GULF WAR ILLNESS

Detecting Chromosome Condensation Defects in Gulf War Illness Patients.

Liu G[1], Ye CJ[2], Chowdhury SK[3], Abdallah BY[1], Horne SD[1], Nichols D[1,2,3,4], Heng HH[1,4].

Curr Genomics. **2018 Apr**;19(3):200-206. doi: 10.2174/1389202918666170705150819. PMCID: PMC5850508. PMID: 29606907.

Background: Gulf War Illness (GWI) impacts 25-30% of gulf war veterans. Due to its heterogeneity in both etiology and symptoms, it has been challenging to establish the commonly accepted case definition for GWI. Equally challenging are the understanding of the general mechanism of GWI and the development of biomarkers useful for its clinical diagnosis and treatment.

Objective: We have observed that chromosome condensation defects can be detected in GWI patients. To document this phenomenon in GWI, we aim to describe and compare different types of chromosomal condensation defects in GWI patients, if possible. Since chromosomal condensation represents an important step of ensuring genome integrity, condensation defects could be used as a potential biomarker of GWI.

Methods: Lymphocytes from GWI patients have been used for short term cell culture followed by chromosome slide preparation. Both Giemsa staining and multiple color spectral karyotyping (SKY) were applied to study chromosome aberrations, focusing on different types of condensation defects.

Results: At least three subtypes of Defective Mitotic Figures (DMFs) were observed. Some individuals displayed elevated frequencies of DMFs. Another type of condensation defect identified as sticky chromosomes were also observed.

Conclusion: Various types of condensation defects have been observed in GWI patients. It is rather surprising that some GWI patients exhibited a high level of chromosomal condensation defects. Previously, the elevated frequency of DMFs was only observed in cancer patients. Since chromosome condensation can be linked to other types of chromosome aberrations, as well as cellular stress conditions, the detailed mechanism and clinical impact should be further studied, especially with increased sample size.

CHRONIC FATIGUE SYNDROME

Treating patients suffering from myalgic encephalopathy/chronic fatigue syndrome (ME/CFS) with sodium dichloroacetate: An open-label, proof-of-principle pilot trial.

Comhaire F[1].

Med Hypotheses. **2018 May**;114:45-48. doi: 10.1016/j.mehy.2018.03.002. Epub 2018 Mar 5.

Twenty-two consecutive patients suffering from refractory myalgic encephalitis/chronic fatigue syndrome (ME/CFS) were treated with an innovative nutriceutical containing sodium dichloroacetate in a proof-of-principle, pilot, open-label prospective cohort trial. Ten patients experienced significant improvement of their health condition with reduction to almost half of their score in the fatigue severity scale. In twelve patients treatment failed to exert any beneficial effect. In the latter patients several other diseases have commonly been revealed by extensive biological and imaging investigations. These preliminary findings sustain the hypothetical role of mitochondrial hypo-metabolism due to inhibition of the activity of the pyruvate dehydrogenase in the pathogenesis of primary ME/CFS, and suggest a possible benefit of nutriceutical treatment by sodium dichloroacetate.

CHRONIC FATIGUE SYNDROME (Continued)

Rituximab impedes natural killer cell function in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis patients: A pilot in vitro investigation.

Eaton N[1,2], Cabanas H[3,4], Balinas C[3,4], Klein A[3,4], Staines D[3,4], Marshall-Gradisnik S[3,4].

BMC Pharmacol Toxicol. **2018 Mar 27**;19(1):12. doi: 10.1186/s40360-018-0203-8. PMCID: PMC5870391. PMID: 29587879.

BACKGROUND: A recent in vitro pilot investigation reported Rituximab significantly reduced natural killer (NK) cell cytotoxicity in healthy donors. Chronic fatigue syndrome/Myalgic encephalomyelitis (CFS/ME) is a debilitating disorder of unknown etiology. A consistent finding is a significant reduction in NK cell cytotoxicity. Rituximab has been reported having questionable potential therapeutic benefits for the treatment of CFS/ME, however, the potential effects of Rituximab on NK cell cytotoxicity in CFS/ME patients are yet to be determined.

METHODS: A total of eight CFS/ME patients (48.63 ± 15.69 years) and nine non-fatigued controls (NFC) (37.56 ± 11.06 years) were included using the Fukuda case definition. Apoptotic function, lytic proteins and degranulation markers were measured on isolated NK cells using flow cytometry following overnight incubation with Rituximab at 10 μg/ml and 100 μg/ml.

