GULF WAR ILLNESS

The Relationship Between Traumatic Brain Injury and Rates of Chronic Symptomatic Illness in 202 Gulf War Veterans.

Chao LL[1,2,3].

Mil Med. **2018 May 18**. doi: 10.1093/milmed/usy109. PMID: 29788089. [Epub ahead of print]

Introduction: Although not a "signature injury" of Operation Desert Shield/Desert Storm (i.e., Gulf War, GW), some GW veterans have a history traumatic brain injury (TBI). For example, a previous study found that 12.2% of the GW veterans from the Fort Devens Cohort Study had self-reported TBIs. The present study sought to build upon this finding by examining the relationship between TBI and chronic symptomatic illness in a different sample of GW veterans.

Materials and Methods: Participants were 202 GW veterans recruited from 2014 to 2018 at the San Francisco Veterans Affairs Medical Center as part of a VA-funded study on the effects of predicted exposure to low levels of sarin and cyclosarin on brain structure and function. The Ohio State University TBI identification method was used to determine lifetime history of TBI. The Kansas Gulf War Military History and Health Questionnaire was used to assess symptoms and to determine cases of Kansas Gulf War Illness (GWI) and Centers for Disease Control and Prevention (CDC) Chronic Multisymptom Illness (CMI).

Results: Nearly half (47%) the sample had a history of TBI, but only 7% of the TBIs were sustained in injuries that occurred during the GW. Most of the TBIs were sustained in injuries that occurred prior to (73%) or after (34%) the GW. History of TBI was not associated with higher rates of symptomatic illness when it was narrowly defined (i.e., Kansas GWI cases or cases of severe CMI). History of TBI was only associated with higher rates of symptomatic illness when it is broadly defined (i.e., CDC CMI or mild-moderate CMI). There was suggestive evidence that veterans who sustained TBIs during the GW (only seven in the present sample) have poorer functional outcomes compared with GW veterans with non-GW related TBIs.

Conclusions: While TBIs were uncommon during the GW, many GW veterans sustained TBIs prior or after the GW. Because TBI and GWI/CMI share some overlapping symptoms, history of TBI may appear to be associated with increased rates of chronic symptomatic illness in GW veterans if chronic symptomatic illness is defined broadly (i.e., CDC CMI or mild-moderate CMI). History of pre-GW TBI did not affect the veterans' response to exposures/experiences from the GW; however, there was suggestive evidence that veterans who sustained TBIs during the GW may have poorer functional outcomes that GW veterans without TBI or even GW veterans with non-GW-related TBIs. Future, better powered studies with randomly and systematically select participants from the larger population of GW veterans will need to confirm this finding.

CHRONIC FATIGUE SYNDROME

Rituximab is Ineffective for Treatment of Fatigue in Primary Biliary Cholangitis: A phase-2 Randomised Controlled Trial.

Khanna A[1,2,3], Jopson L[1,2], Howel D[4], Bryant A[4], Blamire A[1,2], Newton JL[1,2], Jones DE[1,2,3].

Hepatology. **2018 May 23**. doi: 10.1002/hep.30099. PMID: 29790196. [Epub ahead of print]

Primary Biliary Cholangitis (PBC) is a chronic cholestatic liver disease. Half of patients experience debilitating fatigue which is currently untreatable. Previous studies have shown muscle bioenergetic abnormalities in PBC, including increased muscle acidosis with exercise linked to the anti-mitochondrial antibody (AMA) diagnostic of the disease, and reduced anaerobic threshold. In this study we addressed the hypothesis that fatigue in PBC is driven by muscle bioenergetic abnormality related to AMA, and that AMA reduction with B-cell depletion therapy will improve fatigue. In our single-centred Phase II randomised controlled trial (RCT) 57 participants aged ≥18 years with PBC and moderate or severe fatigue were randomized to receive 2 doses of either rituximab (1000mg) or saline (placebo). The primary outcome measure was fatigue severity assessed using the PBC-40 fatigue domain at 3 months. Secondary outcomes measures included patient-reported outcomes, immunological and bioenergetics disease parameters. Experimental outcomes included biochemical markers of disease severity. Improvement in fatigue score at 3 months was seen in both arms, with no significant difference (adjusted mean difference -0.9 95%CI -4.6 to 3.1). Little difference was observed in other patient reported outcomes or physical activity. Significant anaerobic threshold improvement was seen in the Rituximab group only but this was not associated with fatigue improvement. No treatment-emergent SAEs were seen.

