GULF WAR ILLNESS

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

CHRONIC FATIGUE SYNDROME

Silicone breast implants and depression, fibromyalgia and chronic fatigue syndrome in a rheumatology clinic population.

Khoo T[1], Proudman S[2,3], Limaye V[2,3].

Clin Rheumatol. **2019 Jan 31**. doi: 10.1007/s10067-019-04447-y. PMID: 30706290. [Epub ahead of print]

INTRODUCTION: Silicone breast implants (SBI) may induce systemic autoimmune disease as part of autoimmune syndrome induced by adjuvants (ASIA). This syndrome bears similarities to fibromyalgia and chronic fatigue syndrome (CFS). We sought to determine whether there are any associations between SBI and depression, fibromyalgia and CFS in a rheumatology clinic population.

METHODS: The electronic files of rheumatology clinic patients at the Royal Adelaide Hospital between 2000 and 2017 were searched for patients who had received SBI prior to rheumatological diagnosis. Demographics, diagnosis, implant history and whether the patient had depression, fibromyalgia or CFS were recorded. Controls were rheumatology clinic patients, half of whom had systemic sclerosis (SSc) and the other half had systemic lupus erythematosus (SLE). They were matched to cases 3:1 for age (within 2 years) and gender.

RESULTS: Thirty patients had received SBI (mean age 47.9, 100% female). Twelve had a diagnosis of depression, 6 of fibromyalgia and 3 of CFS. Implant rupture was not associated with any of these (p = 1). There was no difference in the incidence of depression (p = 1), fibromyalgia (p = 0.76) or CFS (p = 0.3) between cases and SLE controls. When compared with SSc controls, there were significantly more patients with fibromyalgia and/or CFS in the case group (20.0% of cases vs 2.2% of SSc controls, p = 0.01) but no difference in depression (p = 0.12).

CONCLUSION: Fibromyalgia and CFS are more common in patients with silicone implants than SSc controls but not SLE controls. Prospective study of development of depression, fibromyalgia and CFS in recipients of SBI is required.

HEADACHE and MIGRAINE

Iron deposition in periaqueductal gray matter as a potential biomarker for chronic migraine.

Domínguez C[1], López A[1], Ramos-Cabrer P[1], Vieites-Prado A[1], Pérez-Mato M[1], Villalba C[1], Sobrino T[1], Rodriguez-Osorio X[1], Campos F [1], Castillo J[1], Leira R[2].

Neurology. **2019 Feb 1**. pii: 10.1212/WNL.0000000000007047. doi: 10.1212/WNL.0000000000007047. PMID: 30709968. [Epub ahead of print]

OBJECTIVE: To study iron deposition in red nucleus (RN), globus pallidus (GP), and periaqueductal gray matter (PAG) as a potential biomarker of chronic migraine (CM) and its association with levels of biomarkers related to migraine pathophysiology.

METHODS: This case-control study included 112 patients with migraine (55 CM, 57 episodic migraine [EM]) and 25 headache-free controls. We analyzed iron deposition using 3T MRI and the NIH software platform ImageJ; we analyzed serum levels of markers of inflammation, endothelial dysfunction, and blood-brain barrier (BBB) disruption by ELISA in peripheral blood during interictal periods.

RESULTS: Patients with CM showed larger iron grounds volume in RN compared to patients with EM (70.2 ± 6.8 vs 25.5 ± 7.3 µL, $p < 0.001$) and controls (70.2 ± 6.8 vs 15.1 ± 10.8 µL, $p < 0.001$), as well as larger iron deposits in PAG compared to patients with EM (360.3 ± 6.5 vs 249.7 ± 6.9 µL, $p < 0.001$) and controls (360.3 ± 6.5 vs 168.6 ± 10.3 µL, $p < 0.001$). In PAG, differences were also significant between patients with EM and controls. No significant differences were obtained for GP. Receiver operating characteristic curves showed that the optimal threshold for iron volume was 15 µL in RN (80% sensitivity, 71% specificity) and 240 µL in PAG (93% sensitivity, 97% specificity). Iron grounds volume in PAG was correlated with higher plasma levels of soluble tumor necrosis factor-like WEAK ($r = 0.395$, $p = 0.005$) and cellular fibronectin ($r = 0.294$, $p = 0.040$).

