GULF WAR ILLNESS

Treatment for Gulf War Illness (GWI) with KPAX002 (methylphenidate hydrochloride + GWI nutrient formula) in subjects meeting the Kansas case definition: A prospective, open-label trial (revision 2).

Holodniy M[1], Kaiser JD[2].

J Psychiatr Res. **2019 Aug 9**;118:14-20. doi: 10.1016/j.jpsychires.2019.08.003. PMID: 31446218. [Epub ahead of print]

This study tested the safety, tolerability, and efficacy of KPAX002-a combination of methylphenidate hydrochloride plus a micronutrient formula designed to support mitochondrial function-as a treatment for Gulf War Illness (GWI). This open-label trial enrolled 17 subjects meeting the Kansas case definition for GWI. Of the 17 subjects enrolled, 15 qualified for the Intent-to-Treat (ITT) population with 10 subjects completing the trial per protocol. All analyses were on the ITT population. At 12 weeks, subjects taking KPAX002 experienced a mean 25% reduction in their overall GWI symptoms severity as measured by the GWI Symptoms Assessment Tool (SAT) ($p < 0.001$). Visual analog scale scores were also significantly reduced for fatigue ($p = 0.019$), cognitive symptoms ($p = 0.006$), sleep problems ($p = 0.026$), and pain ($p = 0.05$). Twelve weeks of KPAX002 administration resulted in a significant improvement in GWI symptoms with an acceptable side effect profile. A larger randomized, double-blinded, placebo-controlled trial is necessary to determine if the observed benefit can be replicated.

CHRONIC FATIGUE SYNDROME

Assessing cellular energy dysfunction in CFS/ME using a commercially available laboratory test.

Tomas C[1], Lodge TA[2], Potter M[2], Elson JL[3,4], Newton JL[5,6], Morten KJ[2].

Sci Rep. **2019 Aug 7**;9(1):11464. doi: 10.1038/s41598-019-47966-z. PMID: 31391529.

The mitochondrial energy score (MES) protocol, developed by the Myhill group, is marketed as a diagnostic test for chronic fatigue syndrome/Myalgic Encephalomyelitis (CFS/ME). This study assessed the reliability and reproducibility of the test, currently provided by private clinics, to assess its potential to be developed as an NHS accredited laboratory test. We replicated the MES protocol using neutrophils and peripheral blood mononuclear cells (PBMCs) from CFS/ME patients (10) and healthy controls (13). The protocol was then repeated in PBMCs and neutrophils from healthy controls to investigate the effect of delayed sample processing time used by the Myhill group. Experiments using the established protocol showed no differences between CFS/ME patients and healthy controls in any of the components of the MES ($p \geq 0.059$). Delaying blood sample processing by 24 hours (well within the 72 hour time frame quoted by the Myhill group) significantly altered many of the parameters used to calculate the MES in both neutrophils and PBMCs. The MES test does not have the reliability and reproducibility required of a diagnostic test and therefore should not currently be offered as a diagnostic test for CFS/ME. The differences observed by the Myhill group may be down to differences in sample processing time between cohorts.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Comprehensive Review.

Cortes Rivera M[1], Mastronardi C[2], Silva-Aldana CT[3], Arcos-Burgos M[4], Lidbury BA[5].

Diagnostics (Basel). **2019 Aug 7**;9(3). pii: E91. doi: 10.3390/diagnostics9030091. PMID: 31394725.

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating chronic disease of unknown aetiology that is recognized by the World Health Organization (WHO) and the United States Center for Disease Control and Prevention (US CDC) as a disorder of the brain. The disease predominantly affects adults, with a peak age of onset of between 20 and 45 years with a female to male ratio of 3:1. Although the clinical features of the disease have been well established within diagnostic criteria, the diagnosis of ME/CFS is still of exclusion, meaning that other medical conditions must be ruled out. The pathophysiological mechanisms are unclear but the neuro-immuno-endocrinological pattern of CFS patients gleaned from various studies indicates that these three pillars may be the key point to understand the complexity of the disease. At the moment, there are no specific pharmacological therapies to treat the disease, but several studies' aims and therapeutic approaches have been described in order to benefit patients' prognosis, symptomatology relief, and the recovery of pre-existing function. This review presents a pathophysiological approach to understanding the essential concepts of ME/CFS, with an emphasis on the population, clinical, and genetic concepts associated with ME/CFS.

HEADACHE and MIGRAINE

Is Mindfulness-Based Stress Reduction a Promising and Feasible Intervention for Patients Suffering from Migraine? A Randomized Controlled Pilot Trial.

Simshäuser K[1,2], Lüking M[2,3], Kaube H[2,4], Schultz C[5,6], Schmidt S[7].