CONCLUSIONS: Rituximab was safe over the 12 month study period but showed no evidence of effectiveness for the treatment of fatigue in PBC. Anaerobic threshold improvement was seen; potentially linking AMA with muscle bioenergetics dysfunction, however, this was not related to improvement in fatigue. Rituximab had some evidence of a beneficial effect on alkaline phosphatase levels in this largely UDCA-responding, early disease stage cohort.

CHRONIC FATIGUE SYNDROME (Continued)

Metabolomic markers of fatigue: Association between circulating metabolome and fatigue in women with chronic widespread pain.

Freidin MB[1], Wells HRR[1], Potter T[1], Livshits G[2], Menni C[1], Williams FMK[3].

Biochim Biophys Acta. **2018 Feb**;1864(2):601-606. doi: 10.1016/j.bbadis.2017.11.025. PMCID: PMC5764223. PMID: 29197660. Epub 2017 Dec 2.

BACKGROUND: Fatigue is a sensation of unbearable tiredness that frequently accompanies chronic widespread musculoskeletal pain (CWP) and inflammatory joint disease. Its mechanisms are poorly understood and there is a lack of effective biomarkers for diagnosis and onset prediction. We studied the circulating metabolome in a population sample characterised for CWP to identify biomarkers showing specificity for fatigue.

MATERIAL AND METHODS: Untargeted metabolomic profiling was conducted on fasting plasma and serum samples of 1106 females with and without CWP from the TwinsUK cohort. Linear mixed-effects models accounting for covariates were used to determine relationships between fatigue and metabolites. Receiver operating curve (ROC)-analysis was used to determine predictive value of metabolites for fatigue.

RESULTS: While no association between fatigue and metabolites was identified in twins without CWP (n=711), in participants with CWP (n=395), levels of eicosapentaenoate (EPA) ω-3 fatty acid were significantly reduced in those with fatigue (β=-0.452±0.116; $p=1.2\times10^{-4}$). A significant association between fatigue and two other metabolites also emerged when BMI was excluded from the model: 3-carboxy-4-methyl-5-propyl-2-furanpropanoate (CMPF), and C-glycosyltryptophan ($p=1.5\times10^{-4}$ and $p=3.1\times10^{-4}$, respectively). ROC analysis has identified a combination of 15 circulating metabolites with good predictive potential for fatigue in CWP (AUC=75%; 95% CI 69-80%).

CONCLUSION: The results of this agnostic metabolomics screening show that fatigue is metabolically distinct from CWP, and is associated with a decrease in circulating levels of EPA. Our panel of circulating metabolites provides the starting point for a diagnostic test for fatigue in CWP.

HEADACHE and MIGRAINE

Acupuncture in migraine prophylaxis in Czech patients: an open-label randomized controlled trial.

Musil F[1], Pokladnikova J[1,2], Pavelek Z[3], Wang B[4], Guan X[4], Valis M[3].

Neuropsychiatr Dis Treat. **2018 May 10**;14:1221-1228. doi: 10.2147/NDT.S155119. PMCID: PMC5955045. PMID: 29785113. eCollection 2018.

Background: Adjuvant acupuncture for the symptomatic treatment of migraine reduces the frequency of headaches and may be at least similarly effective to treatment with prophylactic drugs.

Methods: This article describes an open-label randomized controlled clinical trial with two groups: the intervention group (n=42) and the waiting-list control group (n=44). This study occurred at the Czech-Chinese Center for Traditional Chinese Medicine at the University Hospital Hradec Kralove between October 2015 and April 2017.

Results: After 12 weeks of acupuncture, the number of migraine days was reduced by 5.5 and 2.0 days in the acupuncture and the waiting-list control groups, respectively, with a statistically significant inter-group difference of 2.0 migraine days (95% CI: -4 to -1). A significantly greater reduction in the number of migraine days per 4 weeks was reached at the end of the 6-month follow-up period in the acupuncture vs. control groups (Δ -4.0; 95% CI: -6 to -2). A statistically significant difference was observed in the number of responders to treatment (response defined as at least a 50% reduction in average monthly migraine day frequency) in the acupuncture vs waiting-list control groups (50% vs 27%; $p<0.05$) at the end of the intervention. A significantly greater percentage of responders to treatment was noted in the intervention vs control groups at the 6-month follow-up (81% vs 36%; $p<0.001$).