CONCLUSIONS: Patients with CM showed increased iron deposition in RN and PAG compared to patients with EM and controls. Iron grounds volume in PAG identified correctly patients with CM and was associated with elevated biomarkers of endothelial dysfunction and BBB disruption.

HEADACHE and MIGRAINE (Continued)

Parental migraine in relation to migraine in offspring: Family linkage analyses from the HUNT Study.

Børte S[1,2], Zwart JA[1,2,3], Stensland SØ[2,4], Hagen K[5,6], Winsvold BS[2,3].

Cephalalgia. **2019 Feb 2**:333102419828989. doi: 10.1177/0333102419828989. PMID: 30714392. [Epub ahead of print]

BACKGROUND: Migraine is known to run in families. While some clinical studies have indicated that migraine is disproportionally transmitted through the maternal line, this has not been examined in a population-based setting.

METHODS: We utilized a large, population-based cohort study from Norway, the HUNT Study. Using a cross-sectional design, our sample consisted of 13,731 parents and 8970 offspring. Logistic regression was used to calculate odds ratios with 95% confidence intervals for active migraine and non-migrainous headache in offspring, given active maternal or paternal headache.

RESULTS: There was a significant association between maternal migraine and offspring migraine (odds ratio 2.76, 95% confidence interval 2.18-3.51). A weaker association ($p = 0.004$ for comparison with maternal migraine) was found between paternal migraine and offspring migraine (odds ratio 1.67, 95% confidence interval 1.33-2.28). For non-migrainous headache, there was a significant association between mothers and offspring (odds ratio 1.25, 95% confidence interval 1.10-1.43), but not between fathers and offspring.

CONCLUSIONS: Parental migraine is associated with offspring migraine, with a stronger association for maternal migraine. This may indicate maternal-specific transmission.

Impact of early headache neuroimaging on time to malignant brain tumor diagnosis: A retrospective cohort study.

Carey MR[1], Callaghan BC[2], Kerber KA[2], Skolarus LE[2], Burke JF[2].

PLoS One. **2019 Feb 1**;14(2):e0211599. doi: 10.1371/journal.pone.0211599. PMID: 30707721. eCollection 2019.

BACKGROUND: Neuroimaging for headaches is both common and costly. While the costs are well quantified, little is known about the benefit in terms of diagnosing pathology. Our objective was to determine the role of early neuroimaging in the identification of malignant brain tumors in individuals presenting to healthcare providers with headaches.

METHODS: This was a retrospective cohort study using administrative claims data (2001-2014) from a US insurer. Individuals were included if they had an outpatient visit for headaches and excluded for prior headache visits, other neurologic conditions, neuroimaging within the previous year, and cancer. The exposure was early neuroimaging, defined as neuroimaging within 30 days of the first headache visit. A propensity score-matched group that did not undergo early neuroimaging was then created. The primary outcome was frequency of malignant brain tumor diagnoses and median time to diagnosis within the first year after the incident headache visit. The secondary outcome was frequency of incidental findings.

RESULTS: 22.2% of 180,623 individuals had early neuroimaging. In the following year, malignant brain tumors were found in 0.28% (0.23-0.34%) of the early neuroimaging group and 0.04% (0.02-0.06%) of the referent group ($P<0.001$). Median time to diagnosis in the early neuroimaging group was 8 (3-19) days versus 72 (39-189) days for the referent group ($P<0.001$). Likely incidental findings were discovered in 3.17% (3.00-3.34%) of the early neuroimaging group and 0.66% (0.58-0.74%) of the referent group ($P<0.001$).

CONCLUSIONS: Malignant brain tumors in individuals presenting with an incident headache diagnosis are rare and early neuroimaging leads to a small reduction in the time to diagnosis.

HEADACHE and MIGRAINE (Continued)

Effects of onabotulinumtoxinA treatment in chronic migraine patients with and without daily headache at baseline: results from the COMPEL Study.

Young WB[1], Ivan Lopez J[2], Rothrock JF[3], Orejudos A[4], Manack Adams A[4], Lipton RB[5], Blumenfeld AM[6].

J Headache Pain. **2019 Feb 1**;20(1):12. doi: 10.1186/s10194-018-0953-0. PMID: 30709333.