RESULTS: There was a significant reduction in NK cell lysis between CFS/ME patients and NFC following incubation with Rituximab at 100 μg/ml at 12.5:1 and 6.25:1 effecter-target (E:T) ratios ($p < 0.05$). However, there was no significant difference for NFC following incubation with Rituximab at 10 μg/ml and 100 μg/ml. There was no significant difference between CFS/ME patients and NFC for granzyme A and granzyme B prior to incubation with Rituximab and following overnight incubation with Rituximab at 10 μg/ml. There was a significant decrease in granzyme B in CFS/ME patients compared to NFC with 100 μg/ml of Rituximab prior to K562 cells stimulation ($p < 0.05$). There was a significant increase in CD107a ($p < 0.05$) and CD107b expression ($p < 0.01$) in NFC after stimulation with K562 cells prior to incubation with Rituximab. There was a significant increase in CD107b expression between CFS/ME patients and NFC prior to incubation with Rituximab and without stimulation of K562 cells ($p < 0.01$). Importantly, there was a significant increase in CD107b following overnight incubation with 100 μg/ml of Rituximab in NFC prior to K562 cells stimulation ($p < 0.01$).

CONCLUSION: This study reports significant decreases in NK cell lysis and a significant increase in NK cell degranulation following Rituximab incubation in vitro in CFS/ME patients, suggesting Rituximab may be toxic for NK cells. Caution should be observed in clinical trials until further investigations in a safe and controlled in vitro setting are completed.

Graded exercise self-help for chronic fatigue syndrome in GETSET - Authors' reply.

Clark LV[1], Pesola F[2], Thomas JM[3], Vergara-Williamson M[4], Beynon M[5], White PD[5].

Lancet. **2018 Mar 24**;391(10126):1162. doi: 10.1016/S0140-6736(18)30684-6. PMID: 29595495.

In the graded exercise therapy guided self-help treatment (GETSET) trial, we found that addition of guided graded exercise self-help (GES) to specialist medical care (SMC) safely improved fatigue and physical functioning more than did the comparison treatment of SMC alone.

Frank Twisk suggests that GES is not a rehabilitative intervention as the GES group did not return patients to normal levels of fatigue and physical functioning, and Joan Crawford is unimpressed with the effect size of GES for improving functioning. We suggest that an improvement in the main symptom of fatigue with an effect size of 0.53 is clinically useful. We have already acknowledged the small size of the effect on physical functioning (0.20), but our finding that the effect size was greater in those with the worst baseline physical functioning suggests this might represent a ceiling effect.

Therapists reported that 29% of patients did not adhere more than “slightly” to the exercise programme, despite 88% attending at least 75% of their guided support. This area requires more research to understand non-adherence and how it might be improved.

We used the National Institute for Health and Care Excellence (NICE) definition of chronic fatigue syndrome as these are the commonest criteria used by UK clinicians in secondary care. A subgroup analysis using two other definitions of chronic fatigue syndrome made no significant difference to the findings. There were no significant differences in safety outcomes between treatment arms once missing data were accounted for.

[For additional comments and full text of this article see *The Lancet*, 2018-03-24, Vol. 391, Issue 10126, Pg. 1162.]

CHRONIC FATIGUE SYNDROME (Continued)

The etiologic relation between disequilibrium and orthostatic intolerance in patients with myalgic encephalomyelitis (chronic fatigue syndrome).

Miwa K[1], Inoue Y[2].

J Cardiol. **2018 Mar 24**. pii: S0914-5087(18)30058-3. doi: 10.1016/j.jjcc.2018.02.010. PMID: 29588088. [Epub ahead of print]

BACKGROUND: Orthostatic intolerance (OI) causes a marked reduction in the activities of daily living in patients with myalgic encephalomyelitis (ME) or chronic fatigue syndrome. Most symptoms of OI are thought to be related to cerebral hypo-perfusion and sympathetic activation. Because postural stability is an essential element of orthostatic tolerance, disequilibrium may be involved in the etiology of OI.