Conclusion: Acupuncture can reduce symptoms and medication use, both short term and long term, as an adjuvant treatment in migraine prophylaxis in Czech patients.

CHRONIC PAIN

Altered prefrontal correlates of monetary anticipation and outcome in chronic pain.

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Pain**. 2018 Apr 4**. doi: 10.1097/j.pain.0000000000001232. PMID: 29790868. [Epub ahead of print]

Chronic pain may alter both affect- and value-related behaviors, which represents a potentially treatable aspect of chronic pain experience. Current understanding of how chronic pain influences the function of brain reward systems, however, is limited. Using a monetary incentive delay task and functional magnetic resonance imaging (fMRI), we measured neural correlates of reward anticipation and outcomes in female participants with the chronic pain condition of fibromyalgia (N = 17) and age-matched, pain-free, female controls (N = 15). We hypothesized that patients would demonstrate lower positive arousal, as well as altered reward anticipation and outcome activity within corticostriatal circuits implicated in reward processing. Patients demonstrated lower arousal ratings as compared with controls, but no group differences were observed for valence, positive arousal, or negative arousal ratings. Group fMRI analyses were conducted to determine predetermined region of interest, nucleus accumbens (NAcc) and medial prefrontal cortex (mPFC), responses to potential gains, potential losses, reward outcomes, and punishment outcomes. Compared with controls, patients demonstrated similar, although slightly reduced, NAcc activity during gain anticipation. Conversely, patients demonstrated dramatically reduced mPFC activity during gain anticipation-possibly related to lower estimated reward probabilities. Further, patients demonstrated normal mPFC activity to reward outcomes, but dramatically heightened mPFC activity to no-loss (nonpunishment) outcomes. In parallel to NAcc and mPFC responses, patients demonstrated slightly reduced activity during reward anticipation in other brain regions, which included the ventral tegmental area, anterior cingulate cortex, and anterior insular cortex. Together, these results implicate altered corticostriatal processing of monetary rewards in chronic pain.

A 10-yr Analysis of Chronic Pelvic Pain and Chronic Opioid Therapy in the Women Veteran Population.

Cichowski SB[1,2], Rogers RG[1], Komesu Y[1], Murata E[1], Qualls C[2], Murata A[2], Murata G[2].

Mil Med. **2018 May 18**. doi: 10.1093/milmed/usy114. [Epub ahead of print]

Introduction: Chronic pelvic pain (CPP) affects an estimated 30% of women Veterans. Previous research shows high rates of narcotic abuse in the women Veteran population. Narcotics are not recommended for the treatment of CPP. Understanding how CPP impacts narcotic prescribing in the women Veteran population is critical to addressing the public health crisis of opioid abuse. Our objective was to compare chronic opioid therapy (COT) prescribed 5 yr prior to and following CPP diagnosis and to identify predictors of COT as well as adverse events associated with COT. We choose to look at 10 yr of data because we thought this time period would provide unique insight into the longitudinal associations of CPP and COT and was available in the database.

Materials and Methods: Women with non-cancer CPP were included for analyses from the Veteran's Affairs Corporate Database Warehouse. COT was defined as 90 d of opiates/calendar year for each of the 5 yr proceeding and following the diagnosis of CPP. Patient characteristics and potential variables influencing COT were collected. We compared baseline demographics between the women who received COT to the women who did not receive COT to find additional demographic predictors of COT in association with CPP. Multivariable analysis identified predictors of COT in this population of women with CPP. We utilized an interrupted time series analysis to understand the impact of the diagnosis of CPP on COT.