BACKGROUND: OnabotulinumtoxinA is effective in preventing chronic migraine (CM); however, the benefit of onabotulinumtoxinA in patients with CM with daily headache is unknown because these patients are typically excluded from clinical trials. This subanalysis of the COMPEL Study assessed the efficacy and safety of onabotulinumtoxinA in people with CM with and without daily headache.

METHODS: In total, 715 patients received onabotulinumtoxinA 155 U with or without concomitant oral preventive treatment. Patients who had complete daily diary records for the 28 days of the baseline period were stratified based on daily headache status. The primary outcome variable was reduction in headache-day frequency per 28-day period at 108 weeks (after 9 treatment cycles) relative to baseline. Exploratory outcomes included moderate to severe headache days, migraine disability (using the Migraine Disability Assessment [MIDAS] questionnaire), and health-related quality of life (Migraine-Specific Quality-of-Life Questionnaire v2 [MSQ]). Adverse events and their relatedness were recorded.

RESULTS: Overall, 641 patients had complete daily diary records at baseline. In patients with daily headache (n = 138) versus without (n = 503), treatment with onabotulinumtoxinA was associated with a significant mean (SD) reduction in 28-day headache-day frequency relative to baseline at week 108 (- 10.5 [9.2] vs - 12.2 [6.7], respectively; both $P < 0.001$) with no significant between-group difference ($P = 0.132$). The mean (SD) reduction in moderate to severe headache days at week 108 was significant in patients with and without daily headache (- 11.5 [9.4] and - 9.9 [6.4]; $P < 0.001$) with no significant between-group difference ($P = 0.153$). Mean (SD) MIDAS scores significantly improved from baseline at week 108 (- 43.3 [73.4] and - 43.6 [46.7]; both $P < 0.001$), with no significant between-group difference ($P = 0.962$). Similarly, mean (SD) MSQ subscale scores significantly improved from baseline at week 108 for patients with and without daily headache. OnabotulinumtoxinA was well tolerated in patients with and without daily headache.

CONCLUSION: Results indicate that onabotulinumtoxinA is associated with reductions from baseline in headache-day frequency and improvements in disability and quality of life for up to 108 weeks in people with CM with daily headache; however, a longer duration of treatment was required to fully realize the treatment effect on headache. No new safety concerns were identified.

CHRONIC PAIN

Normative data for common pain measures in chronic pain clinic populations: closing a gap for clinicians and researchers.

Nicholas MK[1], Costa DSJ[1], Blanchard M[2], Tardif H[2], Asghari A[1,3], Blyth FM[1,4].

Pain. **2019 Jan 25**. doi: 10.1097/j.pain.0000000000001496. PMID: 30694928. [Epub ahead of print]

Normative data for chronic pain questionnaires are essential to the interpretation of aggregate scores on these questionnaires, for both clinical trials and clinical practice. In this study we summarised data from 13,343 heterogeneous patients on several commonly used pain questionnaires that were routinely collected from 36 pain clinics in Australia and New Zealand as part of the electronic Persistent Pain Outcomes Collaboration (ePPOC) including the Brief Pain Inventory (BPI); the Depression Anxiety and Stress Scales (DASS); the Pain Self-Efficacy Questionnaire (PSEQ); and the Pain Catastrophizing Scale (PCS). The data are presented as summarised normative data, broken down by demographic (age, sex, work status, etc) and pain site/medical variables. The mean BPI severity score was 6.4 (moderate-severe) and mean interference score was 7.0. The mean DASS depression score was 20.2 (moderate-severe), mean DASS anxiety was 14.0 (moderate), and mean DASS stress was 21.0 (moderate). The mean PCS scores were 10.0, 5.9, 14.1 and 29.8 for rumination, magnification, helplessness and total, respectively. The mean PSEQ score was 20.7. Males had slightly worse scores than females on some scales. Scores tended to worsen with age until 31-50 years, after which they improved. Scores were worse for those who had a greater number of pain sites, were unemployed, were injury compensation cases, or whose triggering event was a motor vehicle accident or injury at work or home. These results and comparisons with data on the same measures from other countries, as well as their uses in both clinical practice and clinical trials, are discussed.

CHRONIC PAIN (Continued)

The Oslo University Hospital Pain Registry: development of a digital chronic pain registry and baseline data from 1,712 patients.