METHODS AND RESULTS: The study comprised 44 patients with ME (men, 11 and women, 33; mean age, 37±9 years), who underwent neurological examinations and 10-min standing and sitting tests. Symptoms of OI were detected in 40 (91%) patients and those of sitting intolerance were detected in 30 (68%). Among the 40 patients with OI, disequilibrium with instability on standing with their feet together and eyes shut, was detected in 13 (32.5%) patients and hemodynamic dysfunction during the standing test was detected in 19 (47.5%); both of these were detected in 7 (17.5%) patients. Compared with 31 patients without disequilibrium, 13 (30%) patients with disequilibrium more prevalently reported symptoms during both standing (100% vs. 87%, p=0.43) and sitting (92% vs. 58%, p=0.06) tests. Several (46% vs. 3%, p<0.01) patients failed to complete the 10-min standing test, and some (15% vs. 0%, p=0.15) failed to complete the 10-min sitting test. Among the seven patients with both hemodynamic dysfunction during the standing test and disequilibrium, three (43%) failed to complete the standing test. Among the 6 patients with disequilibrium only, 3 (50%) failed while among the 12 patients with hemodynamic dysfunction only, including 8 patients with postural orthostatic tachycardia, none (0%, p=0.02) failed.

CONCLUSIONS: Patients with ME and disequilibrium reported not only OI but also sitting intolerance. Disequilibrium should be recognized as an important cause of OI and appears to be a more influential cause for OI than postural orthostatic tachycardia in patients with ME.

HEADACHE and MIGRAINE

Migraine is common in patients with sarcoidosis.

Gelfand JM[1], Gelfand AA[2], Goadsby PJ[2,3], Benn BS[4], Koth LL[4].

Cephalalgia. **2018 Jan 1**:333102418768037. doi: 10.1177/0333102418768037. PMID: 29580067. [Epub ahead of print]

Objective: To describe the frequency of migraine and predictors of having migraine in sarcoidosis patients.

Methods: The ID migraine questionnaire was administered to a well-phenotyped observational cohort of sarcoidosis patients (most of whom were seeking specialty care) and healthy controls. Predictors of migraine status were examined using univariate and multivariable logistic regression.

Results: Migraine was seen in 29% of 96 patients with sarcoidosis and 13% of 39 healthy controls, (p = 0.049). Among those with sarcoidosis, in univariate regression analysis only female sex was predictive of having migraine, and in a multivariable regression female sex remained significant (OR 4.6, 95% CI 1.2-18.2). There was no association between migraine and age, depression, dyspnea, immunosuppression use, or ESR.

Conclusions: Migraine is a common comorbidity in sarcoidosis patients. As such, better recognition and targeted treatment of migraine has the potential to improve quality of life as part of a comprehensive care plan for sarcoidosis patients.

HEADACHE and MIGRAINE (Continued)

Migraine and the risk of cardiovascular and cerebrovascular events: a meta-analysis of 16 cohort studies including 1 152 407 subjects.

Mahmoud AN[#1], Mentias A[#2], Elgendy AY[1], Qazi A [2], Barakat AF[3], Saad M[4], Mohsen A[2], Abuzaid A[5], Mansoor H[6], Mojadidi MK[1], Elgendy IY[1].

BMJ Open. **2018 Mar 27**;8(3):e020498. doi: 10.1136/bmjopen-2017-020498. PMID: 29593023.

OBJECTIVES: To perform an updated meta-analysis to evaluate the long-term cardiovascular and cerebrovascular outcomes among migraineurs.

SETTING: A meta-analysis of cohort studies performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

DATA SOURCES: The MEDLINE, Web of Science and Cochrane Central Register of Controlled Trials databases were searched for relevant articles.

PARTICIPANTS: A total of 16 cohort studies (18 study records) with 394 942 migraineurs and 757 465 non-migraineurs were analysed.

PRIMARY AND SECONDARY OUTCOME MEASURES: Major adverse cardiovascular and cerebrovascular events (MACCE), stroke (ie, ischaemic, haemorrhagic or non-specified), myocardial infarction (MI) and all-cause mortality. The outcomes were reported at the longest available follow-up.

DATA ANALYSIS: Summary-adjusted hazard ratios (HR) were calculated by random-effects Der-Simonian and Liard model. The risk of bias was assessed by the Newcastle-Ottawa Scale.