Results: A total of 49,601 women met inclusion criteria with an average age of 40.1 ± 11.5 yr; 37.3% self-characterized as being a racial minority and 24% had a history of military sexual trauma. Chronic use increased significantly ($p < 0.001$) in the 5 yr preceding the diagnosis of CPP from 6.3% (n = 3124) of women at time -5 to 13.6% (n = 6746) at time 0. In the first year following the diagnosis of CPP, 16.8% (n = 8,333) of women with CPP met the criteria for COT ($p < 0.001$) and 15% (n = 7440) of women with CPP remained in the COT group for the remaining 5 yr following the diagnosis. On average women in the COT group had 250-292 d of opioids/year. When comparing women who received chronic narcotics following the diagnosis of CPP versus those who did not receive chronic narcotics, women who received COT were older, more likely to smoke and more frequently diagnosed with other pain conditions such as back pain, headaches, and fibromyalgia. (All $p < 0.001$). In the multivariable model, predictors of COT following CPP diagnosis included prior COT (OR = 10.0 (95% CI 9.4, 10.6), a positive history of military sexual trauma, smoking, and other chronic pain conditions.

Conclusions: The distinct pattern of prescribing shown in this cohort may mean COT is prescribed for CPP and this prescribing pattern contributes to the adverse events associated with COT. As COT is not recommended for CPP, physicians need more education on the therapies available to help CPP patients.

CHRONIC PAIN (Continued)

Patient-relevant outcomes and health-related quality of life in patients with chronic, severe, noncancer pain treated with tapentadol prolonged release-Using criteria of health technology assessment.

Hofmann JF[1], Lal A[2], Steffens M[3], Boettger R[3].

J Opioid Manag. **2016 Sep/Oct**;12(5):323-331. doi: 10.5055/jom.2016.0349. PMID: 27844472.

OBJECTIVE: To perform a systematic comparison of tapentadol prolonged release (PR) and oxycodone controlled release (CR) using patient-relevant endpoints of efficacy, safety, and health-related quality of life (HRQoL) according to criteria used in health technology assessment. To derive a minimal important difference (MID) for the EQ-5D from three pivotal trials to measure patient-relevant changes in HRQoL.

DESIGN: Randomized, double-blind, placebo and active controlled.

SETTING: Outpatient primary care.

PARTICIPANTS: Patients with severe chronic osteoarthritis pain (two pivotal studies) and severe lower-back pain (one pivotal study) were enrolled. The intent-to-treat population of the three studies comprised a total of 2,968 patients (tapentadol PR arms: 978, oxycodone CR arms: 999, and in the placebo arms: 991).

INTERVENTIONS: Tapentadol PR (100-250 mg bid), oxydodone CR (20-50 mg bid), or placebo over a period of 15 weeks (3 weeks titration plus 12 weeks maintenance).

OUTCOME MEASURES: Patient-relevant endpoints of efficacy, safety, tolerability, and HRQoL.

RESULTS: Tapentadol PR demonstrated significant added benefits as compared to oxycodone CR in meta-analyses of the patient-relevant outcomes 30 percent pain relief (Realtive risk [RR]: 0.80 [0.75, 0.87]), treatment discontinuations (RR: 0.55 [0.363, 0.825]), safety (RR: 0.652 [0.599, 0.710]), and HRQoL (RR: 0.78 [0.64, 0.96]) based on a MID derived for the EQ-5D summary index.

CONCLUSIONS: Added benefit of tapentadol in all endpoint categories suggests that it may be beneficial to initiate treatment of chronic severe nonmalignant pain with tapentadol rather than oxycodone.

Brain signature and functional impact of centralized pain: a multidisciplinary approach to the study of chronic pelvic pain (MAPP) network study.

Kutch JJ[1], Ichesco E, Hampson JP, Labus JS, Farmer MA, Martucci KT, Ness TJ, Deutsch G, Apkarian AV, Mackey SC, Klumpp DJ, Schaeffer AJ, Rodriguez LV, Kreder KJ, Buchwald D, Andriole GL, Lai HH, Mullins C, Kusek JW, Landis JR, Mayer EA, Clemens JQ, Clauw DJ, Harris RE; MAPP Research Network.

Pain. **2017 Oct**;158(10):1979-1991. doi: 10.1097/j.pain.0000000000001001. PMCID: PMC5964335. PMID: 28692006.