Granan LP[1,2,3], Reme SE[2,4,5], Jacobsen HB[2,4, 6], Stubhaug A[2,4,7], Ljoså TM[2,4,8].

Scand J Pain. **2019 Jan 30**. pii: /j/sjpain.ahead-of-print/sjpain-2017-0160/sjpain-2017-0160.xml. doi: 10.1515/sjpain-2017-0160. PMID: 30699072.

Background and Aims: Chronic pain is a leading cause to years lived with disability worldwide. However, few of the interventions used in pain medicine have proven efficacy, and evidence from the existing studies may not be valid for the general pain population. Therefore, it is of utmost need that we describe chronic pain conditions in their most relevant aspects, their various guises, as well as the real world outcomes of our clinical interventions. The most obvious and crude way to make these assessments are through large registries where patient characteristics, treatment characteristics (including but not limited to what, when, how often and by whom), treatment outcomes and patient outcomes are scrutinized and recorded.

Methods and Results: This article describes in detail the design and baseline data of the comprehensive Oslo University Hospital Pain Registry (OPR). OPR is the local registry of the largest university and interdisciplinary outpatient pain clinic in Norway. Data registration started in October 2015, and approximately 1,000 patients are assessed and treated at the clinic each year. During the first 2 years of running the OPR (through September 2017), a total of 1,712 patient baseline reports were recorded from 2,001 patients. Clinicians enter data about relevant treatments and interventions, while patients provide self-reported data on aspects related to pain and pain management. The patients complete an electronic registration immediately before their first consultation at the outpatient pain clinic. The baseline questions of the OPR cover: Basic demographics; The Modified Oswestry Disability Index to assess general function; A pain drawing to assess pain location; Questions regarding the temporal aspects of pain; Six 0-10 Numeric Rating Scales to assess pain intensity and bothersomeness; The EQ-5D-5L to measure health-related quality of life; The Hopkins Symptom Check List-25 to assess psychological distress; A single question about self-rated health; The general self-efficacy scale to assess the patient's perceived self-efficacy; The Bodily Distress Syndrome checklist to assess functional disorders; The Injustice Experience Questionnaire to assess whether the patients experience injustice; Chalder Fatigue Questionnaire to assess fatigue; The Insomnia Severity Index to assesses the levels of insomnia symptoms; The Pain Catastrophizing Scale to measure pain catastrophizing and exaggerated negative orientation toward pain stimuli and pain experience; And the SF36v2 to assess patients' self-report of generic health and wellbeing. The baseline data show that chronic pain patients have a high degree of negative impact in all aspects of their lives.

Conclusions and Implications: The OPR is the most comprehensive pain registry for multidisciplinary and interdisciplinary outpatient pain clinics in Norway. Detailed design of the registry and key baseline data are presented. Registries are of great value in that they enable real world effectiveness outcomes for patients with chronic pain conditions. The OPR can thus serve as a model for similar initiatives elsewhere. The OPR cohort may also serve as a historical control in future studies, both with experimental and observational design.

CHRONIC PAIN (Continued)

Compounded Topical Pain Creams to Treat Localized Chronic Pain: A Randomized Controlled Trial.

Brutcher RE[1], Kurihara C[1], Bicket MC[2], Moussavian-Yousefi P[1], Reece DE[3], Solomon LM[4], Griffith SR[3], Jamison DE[3], Cohen SP[5].

Ann Intern Med. **2019 Feb 5**. doi: 10.7326/M18-2736. [Epub ahead of print]

Background: The use of compounded topical pain creams has increased dramatically, yet their effectiveness has not been well evaluated.

Objective: To determine the efficacy of compounded creams for chronic pain.

Design: Randomized controlled trials of 3 interventions. (ClinicalTrials.gov: NCT02497066).

Setting: Military treatment facility.

Participants: 399 patients with localized pain classified by each patient's treating physician as neuropathic (n = 133), nociceptive (n = 133), or mixed (n = 133).

Interventions: Pain creams compounded for neuropathic pain (ketamine, gabapentin, clonidine, and lidocaine), nociceptive pain (ketoprofen, baclofen, cyclobenzaprine, and lidocaine), or mixed pain (ketamine, gabapentin, diclofenac, baclofen, cyclobenzaprine, and lidocaine), or placebo.

