GULF WAR ILLNESS

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

CHRONIC FATIGUE SYNDROME

Assessing chronic fatigue syndrome: Self-reported physical functioning and correlations with physical testing.

Eyskens JB[1], Illegems J[2], De Nil L[3], Nijs J[4], Kampen JK[5], Moorkens G[6].

J Bodyw Mov Ther. **2019 Jul**;23(3):598-603. doi: 10.1016/j.jbmt.2019.03.006. PMID: 31563377. Epub 2019 Mar 16.

The pathophysiology of chronic fatigue syndrome (CFS) remains unclear; no biomarkers have thus far been identified or physical tests designed to underpin its diagnosis. Assessment mainly uses Fukuda's criteria and is based on the exclusion of symptoms related to other diseases/syndromes, subjective self-reporting, and outcomes of self-report questionnaires. In order to improve the baseline assessment and progress evaluation of individuals suspected of CFS and using an association-oriented research strategy and a cross-correlational design, this study investigates possible associations between the performance on two physical tests, i.e. 'Timed Loaded Standing' (TLS), assessing trunk-arm endurance, and the 'Stops Walking with Eyes Closed while performing a secondary Cognitive Task' (SWECCT), measuring impaired automaticity of gait, and the results of two self-report questionnaires, the Checklist Individual Strength (CIS, total score and fatigue subscale score) and the physical functioning and vitality subscales of the Short Form Health Survey (SF-36) to gauge the participants' subjective feelings of fatigue and beliefs regarding their abilities to perform daily-life activities. Comparisons of the outcomes obtained in 27 female patients with a confirmed diagnosis of CFS revealed that trunk-arm endurance as measured with the TLS correlated with the SF-36 physical functioning subscale only (raw p value: 0.004). None of the other correlations were statistically significant. It is concluded that the TLS may have potential as an objective assessment tool to support the diagnosis and monitoring of treatment effects in CFS.

HEADACHE and MIGRAINE

Acute vestibular migraine treatment with noninvasive vagus nerve stimulation.

Beh SC[1], Friedman DI[2].

Neurology. **2019 Sep 25**. pii: 10.1212/WNL.0000000000008388. doi: 10.1212/WNL.0000000000008388. PMID: 31554650.

OBJECTIVE: To report on the benefits of noninvasive vagus nerve stimulation (nVNS) on acute vestibular migraine (VM) treatment.

METHODS: This was a retrospective chart review of patients with VM treated with nVNS in a single tertiary referral center between November 2017 and January 2019. Eighteen patients (16 women) were identified (mean age 45.7 [±14.8] years); 14 were treated for a VM attack and 4 for bothersome interictal dizziness consistent with persistent perceptual postural dizziness (PPPD). Patients graded the severity of vestibular symptoms and headache using an 11-point visual analog scale (VAS; 0 = no symptoms, 10 = worst ever symptoms) before and 15 minutes after nVNS.

RESULTS: In those with acute VM, vertigo improved in 13/14 (complete resolution in 2, at least 50% improvement in 5). The mean vertigo intensity before nVNS was 5.2 (±1.6; median 6), and 3.1 (±2.2; median 3) following stimulation; mean reduction in vertigo intensity was 46.9% (±31.5; median 45%). Five experienced headache with the VM attack; all reported improvement following nVNS. Mean headache severity was 6 (±1.4; median 6) prior to treatment and 2.4 (±1.5; median 3) following nVNS; mean reduction in headache intensity was 63.3% (±21.7; median 50). All 4 treated with nVNS for interictal PPPD reported no benefit.

CONCLUSION: Our study provides preliminary evidence that nVNS may provide rapid relief of vertigo and headache in acute VM, and supports further randomized, sham-controlled studies into nVNS in VM.

CLASSIFICATION OF EVIDENCE: This study provides Class IV evidence that for patients with acute VM, nVNS rapidly relieves vertigo and headache.

HEADACHE and MIGRAINE (Continued)

Does Mindfulness-Based Cognitive Therapy for Migraine Reduce Migraine-Related Disability in People with Episodic and Chronic Migraine? A Phase 2b Pilot Randomized Clinical Trial.

Seng EK[1,2,3], Singer AB[4,5], Metts C[6], Grinberg AS[4], Patel ZS[1], Marzouk M[1], Rosenberg L[1], Day M[7], Minen MT[8], Lipton RB[2], Buse DC[2].

Headache. **2019 Sep 26**. doi: 10.1111/head.13657. PMID: 31557329. [Epub ahead of print]

OBJECTIVE: The current Phase 2b study aimed to evaluate the efficacy of mindfulness-based cognitive therapy for migraine (MBCT-M) to reduce migraine-related disability in people with migraine.