Complement Med Res. **2019 Aug 7**:1-12. doi: 10.1159/000501425. PMID: 31390617. [Epub ahead of print]

AIM: We performed a pilot study in order to evaluate the feasibility and to estimate effect sizes of mindfulness-based stress reduction (MBSR) in a sample of patients suffering from migraine.

METHOD: Migraine patients (n = 62, mean age 44 years, 92% female) were randomly allocated to either MBSR or an active control intervention based on progressive muscle relaxation and psychoeducation. The primary outcome was the number of migraine days per month assessed by headache diaries covering one month before and one month after the intervention. Secondary outcomes included functional impairment, use of medication, psychological symptoms, quality of life, pain acceptance, pain self-efficacy, pain perception and self-attributed mindfulness. To measure feasibility, questionnaires assessing study compliance and contentment were administered.

RESULTS: The primary outcome migraine frequency showed no significant group difference. Compared to the control group, the MBSR group showed greater improvements in variables of psychological symptoms, pain self-efficacy and sensory pain perception. Within the MBSR condition, all variables showed significant improvements over the course span with effect sizes ranging from d = 0.37 to 0.81, apart from the primary outcome (27% reduction in migraine days, p = 0.07). Compliance and contentment rates were good, supporting the feasibility of the MBSR intervention.

CONCLUSION: Overall, participants in the MBSR group showed more adaptive coping strategies and decreased levels of psychological impairment compared to the control group, indicating a reduced impact of migraine on their everyday lives. It is concluded that this feasibility study demonstrates the ability of mindfulness-based interventions to reduce suffering in patients with migraine.

CHRONIC PAIN

Yoga for People With Chronic Pain in a Community-Based Setting: A Feasibility and Pilot RCT.

Schmid AA[1], Fruhauf CA[1], Sharp JL[1], Van Puymbroeck M[2], Bair MJ[3], Portz JD[1,4].

J Evid Based Integr Med. **2019 Jan-Dec**;24:2515690X19863763. doi: 10.1177/2515690X19863763. PMID: 31394910.

The purpose of this feasibility pilot study was to assess benefits of 8 weeks of yoga in people with chronic pain. Participants completed baseline assessments and were randomized to yoga or usual care. Yoga was offered twice a week for 8 weeks. We assessed feasibility and the Brief Pain Inventory (BPI) was the primary outcome, assessing pain-severity and pain interference on daily activities. Eighty-three people were recruited; 67 people completed the study and were included in the analyses. Average age of participants was 50.78 ± 10.43 years and most participants had pain >10 years. The intervention appeared feasible and there were significant improvements ($P < .05$) in multiple measures for the yoga group, including a decrease in BPI interference scores from 7.15 ± 1.70 to 6.14 ± 2.21 ($P = .007$). There was a significant difference in body responsiveness and pain management scores between groups at 8 weeks. It appears that yoga was feasible and positively influenced multiple outcome measures for people with chronic pain.

CHRONIC PAIN (Continued)

Coenzyme Q10 supplementation alleviates pain in pregabalin-treated fibromyalgia patients *via* reducing brain activity and mitochondrial dysfunction.

Sawaddiruk P[1,2,3], Apaijai N[1,2], Paiboonworachat S[3], Kaewchur T[4], Kasitanon N[5], Jaiwongkam T[1,2], Kerdphoo S[1,2], Chattipakorn N[1,2,6], Chattipakorn SC[1,2,7].

Free Radic Res. **2019 Aug 7**:1-9. doi: 10.1080/10715762.2019.1645955. PMID: 31387429. [Epub ahead of print]

Although coenzyme Q10 (CoQ10) supplementation has shown to reduce pain levels in chronic pain, the effects of CoQ10 supplementation on pain, anxiety, brain activity, mitochondrial oxidative stress, antioxidants, and inflammation in pregabalin-treated fibromyalgia (FM) patients have not clearly elucidated. We hypothesised that CoQ10 supplementation reduced pain better than pregabalin alone *via* reducing brain activity, mitochondrial oxidative stress, inflammation, and increasing antioxidant levels in pregabalin-treated FM patients. A double-blind randomised placebo-controlled trial was conducted. Eleven FM patients were enrolled with 2 weeks wash-out then randomly allocated to 2 treatment groups; pregabalin with CoQ10 or pregabalin with placebo for 40 d. Then, patients in CoQ10 group were switched to placebo, and patients in placebo group were switched to CoQ10 for another 40 d. Pain pressure threshold (PPT), FM questionnaire, anxiety, and pain score were examined. Peripheral blood mononuclear cells (PBMCs) were isolated to investigate mitochondrial oxidative stress and inflammation at day 0, 40, and 80. The level of antioxidants and brain positron emission tomography (PET) scan were also determined at these time points. Pregabalin alone reduced pain and anxiety *via* decreasing brain activity compared with their baseline. However, it did not affect mitochondrial oxidative stress and inflammation. Supplementation with CoQ10 effectively reduced greater pain, anxiety and brain activity, mitochondrial oxidative stress, and inflammation. CoQ10 also increased a reduced glutathione levels and superoxide dismutase (SOD) levels in FM patients. These findings provide new evidence that CoQ10 supplementation provides further benefit for relieving pain sensation in pregabalin-treated FM patients, possibly *via* improving mitochondrial function, reducing inflammation, and decreasing brain activity.