Measurements: The primary outcome measure was average pain score 1 month after treatment. A positive categorical response was a reduction in pain score of 2 or more points coupled with a score above 3 on a 5-point satisfaction scale. Secondary outcomes included Short Form-36 Health Survey scores, satisfaction, and categorical response. Participants with a positive outcome were followed through 3 months.

Results: For the primary outcome, no differences were found in the mean reduction in average pain scores between the treatment and control groups for patients with neuropathic pain (-0.1 points [95% CI, -0.8 to 0.5 points]), nociceptive pain (-0.3 points [CI, -0.9 to 0.2 points]), or mixed pain (-0.3 points [CI, -0.9 to 0.2 points]), or for all patients (-0.3 points [CI, -0.6 to 0.1 points]). At 1 month, 72 participants (36%) in the treatment groups and 54 (28%) in the control group had a positive outcome (risk difference, 8% [CI, -1% to 17%]).

Limitations: Generalizability is limited by heterogeneity among pain conditions and formulations of the study interventions. Randomized follow-up was only 1 month.

Conclusion: Compounded pain creams were not better than placebo creams, and their higher costs compared with approved compounds should curtail routine use.

Primary Funding Source: Centers for Rehabilitation Sciences Research, Defense Health Agency, U.S. Department of Defense.

OTHER RESEARCH OF INTEREST

Management of Posttraumatic Stress Disorder.

Ostacher MJ[1], Cifu AS[2].

JAMA. **2018 Dec 17**. doi: 10.1001/jama.2018.19290. [Epub ahead of print]

Individuals who have been personally or indirectly exposed to actual or threatened death, serious injury, or sexual violence have a wide range of psychological responses, from transient, nondebilitating reactions to symptoms that meet the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) criteria for acute stress disorder or PTSD. Between 6% and 7% of adults in the US general population are estimated to experience PTSD during their lifetime. The prevalence is higher in women than in men. In 2016, 10.6% of veterans receiving care in the Veterans Health Administration had a diagnosis of PTSD. Among veterans who served in Iraq and/or Afghanistan, 26.7% of those seeking care in the Veterans Health Administration receive a PTSD diagnosis.

OTHER RESEARCH OF INTEREST (Continued)

Risk factors for upper and lower functional gastrointestinal disorders in Persian Gulf War Veterans during and post-deployment.

Tuteja AK[1,2], Talley NJ[3], Stoddard GJ[4], Samore MH[1], Verne GN[5,6].

Neurogastroenterol Motil. **2019 Jan 29**:e13533. doi: 10.1111/nmo.13533. PMID: 30697884. [Epub ahead of print]

BACKGROUND: Gastroenteritis is a risk factor for irritable bowel syndrome (IBS), but its role in other functional gastrointestinal disorders (FGIDs) is less clear. The aim of this study was to determine the prevalence of FGIDs in Gulf War (GW) Veterans before, during, and after deployment and to determine whether gastroenteritis was a risk factor for upper and lower FGIDs.

METHODS: The Veterans who served during the Persian GW were mailed validated questionnaires inquiring about their bowel habits, psychological and extra-intestinal symptoms, and quality of life (QOL). The lactulose hydrogen breath test (LBT) was performed for small intestinal bacterial overgrowth.

KEY RESULTS: Data were analyzed from 468 GW Veterans. The prevalence of FGID before, during, and 16 years after deployment was 15.7%, 49.9%, and 64.2%, respectively. New FGIDs during deployment was reported by 41.2%, and during 16 years after deployment, 43.7% acquired new FGIDs. FGIDs were associated with psychological disorders, extra-intestinal symptoms, and lower QOL. Gastroenteritis was reported by 44.3% of deployed Veterans and was a risk factor for IBS, dyspepsia, and functional diarrhea post-deployment. The cases and controls did not differ significantly in the frequency of positive LBT.

CONCLUSIONS AND INFERENCES: There is an increase in the prevalence of FGIDs during deployment, and it persists after deployment. There is a further increase in the prevalence of FGIDs after deployment. In addition to IBS, gastroenteritis during deployment is a risk factor for dyspepsia and functional diarrhea post-deployment. Therefore, prevention of gastroenteritis during deployment and screening of Veterans for FGIDs post-deployment would be of value for Veterans' long-term health.