RESULTS: Migraine was associated with a higher risk of MACCE (adjusted HR 1.42, 95% confidence interval [CI] 1.26 to 1.60, P<0.001, I^2=40%) driven by a higher risk of stroke (adjusted HR 1.41, 95% CI 1.25 to 1.61, P<0.001, I^2=72%) and MI (adjusted HR 1.23, 95% CI 1.03 to 1.43, P=0.006, I^2=59%). There was no difference in the risk of all-cause mortality (adjusted HR 0.93, 95% CI 0.78 to 1.10, P=0.38, I^2=91%), with a considerable degree of statistical heterogeneity between the studies. The presence of aura was an effect modifier for stroke (adjusted HR aura 1.56, 95% CI 1.30 to 1.87 vs adjusted HR no aura 1.11, 95% CI 0.94 to 1.31, $P_{interaction}$=0.01) and all-cause mortality (adjusted HR aura 1.20, 95% CI 1.12 to 1.30 vs adjusted HR no aura 0.96, 95% CI 0.86 to 1.07, $P_{interaction}$<0.001).

CONCLUSION: Migraine headache was associated with an increased long-term risk of cardiovascular and cerebrovascular events. This effect was due to an increased risk of stroke (both ischaemic and haemorrhagic) and MI. There was a moderate to severe degree of heterogeneity for the outcomes, which was partly explained by the presence of aura.

PROSPERO REGISTRATION NUMBER: CRD42016052460.

Exercise-Induced Change in Plasma IL-12p70 Is Linked to Migraine Prevention and Anxiolytic Effects in Treatment-Naïve Women: A Randomized Controlled Trial.

Oliveira AB[1], Bachi ALL[2], Ribeiro RT[1], Mello MT[3], Vaisberg M[4], Peres MFP[5,6].

Neuroimmunomodulation. **2018 Mar 29**. doi: 10.1159/000487141. PMID: 29597198. [Epub ahead of print]

OBJECTIVE: To conduct a randomized controlled trial to evaluate the effect of a 12-week aerobic exercise program for migraine prevention, plasma cytokines concentrations (TNF-α, interleukin [IL]-1β, IL-6, IL-8, IL-10, and IL-12p70), and anxiety in women with migraine.

METHODS: Women with episodic migraine (ICHD-II), aged between 20 and 50 years, who had never taken any prophylactic medication, and were physically inactive in the past 12 months were recruited from the university's hospital and a tertiary headache clinic between March 2012 and March 2015. Migraine attacks were recorded in headache diaries, cytokines were quantified by flow cytometry, and anxiety was assessed by the 7-item General Anxiety Disorder (GAD-7) scale. Blood sampling and psychometric interviews were undertaken on headache-free days.

RESULTS: Twenty participants ([mean ± SD] age 33.8 ± 10.5; BMI 26 ± 5.2) were randomly assigned and received intervention ("trained": n = 10) or entered on a waitlist ("inactive": n = 10). There were no differences between groups regarding patients' characteristics and baseline data. Days with migraine (p = 0.001), IL-12p70 levels (p = 0.036), and GAD-7 score (p = 0.034) were significantly reduced in the trained group after the intervention period, but there were no significant changes in these variables in the inactive group. There was no change in the levels of the other cytokines in either group. There were positive correlations between a reduction in IL-12p70 level and a reduction in the number of days with migraine (R2 = 0.19, p = 0.045), and GAD-7 score (R2 = 0.53, p < 0.001).

CONCLUSION: The clinical and psychological therapeutic effects of aerobic exercise in treatment-naïve women with migraine may involve the downregulation of IL-12p70.

CHRONIC PAIN

Traumatic Brain Injury and Receipt of Prescription Opioid Therapy for Chronic Pain in Iraq and Afghanistan Veterans: Do Clinical Practice Guidelines Matter?

Seal KH[1], Bertenthal D[2], Barnes DE[3], Byers AL[3], Gibson CJ[3], Yaffe K[3]; Chronic Effects of Neurotrauma Consortium Study Group.