Chronic pain is often measured with a severity score that overlooks its spatial distribution across the body. This widespread pain is believed to be a marker of centralization, a central nervous system process that decouples pain perception from nociceptive input. Here, we investigated whether centralization is manifested at the level of the brain using data from 1079 participants in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research Network (MAPP) study. Participants with a clinical diagnosis of urological chronic pelvic pain syndrome (UCPPS) were compared to pain-free controls and patients with fibromyalgia, the prototypical centralized pain disorder. Participants completed questionnaires capturing pain severity, function, and a body map of pain. A subset (UCPPS N = 110; fibromyalgia N = 23; healthy control N = 49) underwent functional and structural magnetic resonance imaging. Patients with UCPPS reported pain ranging from localized (pelvic) to widespread (throughout the body). Patients with widespread UCPPS displayed increased brain gray matter volume and functional connectivity involving sensorimotor and insular cortices ($P < 0.05$ corrected). These changes translated across disease diagnoses as identical outcomes were present in patients with fibromyalgia but not pain-free controls. Widespread pain was also associated with reduced physical and mental function independent of pain severity. Brain pathology in patients with centralized pain is related to pain distribution throughout the body. These patients may benefit from interventions targeting the central nervous system.

CHRONIC PAIN (Continued)

Pain clinic definitions in the medical literature and U.S. state laws: an integrative systematic review and comparison.

Andraka-Christou B[1], Rager JB[2], Brown-Podgorski B[3], Silverman RD[4], Watson DP[5].

Subst Abuse Treat Prev Policy. **2018 May 22**;13(1):17. doi: 10.1186/s13011-018-0153-6. PMCID: PMC5964673. PMID: 29789018.

BACKGROUND: In response to widespread opioid misuse, ten U.S. states have implemented regulations for facilities that primarily manage and treat chronic pain, called "pain clinics." Whether a clinic falls into a state's pain clinic definition determines the extent to which it is subject to oversight. It is unclear whether state pain clinic definitions model those found in the medical literature, and potential differences lead to discrepancies between scientific and professionally guided advice found in the medical literature and actual pain clinic practice. Identifying discrepancies could assist states to design laws that are more compatible with best practices suggested in the medical literature.

METHODS: We conducted an integrative systematic review to create a taxonomy of pain clinic definitions using academic medical literature. We then identified existing U.S. state pain clinic statutes and regulations and compared the developed taxonomy using a content analysis approach to understand the extent to which medical literature definitions are reflected in state policy.

RESULTS: In the medical literature, we identified eight categories of pain clinic definitions: 1) patient case mix; 2) single-modality treatment; 3) multidisciplinary treatment; 4) interdisciplinary treatment; 5) provider supervision; 6) provider composition; 7) marketing; and 8) outcome. We identified ten states with pain clinic laws. State laws primarily include the following definitional categories: patient case mix; single-modality treatment, and marketing. Some definitional categories commonly found in the medical literature, such as multidisciplinary treatment and interdisciplinary treatment, rarely appear in state law definitions.

CONCLUSIONS: This is the first study to our knowledge to develop a taxonomy of pain clinic definitions and to identify differences between pain clinic definitions in U.S. state law and medical literature. Future work should explore the impact of different legal pain clinic definitions on provider decision-making and state-level health outcomes.

Randomized Trial of a Group Music and Imagery Method (GrpMI) for Women with Fibromyalgia.

Torres E[1], Pedersen IN[2], Pérez-Fernández JI[3].

J Music Ther. **2018 May 18**. doi: 10.1093/jmt/thy005. PMID: 29788133. [Epub ahead of print]

Background: Fibromyalgia (FM) affects about 2-4% of the world population. Patients, mostly women, experience chronic widespread pain, fatigue, stiffness, sleep disturbances, and psychological disorders, especially depression and anxiety.

Objective: The aim of this study was to examine preliminary efficacy of a Group Music and Imagery (GrpMI) intervention, which included relaxation, music listening, and spontaneous imagery, to improve subjective psychological well-being, functional capacity and health, pain perception, anxiety, and depression in women with FM.

Methods: Fifty-six women aged 35 to 65 years (M = 51.3) diagnosed with FM were randomly assigned to either GrpMI treatment (n = 33) or control (n = 26) condition. Experimental group participants received 12 weekly GrpMI sessions, and control group participants who did not receive any additional service completed measures at the same time points as the experimental group.