The neuroactive potential of the human gut microbiota in quality of life and depression.

Valles-Colomer M[1,2], Falony G[1,2], Darzi Y[1,2], Tigchelaar EF[3], Wang J[1,2], Tito RY[1,2,4], Schiweck C[5], Kurilshikov A[3], Joossens M[1,2], Wijmenga C[3,6], Claes S[5,7], Van Oudenhove L[7,8], Zhernakova A[3], Vieira-Silva S[1,2], Raes J[9,10].

Nat Microbiol. **2019 Feb 4**. doi: 10.1038/s41564-018-0337-x. PMID: 30718848. [Epub ahead of print]

Comment in: **Links between gut microbes and depression strengthened.** [**Nature. 2019**]

The relationship between gut microbial metabolism and mental health is one of the most intriguing and controversial topics in microbiome research. Bidirectional microbiota-gut-brain communication has mostly been explored in animal models, with human research lagging behind. Large-scale metagenomics studies could facilitate the translational process, but their interpretation is hampered by a lack of dedicated reference databases and tools to study the microbial neuroactive potential. Surveying a large microbiome population cohort (Flemish Gut Flora Project, n = 1,054) with validation in independent data sets (n_{total} = 1,070), we studied how microbiome features correlate with host quality of life and depression. Butyrate-producing Faecalibacterium and Coprococcus bacteria were consistently associated with higher quality of life indicators. Together with Dialister, Coprococcus spp. were also depleted in depression, even after correcting for the confounding effects of antidepressants. Using a module-based analytical framework, we assembled a catalogue of neuroactive potential of sequenced gut prokaryotes. Gut-brain module analysis of faecal metagenomes identified the microbial synthesis potential of the dopamine metabolite 3,4-dihydroxyphenylacetic acid as correlating positively with mental quality of life and indicated a potential role of microbial γ-aminobutyric acid production in depression. Our results provide population-scale evidence for microbiome links to mental health, while emphasizing confounder importance.

OTHER RESEARCH OF INTEREST (Continued)

Understanding and Overcoming the Challenge of Obesity and Overweight in the Armed Forces: Proceedings of a Workshop

Roundtable on Obesity Solutions, Children and Families, Food and Nutrition, Public Health

Washington (DC): National Academies Press (US); **2019 January 3**.

On May 7, 2018, the Roundtable on Obesity Solutions held a workshop titled "Understanding and Overcoming the Challenge of Obesity and Overweight in the Armed Forces." Speakers examined how obesity and overweight are measured in the armed forces and how they affect recruitment, retention, resilience, and readiness; discussed service-specific issues related to these problems and highlighted innovative strategies to address them through improved nutrition, physical activity, and stress management; and offered perspectives from outside of the armed forces on approaches to prevent and treat obesity. Reflecting on the speakers' presentations, the moderators of the sessions discussed the challenges and opportunities related to overcoming the concerns posed by obesity and overweight in the armed forces, military families, and their communities, including potential cross-sector opportunities.

Risk of Posttraumatic Stress Disorder and Major Depression in Civilian Patients After Mild Traumatic Brain Injury: A TRACK-TBI Study.

Stein MB[1,2,3], Jain S[2], Giacino JT[4,5], Levin H[6], Dikmen S[7], Nelson LD[8], Vassar MJ[9,10], Okonkwo DO[11], Diaz-Arrastia R[12], Robertson CS[6], Mukherjee P[9,13,14], McCrea M[8], Mac Donald CL[15], Yue JK[9], Yuh E[9,13,14], Sun X[2], Campbell-Sills L[1], Temkin N[15,16], Manley GT[9,10]; and the TRACK-TBI Investigators, Adeoye O[17], Badjatia N[18], Boase K[7], Bodien Y[19], Bullock MR[20], Chesnut R[15], Corrigan JD[21], Crawford K[22], Diaz-Arrastia R[12], Dikmen S[7], Duhaime AC[23], Ellenbogen R[15], Feeser VR[24], Ferguson A[10], Foreman B[17], Gardner R[25], Gaudette E[22], Giacino JT[4,5], Gonzalez L[26], Gopinath S[27], Gullapalli R[18], Hemphill JC[25], Hotz G[20], Jain S[2], Korley F[28], Kramer J[25], Kreitzer N[17], Levin H[6], Lindsell C[29], Machamer J[7], Madden C[30], Martin A[13], McAllister T[31], McCrea M[8], Merchant R[32], Mukherjee P[9,13,14], Nelson LD[8], Noel F[33], Okonkwo DO[11], Palacios E[13], Perl D[34], Puccio A[11], Rabinowitz M[12], Robertson CS[6], Rosand J[19], Sander A[6], Satris G[9], Schnyer D[35], Seabury S[22], Sherer M[26], Stein MB[1,2,3], Taylor S[10], Toga A[22], Temkin N[15,16], Valadka A[36], Vassar MJ[9,10], Vespa P[37], Wang K[38], Yue JK[9], Yuh E[9,13,14], Zafonte R[4].