J Pain. **2018 Mar 26**. pii: S1526-5900(18)30116-0. doi: 10.1016/j.jpain.2018.03.005. PMID: 29597083. [Epub ahead of print]

Clinical practice guidelines admonish against prescribing opioids for individuals with chronic pain and traumatic brain injury (TBI) given increased risk for adverse outcomes, yet no studies have described opioid prescribing patterns in these higher risk patients. Between October 2007 and March 2015, 53,124 Iraq and Afghanistan veterans with chronic pain not prescribed opioids in the previous year were followed for one year after completing a Comprehensive TBI Evaluation (CTBIE) within Department of Veterans Affairs health care facilities. Veterans reporting the most severe TBI sequelae (e.g., loss of consciousness > 30 minutes) were significantly more likely to receive short-term and long-term opioid therapy than those with less severe or no TBI sequelae (p-values < 0.001). In analyses adjusted for sociodemographics, military service, pain disability, and prior non-opioid treatment modalities, veterans with moderate to severe TBI had a significantly increased risk of receiving opioid therapy. Veterans with moderate to severe TBI plus comorbid PTSD and depression had an even greater risk of initiating long-term opioid therapy in the year following CTBIE [Adjusted Relative Risk=3.57 (95% Confidence Interval=2.85,4.47)]. Higher-risk patients with chronic pain and TBI with mental health comorbidities may benefit from improved access to behavioral health and non-pharmacological therapies for chronic pain.

PERSPECTIVE: Paradoxically, veterans with greater traumatic brain injury (TBI) severity and comorbid mental health burden are more likely to be prescribed opioids for chronic pain. More vulnerable veterans may benefit from improved access to behavioral health and non-pharmacological modalities for chronic pain, given the health and safety risks of opioids.

Evaluation of Complementary and Integrative Health Approaches Among US Veterans with Musculoskeletal Pain Using Propensity Score Methods.

Han L[1,2], Goulet JL[3,4,5,2], Skanderson M[2], Bathulapalli H[2], Luther SL[6], Kerns RD[3,4,5,2], Brandt CA[3,4,5,2].

Pain Med. **2018 Mar 23**. doi: 10.1093/pm/pny027. PMID: 29584926. [Epub ahead of print]

Objectives: To examine the treatment effectiveness of complementary and integrative health approaches (CIH) on chronic pain using Propensity Score (PS) methods.

Design, Settings, and Participants: A retrospective cohort of 309,277 veterans with chronic musculoskeletal pain assessed over three years after initial diagnosis.

Methods: CIH exposure was defined as one or more clinical visits for massage, acupuncture, or chiropractic care. The treatment effect of CIH on self-rated pain intensity was examined using a longitudinal model. PS-matching and inverse probability of treatment weighting (IPTW) were used to account for potential selection and confounding biases.

Results: At baseline, veterans with (7,621) and without (301,656) CIH exposure differed significantly in 21 out of 35 covariates. During the follow-up period, on average CIH recipients had 0.83 (95% confidence interval [CI] = 0.77 to 0.89) points higher pain intensity ratings (range = 0-10) than nonrecipients. This apparent unfavorable effect size was reduced to 0.37 (95% CI = 0.28 to 0.45) after PS matching, 0.36 (95% CI = 0.29 to 0.44) with IPTW on the treated (IPTW-T) weighting, and diminished to null when integrating IPTW-T with PS matching (0.004, 95% CI = -0.09 to 0.10). An alternative IPTW model and conventional covariate adjustment appeared least powerful in terms of potential bias reduction. Sensitivity analyses restricting the follow-up period to one year after CIH initiation derived consistent results.

Conclusions: PS-based causal methods successfully eliminated baseline difference between exposure groups in all measured covariates, yet they did not detect a significant difference in the self-rated pain intensity outcome between veterans who received CIHs and those who did not during the follow-up period.

CHRONIC PAIN (Continued)

Altered insula-default mode network connectivity in fibromyalgia: a resting-state magnetoencephalographic study.

Hsiao FJ[1,2], Wang SJ[1,2,3,4], Lin YY[1,2,3,4], Fuh JL[1,3,4], Ko YC[3,5], Wang PN[1,3,4], Chen WT[6,7,8,9].

J Headache Pain. **2017 Aug 23**;18(1):89. doi: 10.1186/s10194-017-0799-x. PMCID: PMC5567574. PMID: 28831711.

BACKGROUND: Fibromyalgia (FM) is a disabling chronic pain syndrome with unknown pathophysiology. Functional magnetic resonance imaging studies on FM have suggested altered brain connectivity between the insula and the default mode network (DMN). However, this connectivity change has not been characterized through direct neural signals for exploring the embedded spectrotemporal features and the pertinent clinical relevance.