BACKGROUND: Mindfulness-based interventions represent a promising avenue to investigate effects in people with migraine. MBCT teaches mindfulness meditation and cognitive-behavioral skills and directly applies these skills to address disease-related cognitions.

METHODS: Participants with migraine (6-30 headache days/month) were recruited from neurology office referrals and local and online advertisements in the broader New York City area. During the 30-day baseline period, all participants completed a daily headache diary. Participants who met inclusion and exclusion criteria were randomized in a parallel design, stratified by chronic migraine status, to receive either 8 weekly individual MBCT-M sessions or 8 weeks of waitlist/treatment as usual (WL/TAU). All participants completed surveys including primary outcome evaluations at Months 0, 1, 2, and 4. All participants completed a headache diary during the 30-day posttreatment evaluation period. Primary outcomes were the change from Month 0 to Month 4 in the headache disability inventory (HDI) and the Migraine Disability Assessment (MIDAS) (total score ≥ 21 indicating severe disability); secondary outcomes (headache days/30 days, average headache attack pain intensity, and attack-level migraine-related disability [Migraine Disability Index (MIDI)]) were derived from the daily headache diary.

RESULTS: Sixty participants were randomized to receive MBCT-M (n = 31) or WL/TAU (n = 29). Participants (M age = 40.1, SD = 11.7) were predominantly White (n = 49/60; 81.7%) and Non-Hispanic (N = 50/60; 83.3%) women (n = 55/60; 91.7%) with a graduate degree (n = 35/60; 55.0%) who were working full-time (n = 38/60; 63.3%). At baseline, the average HDI score (51.4, SD = 19.0) indicated a moderate level of disability and the majority of participants (50/60, 83.3%) fell in the "Severe Disability" range in the MIDAS. Participants recorded an average of 16.0 (SD = 5.9) headache days/30 days, with an average headache attack pain intensity of 1.7 on a 4-point scale (SD = 0.3), indicating moderate intensity. Average levels of daily disability reported on the MIDI were 3.1/10 (SD = 1.8). For the HDI, mean scores decreased more from Month 0 to Month 4 in the MBCT-M group (-14.3) than the waitlist/treatment as an usual group (-0.2; P < .001). For the MIDAS, the group*month interaction was not significant when accounting for the divided alpha, P = .027; across all participants in both groups, the estimated proportion of participants falling in the "Severe Disability" category fell significantly from 88.3% at Month 0 to 66.7% at Month 4, P < .001. For diary-reported headache days/30 days an average headache attack pain intensity, neither the group*month interaction (Ps = .773 and .888, respectively) nor the time effect (Ps = .059 and .428, respectively) was significant. Mean MIDI scores decreased in the MBCT-M group (-0.6/10), whereas they increased in the waitlist/treatment as an usual group (+0.3/10), P = .007.

CONCLUSIONS: MBCT-M demonstrated efficacy to reduce headache-related disability and attack-level migraine-related disability. MBCT-M is a promising emerging treatment for addressing migraine-related disability.

The Efficacy of Botulinum Toxin in Cluster Headache: A Systematic Review.

Freund B, Kotchetkov IS, Rao A.

J Oral Facial Pain Headache. **2019 Sep 27**. doi: 10.11607/ofph.2444. PMID: 31560734. [Epub ahead of print]

AIMS: To conduct a systematic review of the literature on the use of botulinum toxin for the treatment of cluster headache.

METHODS: A systematic review and data quality analysis were performed using PRISMA and GRADE guidelines, respectively. Inclusion and exclusion criteria were outlined prior to the search and aimed to select prospective studies that examined the use of botulinum toxin for the treatment of cluster headache.

RESULTS: Three studies resulted from the search that each included 10 to 17 subjects. All three demonstrated significant improvement in the frequency of headaches that occurred as quickly as 1 week following treatment. There was low-quality evidence that botulinum toxin was effective in reducing headache frequency and severity by at least 50%. Injections into the sphenopalatine ganglion may have a higher incidence of adverse events.

CONCLUSION: This review summarizes the only prospectively collected efficacy and safety data regarding the use of botulinum toxin in cluster headache. Off-label use should be considered in certain cases. Further study is warranted to better characterize injection paradigms and patient selection, given the encouraging but limited data available.

HEADACHE and MIGRAINE (Continued)

Association of rs2651899 Polymorphism in the Positive Regulatory Domain 16 and Common Migraine Subtypes: A Meta-Analysis.

Lee HH[1,2,3], Chen CC[2,3,4,5], Ong JR[6], Lin YF[1], Lee FP[1,7,8], Hu CJ[2,3,4,5], Wang YH[1,9].