Results: Intra-group analyses showed that GrpMI participants had a significant increase in psychological well-being and significant decrease in the impact of FM on functional capacity and health, pain perception, anxiety, and depression post-treatment, with sustained benefit at three-month follow-up for all variables except psychological well-being. Control group participants showed decreases in trait anxiety and depression at post-treatment, with no significant benefit at three-month follow-up. Inter-group analyses showed that compared with control participants, GRpMI participants had significantly higher scores for psychological well-being and lower-state anxiety post-treatment; however, no differences were observed between groups at three-month follow-up.

Conclusions: Findings offer preliminary evidence for the benefit of GrpMI to improve well-being and reduce anxiety in women with FM. Findings also suggest that GrpMI may help diminish pain intensity, state depression, and the impact of FM on functional capacity and health, but further studies are needed to establish efficacy.

OTHER RESEARCH OF INTEREST

Association of Mild Traumatic Brain Injury With and Without Loss of Consciousness With Dementia in US Military Veterans.

Barnes DE[1,2,3], Byers AL[1,2,3], Gardner RC[1,4], Seal KH[1,2,5], Boscardin WJ[1,5], Yaffe K[1,2,3,4].

JAMA Neurol. **2018 May 7**. doi: 10.1001/jamaneurol.2018.0815. PMID: 29801145. [Epub ahead of print]

Importance: Traumatic brain injury (TBI) is common in both veteran and civilian populations. Prior studies have linked moderate and severe TBI with increased dementia risk, but the association between dementia and mild TBI, particularly mild TBI without loss of consciousness (LOC), remains unclear.

Objective: To examine the association between TBI severity, LOC, and dementia diagnosis in veterans.

Design, Setting, and Participants: This cohort study of all patients diagnosed with a TBI in the Veterans Health Administration health care system from October 1, 2001, to September 30, 2014, and a propensity-matched comparison group. Patients with dementia at baseline were excluded. Researchers identified TBIs through the Comprehensive TBI Evaluation database, which is restricted to Iraq and Afghanistan veterans, and the National Patient Care Database, which includes veterans of all eras. The severity of each TBI was based on the most severe injury recorded and classified as mild without LOC, mild with LOC, mild with LOC status unknown, or moderate or severe using Department of Defense or Defense and Veterans Brain Injury Center criteria. International Classification of Diseases, Ninth Revision codes were used to identify dementia diagnoses during follow-up and medical and psychiatric comorbidities in the 2 years prior to the index date.

Main Outcomes and Measures: Dementia diagnosis in veterans who had experienced TBI with or without LOC and control participants without TBI exposure.

Results: The study included 178 779 patients diagnosed with a TBI in the Veterans Health Administration health care system and 178 779 patients in a propensity-matched comparison group. Veterans had a mean (SD) age of nearly 49.5 (18.2) years at baseline; 33 250 (9.3%) were women, and 259 136 (72.5%) were non-Hispanic white individuals. Differences between veterans with and without TBI were small. A total of 4698 veterans (2.6%) without TBI developed dementia compared with 10 835 (6.1%) of those with TBI. After adjustment for demographics and medical and psychiatric comobidities, adjusted hazard ratios for dementia were 2.36 (95% CI, 2.10-2.66) for mild TBI without LOC, 2.51 (95% CI, 2.29-2.76) for mild TBI with LOC, 3.19 (95% CI, 3.05-3.33) for mild TBI with LOC status unknown, and 3.77 (95% CI, 3.63-3.91) for moderate to severe TBI.

Conclusions and Relevance: In this cohort study of more than 350 000 veterans, even mild TBI without LOC was associated with more than a 2-fold increase in the risk of dementia diagnosis. Studies of strategies to determine mechanisms, prevention, and treatment of TBI-related dementia in veterans are urgently needed.

Taking a Closer Look at the Biomarker Test for Mild Traumatic Brain Injury.

Voelker R. [See full text of article in JAMA Medical News & Perspectives.]

JAMA. **2018 May 22**;319(20):2066-2067. doi: 10.1001/jama.2018.4644. PMID: 29800154

Not long after a first-of-its-kind blood test received approval to evaluate patients with mild traumatic brain injury, headlines dubbed it a “concussion test.” But experts in biomarkers are clarifying certain misconceptions about what the test can and can’t reveal.