JAMA Psychiatry. **2019 Jan 30**. doi: 10.1001/jamapsychiatry.2018.4288. PMID: 30698636. [Epub ahead of print]

Importance: Traumatic brain injury (TBI) has been associated with adverse mental health outcomes, such as posttraumatic stress disorder (PTSD) and major depressive disorder (MDD), but little is known about factors that modify risk for these psychiatric sequelae, particularly in the civilian sector.

Objective: To ascertain prevalence of and risk factors for PTSD and MDD among patients evaluated in the emergency department for mild TBI (mTBI).

Design, Setting, and Participants: Prospective longitudinal cohort study (February 2014 to May 2018). Posttraumatic stress disorder and MDD symptoms were assessed using the PTSD Checklist for DSM-5 and the Patient Health Questionnaire-9 Item. Risk factors evaluated included preinjury and injury characteristics. Propensity score weights-adjusted multivariable logistic regression models were performed to assess associations with PTSD and MDD. A total of 1155 patients with mTBI (Glasgow Coma Scale score, 13-15) and 230 patients with nonhead orthopedic trauma injuries 17 years and older seen in 11 US hospitals with level 1 trauma centers were included in this study.

Main Outcomes and Measures: Probable PTSD (PTSD Checklist for DSM-5 score, ≥33) and MDD (Patient Health Questionnaire-9 Item score, ≥15) at 3, 6, and 12 months postinjury.

Results: Participants were 1155 patients (752 men [65.1%]; mean [SD] age, 40.5 [17.2] years) with mTBI and 230 patients (155 men [67.4%]; mean [SD] age, 40.4 [15.6] years) with nonhead orthopedic trauma injuries. Weights-adjusted prevalence of PTSD and/or MDD in the mTBI vs orthopedic trauma comparison groups at 3 months was 20.0% (SE, 1.4%) vs 8.7% (SE, 2.2%) ($P < .001$) and at 6 months was 21.2% (SE, 1.5%) vs 12.1% (SE, 3.2%) ($P = .03$). Risk factors for probable PTSD at 6 months after mTBI included less education (adjusted odds ratio, 0.89; 95% CI, 0.82-0.97 per year), being black (adjusted odds ratio, 5.11; 95% CI, 2.89-9.05), self-reported psychiatric history (adjusted odds ratio, 3.57; 95% CI, 2.09-6.09), and injury resulting from assault or other violence (adjusted odds ratio, 3.43; 95% CI, 1.56-7.54). Risk factors for probable MDD after mTBI were similar with the exception that cause of injury was not associated with increased risk.

Conclusions and Relevance: After mTBI, some individuals, on the basis of education, race/ethnicity, history of mental health problems, and cause of injury were at substantially increased risk of PTSD and/or MDD. These findings should influence recognition of at-risk individuals and inform efforts at surveillance, follow-up, and intervention.

OTHER RESEARCH OF INTEREST (Continued)

Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease.

Preische O[1,2], Schultz SA[3], Apel A[1,2], Kuhle J[4], Kaeser SA[1,2], Barro C[4], Gräber S[1], Kuder-Buletta E[1], LaFougere C[1], Laske C[1,2], Vöglein J[5,6], Levin J[5,6], Masters CL[7], Martins R[8,9], Schofield PR[10,11], Rossor MN[12], Graff-Radford NR[13], Salloway S[14], Ghetti B[15], Ringman JM[16], Noble JM[17], Chhatwal J[18], Goate AM[19], Benzinger TLS[3], Morris JC[3], Bateman RJ[3], Wang G[3], Fagan AM[3], McDade EM[3], Gordon BA[3], Jucker M[20,21]; Dominantly Inherited Alzheimer Network.