METHODS: We recorded the resting-state magnetoencephalographic activities of 28 patients with FM and 28 age- and sex-matched controls, and analyzed the source-based functional connectivity between the insula and the DMN at 1-40 Hz by using the minimum norm estimates and imaginary coherence methods. We also measured the connectivity between the DMN and the primary visual (V1) and somatosensory (S1) cortices as intrapatient negative controls. Connectivity measurement was further correlated with the clinical parameters of FM.

RESULTS: Compared with the controls, patients with FM reported more tender points (15.2±2.0 vs. 5.9±3.7) and higher total tenderness score (TTS; 29.1±7.0 vs. 7.7±5.5; both $p < 0.001$); they also had decreased insula-DMN connectivity at the theta band (4-8 Hz; left, $p = 0.007$; right, $p = 0.035$), but displayed unchanged V1-DMN and S1-DMN connectivity ($p > 0.05$). When patients with FM and the controls were combined together, the insula-DMN theta connectivity was negatively correlated with the number of tender points (left insula, $r = -0.428$, $p = 0.001$; right insula, $r = -0.4$, $p = 0.002$) and TTS score (left insula, $r = -0.429$, $p = 0.001$; right insula, $r = -0.389$, $p = 0.003$). Furthermore, in patients with FM, the right insula-DMN connectivity at the beta band (13-25 Hz) was negatively correlated with the number of tender points ($r = -0.532$, $p = 0.004$) and TTS ($r = -0.428$, $p = 0.023$), and the bilateral insula-DMN connectivity at the delta band (1-4 Hz) was negatively correlated with FM Symptom Severity (left: $r = -0.423$, $p = 0.025$; right: $r = -0.437$, $p = 0.020$) and functional disability (Fibromyalgia Impact Questionnaire; left: $r = -0.415$, $p = 0.028$; right: $r = -0.374$, $p = 0.050$).

CONCLUSIONS: We confirmed the frequency-specific reorganization of the insula-DMN connectivity in FM. The clinical relevance of this connectivity change may warrant future studies to elucidate its causal relationship and potential as a neurological signature for FM.

Association of body mass index with chronic pain prevalence: a large population-based cross-sectional study in Japan.

Yamada K[1], Kubota Y[2], Iso H[3], Oka H[4], Katsuhira J[4,5], Matsudaira K[4,6].

J Anesth. **2018 Mar 26**. doi: 10.1007/s00540-018-2486-8. PMID: 29582154. [Epub ahead of print]

PURPOSE: The aim of this study was to examine the association between body mass index and chronic pain.

METHODS: The outcome was chronic pain prevalence by body mass index (BMI). BMIs of less than 18.5, 18.5-25.0, 25.0-30.0, and 30.0 or over kg/m^2 were defined as underweight, normal weight, overweight, and obese.

SUBJECTS: We used data from 4993 participants (2464 men and 2529 women aged 20-79 years) of the Pain Associated Cross-sectional Epidemiological survey in Japan. Sex-stratified multivariable-adjusted odds ratios were calculated with 95% confidence intervals using a logistic regression model including age, smoking, exercise, sleep time, monthly household expenditure, and presence of severe depression. We analyzed all ages and age subgroups, 20-49 and 50-79 years.

RESULTS: The prevalence of chronic pain was higher among underweight, overweight, and obese male respondents than those reporting normal weight, with multivariable odds ratios of 1.52 (1.03-2.25), 1.55 (1.26-1.91), and 1.71 (1.12-2.60). According to underweight, only older men showed higher prevalence of chronic pain than normal weight men with odd ratios, 2.19 (1.14-4.20). Being overweight and obese were also associated with chronic pain in women; multivariable odds ratios were 1.48 (1.14-1.93) and 2.09 (1.20-3.64). Being underweight was not associated with chronic pain.

CONCLUSION: There was a U-shaped association between BMI and chronic pain prevalence among men ≥ 50 years, and a dose-response association among women. Our finding suggests that underweight should be considered in older men suffering chronic pain.

OTHER RESEARCH OF INTEREST

Using Smartphones and Machine Learning to Quantify Parkinson Disease Severity: The Mobile Parkinson Disease Score.

Zhan A[1], Mohan S[1], Tarolli C[2,3], Schneider RB[2], Adams JL[2,3], Sharma S[3], Elson MJ[3], Spear KL[3], Glidden AM[3], Little MA[4], Terzis A[1], Dorsey ER[2,3], Saria S[1,5,6].

