72 to 6.68]; P = .02). At 2 weeks posttreatment, mean PSS-I score was 18.03 for spaced therapy (decrease, 7.29; difference in means vs massed therapy, 0.79 [1-sided 95% CI, -∞ to 2.29; P = .049 for noninferiority]) and at 12 weeks posttreatment was 18.88 for massed therapy (decrease, 6.32) and 18.34 for spaced therapy (decrease, 6.97; difference, 0.55 [1-sided 95% CI, -∞ to 2.05; P = .03 for noninferiority]). At posttreatment, PSS-I scores for PCT were 18.65 (decrease, 7.31; difference in decrease vs spaced therapy, 0.10 [95% CI, -2.48 to 2.27]; P = .93).

Conclusions and Relevance: Among active duty military personnel with PTSD, massed therapy (10 sessions over 2 weeks) reduced PTSD symptom severity more than MCC at 2-week follow-up and was noninferior to spaced therapy (10 sessions over 8 weeks), and there was no significant difference between spaced therapy and PCT. The reductions in PTSD symptom severity with all treatments were relatively modest, suggesting that further research is needed to determine the clinical importance of these findings.

Trial Registration: clinicaltrials.gov Identifier: NCT01049516.

OTHER RESEARCH OF INTEREST (Continued)

The Gulf War era multiple sclerosis cohort: 3. Early clinical features.

Wallin MT[1,2,3], Culpepper WJ[1,3], Maloni H[1], Kurtzke JF[1,2].

Acta Neurol Scand. **2018 Jan**;137(1):76-84. doi: 10.1111/ane.12810. PMID: 28832890. Epub 2017 Aug 22.

OBJECTIVES: To present clinical features at diagnosis for a large nationwide incident cohort of multiple sclerosis (MS) among those serving in the US military during the Gulf War era (GWE).

MATERIALS & METHODS: Medical records and databases from the Department of Veterans Affairs (VA) for cases of MS with onset in or after 1990, active duty between 1990 and 2007 and service connection by the VA, were reviewed for diagnosis and demographic variables. Neurological involvement was summarized by the Kurtzke Disability Status Scale (DSS) and the Multiple Sclerosis Severity Score (MSSS).

RESULTS: Among 1919 cases of clinically definite MS, 94% had a relapsing-remitting course and 6% were primary progressive at diagnosis. More males of all races and blacks of both sexes were progressive. At diagnosis, functional system involvement was pyramidal 69%, cerebellar 58%, sensory 55%, brainstem 45%, bowel/bladder 23%, cerebral 23%, visual 18%, and other 5%. Mean DSS scores were: white males, females 2.9, 2.7; black males, females 3.3, 2.8; and other-race males, females 3.2, 2.6. Mean and median MSSS were marginally greater in black males and other males compared to the other sex-race groups.

CONCLUSIONS: In this incident cohort, males and blacks had significantly higher proportions of primary progressive MS. DSS at diagnosis was significantly more severe in blacks and significantly less so in whites and in women vs men, but MSSS was only marginally greater in black males and other-race males. This morbidity assessment early in the course of MS provides population-based data for diagnosis, management, and prognosis.

Trauma Sequelae are Uniquely Associated with Components of Self-Reported Sleep Dysfunction in OEF/OIF/OND Veterans.

DeGutis J[1,2,3], Chiu C[1,2], Thai M[1,2], Esterman M[1,2,4], Milberg W[2,5], McGlinchey R[2,5].

Behav Sleep Med. **2018 Jan-Feb**;16(1):38-63. doi: 10.1080/15402002.2016.1173550. Epub 2016 May 16.

While the associations between psychological distress (e.g., posttraumatic stress disorder [PTSD], depression) and sleep dysfunction have been demonstrated in trauma-exposed populations, studies have not fully explored the associations between sleep dysfunction and the wide range of common physical and physiological changes that can occur after trauma exposure (e.g., pain, cardiometabolic risk factors). We aimed to clarify the unique associations of psychological and physical trauma sequelae with different aspects of self-reported sleep dysfunction. A comprehensive psychological and physical examination was administered to 283 combat-deployed trauma-exposed Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND) veterans. The Pittsburgh Sleep Quality Index (PSQI) and PSQI Addendum for PSTD (PSQI-A) were administered along with measures of PTSD, depression, anxiety, pain, traumatic brain injury, alcohol use, nicotine dependence, and cardiometabolic symptoms. We first performed a confirmatory factor analysis of the PSQI and then conducted regressions with the separate PSQI factors as well as the PSQI-A to identify unique associations between trauma-related measures and the separate aspects of sleep. We found that the PSQI global score was composed of three factors: Sleep Efficiency (sleep efficiency/sleep duration), Perceived Sleep Quality (sleep quality/sleep latency/sleep medication) and Daily Disturbances (sleep disturbances/daytime dysfunction). Linear regressions demonstrated that PTSD symptoms were uniquely associated with the PSQI global score and all three factors, as well as the PSQI-A. For the other psychological distress variables, anxiety was independently associated with PSQI global as well as Sleep Efficiency, Perceived Sleep Quality, and PSQI-A, whereas depression was uniquely associated with Daily Disturbances and PSQI-A. Notably, cardiometabolic symptoms explained independent variance in PSQI global and Sleep Efficiency. These findings help lay the groundwork for further investigations of the mechanisms of sleep dysfunction in trauma-exposed individuals and may help in the development of more effective, individualized treatments.

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