Nat Med. **2019 Jan 21**. doi: 10.1038/s41591-018-0304-3. PMID: 30664784. [Epub ahead of print]

Neurofilament light chain (NfL) is a promising fluid biomarker of disease progression for various cerebral proteopathies. Here we leverage the unique characteristics of the Dominantly Inherited Alzheimer Network and ultrasensitive immunoassay technology to demonstrate that NfL levels in the cerebrospinal fluid (n = 187) and serum (n = 405) are correlated with one another and are elevated at the presymptomatic stages of familial Alzheimer's disease. Longitudinal, within-person analysis of serum NfL dynamics (n = 196) confirmed this elevation and further revealed that the rate of change of serum NfL could discriminate mutation carriers from non-mutation carriers almost a decade earlier than cross-sectional absolute NfL levels (that is, 16.2 versus 6.8 years before the estimated symptom onset). Serum NfL rate of change peaked in participants converting from the presymptomatic to the symptomatic stage and was associated with cortical thinning assessed by magnetic resonance imaging, but less so with amyloid-β deposition or glucose metabolism (assessed by positron emission tomography). Serum NfL was predictive for both the rate of cortical thinning and cognitive changes assessed by the Mini-Mental State Examination and Logical Memory test. Thus, NfL dynamics in serum predict disease progression and brain neurodegeneration at the early presymptomatic stages of familial Alzheimer's disease, which supports its potential utility as a clinically useful biomarker.

Randomized Delayed-Start Trial of Levodopa in Parkinson's Disease.

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BACKGROUND: Levodopa is the main treatment for symptoms of Parkinson's disease. Determining whether levodopa also has a disease-modifying effect could provide guidance as to when in the course of the disease the treatment with this drug should be initiated.

METHODS: In a multicenter, double-blind, placebo-controlled, delayed-start trial, we randomly assigned patients with early Parkinson's disease to receive levodopa (100 mg three times per day) in combination with carbidopa (25 mg three times per day) for 80 weeks (early-start group) or placebo for 40 weeks followed by levodopa in combination with carbidopa for 40 weeks (delayed-start group). The primary outcome was the between-group difference in the mean change from baseline to week 80 in the total score on the Unified Parkinson's Disease Rating Scale (UPDRS; scores range from 0 to 176, with higher scores signifying more severe disease). Secondary analyses included the progression of symptoms, as measured by the UPDRS score, between weeks 4 and 40 and the noninferiority of early initiation of treatment to delayed initiation between weeks 44 and 80, with a noninferiority margin of 0.055 points per week.

RESULTS: A total of 445 patients were randomly assigned: 222 to the early-start group and 223 to the delayed-start group. The mean (±SD) UPDRS score at baseline was 28.1±11.4 points in the early-start group and 29.3±12.1 points in the delayed-start group. The change in UPDRS score from baseline to week 80 was -1.0±13.1 points and -2.0±13.0 points, respectively (difference, 1.0 point; 95% confidence interval [CI], -1.5 to 3.5; P=0.44); this finding of no significant between-group difference at week 80 implies that levodopa had no disease-modifying effect. Between weeks 4 and 40, the rate of progression of symptoms, as measured in UPDRS points per week, was 0.04±0.23 in the early-start group and 0.06±0.34 in the delayed-start group (difference, -0.02; 95% CI, -0.07 to 0.03). The corresponding rates between weeks 44 and 80 were 0.10±0.25 and 0.03±0.28 (difference, 0.07; two-sided 90% CI, 0.03 to 0.10); the difference in the rate of progression between weeks 44 and 80 did not meet the criterion for noninferiority of early receipt of levodopa to delayed receipt. The rates of dyskinesia and levodopa-related fluctuations in motor response did not differ significantly between the two groups.

CONCLUSIONS: Among patients with early Parkinson's disease who were evaluated over the course of 80 weeks, treatment with levodopa in combination with carbidopa had no disease-modifying effect. (Funded by the Netherlands Organization for Health Research and Development and others; LEAP Current Controlled Trials number, ISRCTN30518857.).

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