JAMA Neurol. **2018 Mar 26**. doi: 10.1001/jamaneurol.2018.0809. PMID: 29582075. [Epub ahead of print]

Importance: Current Parkinson disease (PD) measures are subjective, rater-dependent, and assessed in clinic. Smartphones can measure PD features, yet no smartphone-derived rating score exists to assess motor symptom severity in real-world settings.

Objectives: To develop an objective measure of PD severity and test construct validity by evaluating the ability of the measure to capture intraday symptom fluctuations, correlate with current standard PD outcome measures, and respond to dopaminergic therapy.

Design, Setting, and Participants: This observational study assessed individuals with PD who remotely completed 5 tasks (voice, finger tapping, gait, balance, and reaction time) on the smartphone application. We used a novel machine-learning-based approach to generate a mobile Parkinson disease score (mPDS) that objectively weighs features derived from each smartphone activity (eg, stride length from the gait activity) and is scaled from 0 to 100 (where higher scores indicate greater severity). Individuals with and without PD additionally completed standard in-person assessments of PD with smartphone assessments during a period of 6 months.

Main Outcomes and Measures: Ability of the mPDS to detect intraday symptom fluctuations, the correlation between the mPDS and standard measures, and the ability of the mPDS to respond to dopaminergic medication.

Results: The mPDS was derived from 6148 smartphone activity assessments from 129 individuals (mean [SD] age, 58.7 [8.6] years; 56 [43.4%] women). Gait features contributed most to the total mPDS (33.4%). In addition, 23 individuals with PD (mean [SD] age, 64.6 [11.5] years; 11 [48%] women) and 17 without PD (mean [SD] age 54.2 [16.5] years; 12 [71%] women) completed in-clinic assessments. The mPDS detected symptom fluctuations with a mean (SD) intraday change of 13.9 (10.3) points on a scale of 0 to 100. The measure correlated well with the Movement Disorder Society Unified Parkinson Disease's Rating Scale total ($r = 0.81$; $P < .001$) and part III only ($r = 0.88$; $P < .001$), the Timed Up and Go assessment ($r = 0.72$; $P = .002$), and the Hoehn and Yahr stage ($r = 0.91$; $P < .001$). The mPDS improved by a mean (SD) of 16.3 (5.6) points in response to dopaminergic therapy.

Conclusions and Relevance: Using a novel machine-learning approach, we created and demonstrated construct validity of an objective PD severity score derived from smartphone assessments. This score complements standard PD measures by providing frequent, objective, real-world assessments that could enhance clinical care and evaluation of novel therapeutics.

A mixed methods study of Tai Chi exercise for patients with chronic heart failure aged 70 years and older.

Hägglund L[1], Boman K[2,3], Brännström M[1].

Nurs Open. **2018 Feb 21**;5(2):176-185. doi: 10.1002/nop2.127. eCollection 2018 Apr. PMCID: PMC5867290. PMID: 29599993.

Aims and objectives: This study aimed to evaluate Tai Chi group training among patients with chronic heart failure (CHF) aged 70 years and older.

Background: Physical activity is recommended for CHF treatment. Tai Chi is found to be beneficial to different patient groups, although few studies focus on older patients with CHF.

Design: A mixed methods study. Participants were randomly assigned to Tai Chi training twice a week for 16 weeks ($N = 25$) or control ($N = 20$). Quantitative data were collected at baseline, at the end of the training period and 6 months after training, assessing self-rated fatigue and quality of life, natriuretic peptides and physical performance. Individual qualitative interviews were conducted with participants ($N = 10$) in the Tai Chi training group.

Results: No statistical differences between the Tai Chi training group and the control group in quality of life or natriuretic peptides was found. After 16 weeks, the training group tended to rate more reduced activity and the control group rated more mental fatigue. Participants in the training group rated increased general fatigue at follow-up compared with baseline. Qualitative interviews showed that Tai Chi training was experienced as a new, feasible and meaningful activity. The importance of the leader and the group was emphasized. Improvements in balance were mentioned and there was no physical discomfort.

Conclusion: Tai Chi was experienced as a feasible and meaningful form of physical exercise for patients with CHF aged over 70 years despite lack of achieved health improvement. Further investigations, using feasibility and meaningfulness as outcome variables seems to be useful.