IRRITABLE BOWEL SYNDROME

Effects of Irritable Bowel Syndrome on Daily Activities Vary Among Subtypes Based on Results From the IBS in America Survey.

Ballou S[1], McMahon C[2], Lee HN[2], Katon J[2], Shin A[3], Rangan V[2], Singh P[2], Nee J[2], Camilleri M[4], Lembo A[2], Iturrino J[2].

Clin Gastroenterol Hepatol. 2019 Nov;17(12):2471-2478.e3. doi: 10.1016/j.cgh.2019.08.016. PMID: 31419572. Epub **2019 Aug 13**.

BACKGROUND & AIMS: Irritable bowel syndrome (IBS) is associated with significant disease burden and decreased quality of life (QOL). We investigated the effects of IBS on different areas of daily function and compared these among disease subtypes.

METHODS: The Life with IBS survey was conducted by Gfk Public Affairs & Corporate Communications from September through October 2015. Respondents met Rome III criteria for constipation-predominant or diarrhea-predominant IBS (IBS-C and IBS-D, respectively). Data were collected from 3254 individuals (mean age, 47 years; 81% female; and 90% Caucasian) who met IBS criteria.

RESULTS: Respondents who were employed or in school (n = 1885) reported that IBS symptoms affected their productivity an average of 8.0 days out of the month and they missed approximately 1.5 days of work/school per month because of IBS. More than half the individuals reported that their symptoms were very bothersome. Individuals with IBS-C were more likely than with IBS-D to report avoiding sex, difficulty concentrating, and feeling self-conscious. Individuals with IBS-D reported more avoidance of places without bathrooms, difficulty making plans, avoiding leaving the house, and reluctance to travel. These differences remained when controlling for symptom bothersomeness, age, sex, and employment status. In exchange for 1 month of relief from IBS, more than half of the sample reported they would be willing to give up caffeine or alcohol, 40% would give up sex, 24.5% would give up cell phones, and 21.5% would give up the internet for 1 month.

CONCLUSIONS: Although the perceived effects of IBS symptoms on productivity are similar among its subtypes, patients with IBS-C and IBS-D report differences in specific areas of daily function.

OTHER RESEARCH OF INTEREST

Increasing Mental Health Care Access, Continuity, and Efficiency for Veterans Through Telehealth With Video Tablets.

Jacobs JC[1], Blonigen DM[1], Kimerling R[1], Slightam C[1], Gregory AJ[1], Gurmessa T[1], Zulman DM[1].

Psychiatr Serv. **2019 Aug 5**:appips201900104. doi: 10.1176/appi.ps.201900104. PMID: 31378193. [Epub ahead of print]

OBJECTIVE: In 2016, the Veterans Health Administration (VHA) began distributing video-enabled tablets to veterans with access barriers. This study evaluated the implementation of this initiative for veterans with mental health conditions, including the impact of tablet receipt on access to and continuity of mental health care, missed opportunities for care, and use of urgent care.

METHODS: A retrospective matched cohort study was conducted, matching tablet recipients with diagnoses of mental disorders (N=728) to a comparison group (N=1,020) on the basis of sociodemographic characteristics, mental health utilization and diagnoses, and wireless coverage. A difference-in-differences approach was used to compare 6-month pre-post changes in number of psychotherapy and medication management visits, continuity of psychotherapy based on VHA's quality metric for mental health care continuity, missed opportunity rate (i.e., the proportion of mental health appointments that were missed or canceled), and probability of any and number of emergency department (ED) or urgent care visits.

RESULTS: Compared with the matched control group, tablet recipients experienced an increase of 1.94 ($p<0.001$) psychotherapy encounters, an increase of 1.05 ($p<0.001$) medication management visits, an 18.54 percentage point ($p<0.001$) increase in their likelihood of receiving recommended mental health care necessary for continuity of care, and a 20.24 percentage point ($p<.001$) decrease in their missed opportunity rate in the 6-month period following receipt of tablets (or the index date for the matched sample). No significant differences in ED or urgent care use were found.