Headache. **2019 Sep 26**. doi: 10.1111/head.13670. PMID: 31557325. [Epub ahead of print]

BACKGROUND: Migraine is a neurovascular disease with recurrent headache attacks. A polymorphism (rs2651899) of the PRDM16 gene, which is associated with migraine, was identified in recent genome-wide association studies. The potential role of the PRDM16 rs2651899 polymorphism in migraine is still unknown. Therefore, we conducted this systematic review and meta-analysis to examine this issue.

METHODS: We performed a comprehensive literature search of the PubMed, Embase, and Google Scholar databases to identify eligible studies published before October 2018. Individual odds ratio and 95% confidence interval was used to estimate the pooled strength of the association between the PRDM16 rs2651899 polymorphism and common migraine subtypes, including migraine with aura (MA) and migraine without aura (MO).

RESULTS: Six studies with 2853 cases and 9319 controls that fulfilled the inclusion and exclusion criteria were selected for this meta-analysis. Of the 6 included studies, 4 studies had available data for MWA and another 4 studies had data for MWoA. Overall, significant migraine risks of 1.257, 1.305, and 1.419 were found under allele model (C vs T), dominant model (C/C+T/C vs T/T), and recessive model (C/C vs T/C+T/T), respectively. In the recessive model, significantly increased risks of 1.454 and 1.546 were found for MA and MO, respectively.

CONCLUSION: Our major findings suggest that PRDM16 rs2651899 polymorphism is associated with the risk of migraine. Furthermore, we found that PRDM16 rs2651899 polymorphism is significantly related to common migraine subtypes (MA and MO).

Recent Advances in Pharmacotherapy for Episodic Migraine.

Chan C[1,2], Goadsby PJ[3,4].

CNS Drugs. **2019 Sep 25**. doi: 10.1007/s40263-019-00665-9. PMID: 31556018. [Epub ahead of print]

In 2018, three calcitonin gene-related peptide (CGRP) pathway monoclonal antibodies, erenumab, fremanezumab and galcanezumab, were approved in various parts of the world, including Europe and the US, and another, eptinezumab, is pending, for the prevention of migraine. In this article, episodic migraine treatment is reviewed, although these medicines are approved and are just as effective for chronic migraine. These new medicines usher a new phase in the preventive management of migraine with migraine-specific treatments. Data from phase III trials of CGRP pathway monoclonal antibodies have shown they are efficacious, with adverse effect rates comparable to placebo. The combination of clear efficacy and excellent tolerability will be welcome in an area where poor adherence to current preventives is common. Rimegepant, ubrogepant and lasmiditan are migraine-specific acute therapies yet to be approved by regulators. Phase III data for the respective CGRP receptor antagonists, the gepants, and the serotonin 5-HT_{1F} receptor agonist, the ditan, have been positive and free of cardiovascular adverse effects. These medicines are not vasoconstrictors. When approved, they could meet the acute therapy demand of patients with cardiovascular risk factors where triptans are contraindicated. Beyond this, gepants will see the most disruptive development in migraine management in generations with medicines that can have both acute and preventive effects, the latter evidenced by data from the discontinued drug telcagepant and the early-phase drug atogepant. Moreover, one can expect no risk of medication overuse syndromes with gepants since the more patients take, the less migraines they have. During the next years, as experience with monoclonal antibodies grows in clinical practice, we can expect an evolution in migraine management to take shape. Clinicians will be able to offer treatment patients want rather than trying to fit migraineurs into therapeutic boxes for their management. Despite pessimistic susurrations of a largely addlepated form, many patients, and physicians, will welcome new options, and the challenges of new treatment paradigms, with optimism.

HEADACHE and MIGRAINE (Continued)

Monoclonal antibodies for the prevention of migraine.

Raffaelli B[1,2], Neeb L[1], Reuter U[1].

Expert Opin Biol Ther. **2019 Sep 25**. doi: 10.1080/14712598.2019.1671350. PMID: 31550937. [Epub ahead of print]

Introduction: Calcitonin Gene-Related Peptide (CGRP) plays a crucial role in migraine pathophysiology. A novel specific treatment strategy for the prevention of migraine incorporates monoclonal antibodies (mAbs) against CGRP and its canonical receptor. Eptinezumab, fremanezumab and galcanezumab block CGRP mediated effects by binding to the peptide, while erenumab blocks the CGRP receptor.

Areas covered: Following a brief overview of pharmacological characteristics, we will review phase III trials for the use of CGRP mAbs in the prevention of episodic and chronic migraine.