“It’s used to rule out the need for a [computed tomography] scan within 12 hours” after a suspected mild traumatic brain injury (TBI), said Steven Richieri, MBA, president and chief operating officer of San Diego-based Banyan Biomarkers Inc, which developed the test.

The test measures 2 proteins—glial fibrillary acidic protein and ubiquitin C-terminal hydrolase L1—that can be detected in peripheral blood within an hour after a mild TBI. A positive result would indicate a higher risk of more severe injury that could be detected on a computed tomography (CT) scan. A negative result would denote a far lower risk of serious injury. The test doesn’t specifically diagnose concussion.

“A positive test [result] in this case would actually be indicative of something we might call a complicated mild traumatic brain injury,” said Christopher Giza, MD, professor of pediatrics and neurosurgery at the University of California, Los Angeles (UCLA) and director of the UCLA Steve Tisch BrainSPORT Program. “It looks a little bit like a concussion but then there’s some bleeding or bruising in the brain or something else that would be detected on a CT scan,” added Giza, lead author of the American Academy of Neurology’s sports concussion guideline.

Even though a clinical definition of concussion isn’t exactly written in stone, Giza offered a description of the condition that he conceded is still subject to some debate. “Concussion is a type of mild traumatic brain injury,” he explained. “Within mild TBI you could have a small bleed in your head and it could still be mild or you could have a concussion where there shouldn’t be any bleeding or bruising on the brain.

“Think of concussion almost as kind of a subset of mild traumatic brain injury.”

OTHER RESEARCH OF INTEREST (Continued)

Association of Efficacy of Resistance Exercise Training With Depressive Symptoms: Meta-analysis and Meta-regression Analysis of Randomized Clinical Trials.

Gordon BR[1], McDowell CP[1], Hallgren M[2], Meyer JD[3], Lyons M[1], Herring MP[1,4].

JAMA Psychiatry. **2018 May 9**. doi: 10.1001/jamapsychiatry.2018.0572. PMID: 29800984. [Epub ahead of print]

Importance: The physical benefits of resistance exercise training (RET) are well documented, but less is known regarding the association of RET with mental health outcomes. To date, no quantitative synthesis of the antidepressant effects of RET has been conducted.

Objectives: To estimate the association of efficacy of RET with depressive symptoms and determine the extent to which logical, theoretical, and/or prior empirical variables are associated with depressive symptoms and whether the association of efficacy of RET with depressive symptoms accounts for variability in the overall effect size.

Data Sources: Articles published before August 2017, located using Google Scholar, MEDLINE, PsycINFO, PubMed, and Web of Science.

Study Selection: Randomized clinical trials included randomization to RET (n = 947) or a nonactive control condition (n = 930).

Data Extraction and Synthesis: Hedges d effect sizes were computed and random-effects models were used for all analyses. Meta-regression was conducted to quantify the potential moderating influence of participant and trial characteristics.

Main Outcomes and Measures: Randomized clinical trials used validated measures of depressive symptoms assessed at baseline and midintervention and/or postintervention. Four primary moderators were selected a priori to provide focused research hypotheses about variation in effect size: total volume of prescribed RET, whether participants were healthy or physically or mentally ill, whether or not allocation and/or assessment were blinded, and whether or not the RET intervention resulted in a significant improvement in strength.

Results: Fifty-four effects were derived from 33 randomized clinical trials involving 1877 participants. Resistance exercise training was associated with a significant reduction in depressive symptoms with a moderate-sized mean effect Δ of 0.66 (95% CI, 0.48-0.83; z = 7.35; P < .001). Significant heterogeneity was indicated (total Q = 216.92, df = 53; P < .001; I2 = 76.0% [95% CI, 72.7%-79.0%]), and sampling error accounted for 32.9% of observed variance. The number needed to treat was 4. Total volume of prescribed RET, participant health status, and strength improvements were not significantly associated with the antidepressant effect of RET. However, smaller reductions in depressive symptoms were derived from randomized clinical trials with blinded allocation and/or assessment.

Conclusions and Relevance: Resistance exercise training significantly reduced depressive symptoms among adults regardless of health status, total prescribed volume of RET, or significant improvements in strength. Better-quality randomized clinical trials blinding both allocation and assessment and comparing RET with other empirically supported treatments for depressive symptoms are needed.

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