CONCLUSIONS: Distributing video-enabled tablets to veterans with mental health conditions appeared to improve access to and continuity of mental health services while also improving clinical efficiency by decreasing missed opportunities for care.

Clinical Complexity in Women Veterans: A Systematic Review of the Recent Evidence on Mental Health and Physical Health Comorbidities.

Creech SK[1,2], Pulverman CS[1,2], Crawford JN[3,4], Holliday R[5,6], Monteith LL[5,6], Lehavot K[7,8,9], Olson-Madden J[5,6], Kelly UA[10,11].

Behav Med. **2019 Aug 12**:1-19. doi: 10.1080/08964289.2019.1644283. PMID: 31403895. [Epub ahead of print]

A recent evidence map focused on women veterans underscored the limited number of articles published on mental health comorbid with physical health conditions in this population. The quality of this small body of research has yet to be evaluated. The aim of this systematic review was to evaluate and synthesize research published between 2008 and 2015 and identified in the Women Veterans' Health Research Evidence Map as related to mental and physical health comorbidities among women veterans. Following PRISMA guidelines, 23 published studies were identified and 21 were included in the review. In general, significant associations between several mental health conditions (e.g., depression, posttraumatic stress disorder, substance use disorders) and physical health disorders (e.g., cardiovascular disease, diabetes, gastrointestinal disorders, hypertension, obesity, pain, and urinary symptoms) and health behaviors (e.g., preventative care and treatment adherence) were noted. The majority of studies were rated as low risk of bias, with selection and detection bias most frequently observed across studies. Additionally, gaps in the recent literature were observed, including the need for further investigation of the role of medical conditions in complicating mental health symptoms and care provision. Results underscore the importance of healthcare providers attending to women veterans' mental and physical health simultaneously and irrespective of setting. Further, while the Department of Veterans Affairs continues to make sizable gains in its focus on women veterans' health, continued research on several health domains is needed to ensure adequate understanding of the health needs of women veterans.

OTHER RESEARCH OF INTEREST (Continued)

Understanding the Needs of Female Veterans.

Ritchie EC[1].

J Am Acad Psychiatry Law. **2019 Aug 8**. pii: JAAPL.003869-19. doi: 10.29158/JAAPL.003869-19. PMID: 31395623. [Epub ahead of print]

This commentary attempts to frame the article, "Safer Housing for Homeless Women Veterans," in a wider context. It defines female veterans, homelessness, and military sexual trauma. This commentary also tackles a question that often confuses civilian providers regarding who has access to care at the Veterans Health Administration. It does not repeat in detail all of the recommendations in the article, but it advocates their broader use in shelters and transitional housing. Finally, I close with some thoughts about a new generation of young, homeless, female veterans who may have children and how to accommodate their needs.

WISH-R– a fast and efficient tool for construction of epistatic networks for complex traits and diseases.

Carmelo VAO[1,2], Kogelman LJA[2,3], Madsen MB[4], Kadarmideen HN[5,6].

BMC Bioinformatics. **2018 Jul 31**;19(1):277. doi: 10.1186/s12859-018-2291-2. PMCID: PMC6069724. PMID: 30064383.

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

BACKGROUND: Genetic epistasis is an often-overlooked area in the study of the genomics of complex traits. Genome-wide association studies are a useful tool for revealing potential causal genetic variants, but in this context, epistasis is generally ignored. Data complexity and interpretation issues make it difficult to process and interpret epistasis. As the number of interaction grows exponentially with the number of variants, computational limitation is a bottleneck. Gene Network based strategies have been successful in integrating biological data and identifying relevant hub genes and pathways related to complex traits. In this study, epistatic interactions and network-based analysis are combined in the Weighted Interaction SNP hub (WISH) method and implemented in an efficient and easy to use R package.

RESULTS: The WISH R package (WISH-R) was developed to calculate epistatic interactions on a genome-wide level based on genomic data. It is easy to use and install, and works on regular genomic data. The package filters data based on linkage disequilibrium and calculates epistatic interaction coefficients between SNP pairs based on a parallelized efficient linear model and generalized linear model implementations. Normalized epistatic coefficients are analyzed in a network framework, alleviating multiple testing issues and integrating biological signal to identify modules and pathways related to complex traits. Functions for visualizing results and testing runtimes are also provided.

CONCLUSION: The WISH-R package is an efficient implementation for analyzing genome-wide epistasis for complex diseases and traits. It includes methods and strategies for analyzing epistasis from initial data filtering until final data interpretation. WISH offers a new way to analyze genomic data by combining epistasis and network based analysis in one method and provides options for visualizations. This alleviates many of the existing hurdles in the analysis of genomic interactions.

OTHER RESEARCH OF INTEREST (Continued)

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

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

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

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

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

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

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

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

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