Expert opinion: All four CGRP mAbs demonstrated an excellent safety, tolerability and efficacy profile in migraine patients. Across all trials mAbs showed superior efficacy for the reduction of monthly migraine days compared to placebo with a net benefit of 2.8 days. Neither cardiovascular nor immunological safety concerns have emerged from clinical trials. Fremanezumab, galcanezumab, and erenumab are approved in the USA and Europe. Based on trial data there is no reason why these mAbs should not become first line therapies in future. For now, we advocate for the use of mAbs in migraine prevention for patients who failed a minimum of two standard oral treatments based on the novelty and costs of this approach. mAbs are also effective in patients with medication overuse and with comorbid depression or anxiety disorders. Taken together, mAbs are likely to usher in a new era in migraine prevention and provide significant value to patients.

Novel Medications for the Treatment of Migraine.

Ceriani CEJ[1], Wilhour DA[1], Silberstein SD[1].

Headache. **2019 Sep 26**. doi: 10.1111/head.13661. PMID: 31559638. [Epub ahead of print]

OBJECTIVE: To describe the new classes of medication for headache management and their roles in clinical practice.

BACKGROUND: Calcitonin gene-related peptide (CGRP) is a key component in the underlying pathophysiology of migraine. Research focused on targeting CGRP for headache treatment has led to the development of entirely new classes of medications - the gepants and the CGRP monoclonal antibodies (mAbs) - for both acute and preventive treatment. A third class, the ditans, is being developed to target the 5-HT_{1F} receptor to provide acute treatment without vasoconstrictive effects.

METHODS: This article reviews the pathophysiology of migraine that has led to these new pharmacologic developments. Available information from randomized controlled trials, abstracts, press releases, and relevant preclinical studies is summarized for each class of medications.

RESULTS: At the time of this writing, one ditan has been submitted to the U.S. Food and Drug Administration (FDA) for approval. One gepant is anticipated to be submitted within the first quarter of 2019, and others are in clinical trials. Three CGRP mAbs have been FDA approved and are now available in clinical practice, and a fourth was submitted in the first quarter of 2019.

CONCLUSIONS: The development of new migraine-specific classes of medications provides more treatment options for both acute and preventive treatment of migraine.

CHRONIC PAIN

Depression Trends in Patients with Chronic Pain: An Analysis of the Nationwide Inpatient Sample.

Orhurhu V[1], Olusunmade M[2], Akinola Y[3], Urits I[1], Orhurhu MS[4], Viswanath O[5], Hirji S[6], Kaye AD[7], Simopoulos T[1], Gill JS[8].

Pain Physician. **2019 Sep**;22(5):E487-E494. PMID: 31561661.

BACKGROUND: Chronic pain remains a major public health issue that affects the lives of many worldwide, including patients with chronic pain. Comorbidities like depression have been associated with decreased quality of sleep, decreased enjoyment of life activities, increased anxiety, and decreased efficacy in treatments among patients with chronic pain. Despite these associations, the trends and demographic characteristics of patients with chronic pain with depression is yet to be investigated.

OBJECTIVES: To investigate the trends and demographic characteristics of hospitalized patients with chronic pain with comorbid depression from years 2011 to 2015 in the United States.

STUDY DESIGN: This was an observational study.

SETTING: Patients were identified from a Healthcare Cost and Utilization Project database called National Inpatient Sample (NIS) documentation.

METHODS: Patients were identified from the NIS database using International Classification of Diseases, Ninth and Tenth Revision (ICD-9 and ICD-10) diagnosis codes for chronic pain and comorbid depression from years 2011 to 2015.

RESULTS: Between 2011 and 2015, an estimated 9.3 million patients with chronic pain were identified. Of this cohort, 2.2 million patients (22.9%) were diagnosed with comorbid depression. The estimated number of patients with depression varied from 399,865 (22.6%) in 2011 to 421,490 (23.1%) in 2015 (P = 0.13). From 2011 to 2015, there was a significant upward trend of depression among blacks (8.1 ± 0.42% to 9.7 ± 0.27%), patients aged 65 to 84 years (29.0 ± 0.39% to 32.4 ± 0.23%), Medicare insured patients (56.1 ± 0.54% to 58.5 ± 0.29%), Medicaid insured patients (14.7 0.4% to 17.1 ± 0.24%), and patients from zip code areas with lowest annual household income (29.2 ± 1.3% to 32.0 ± 0.59%). Among patients with depression, the adjusted total hospitalization cost increased from $43,584 in 2011 to $49,923 in 2015 (P< 0.001), with average length of hospital stay stable around 5.05 ± 0.02 days. Most patients were discharged home or with self-care compared with short-term facility (57.9 ± 0.14% vs. 2.0 ± 0.03%).

LIMITATIONS: Large database research comes with several limitations. The NIS database does not contain variables that can evaluate disease severity such as depression. In addition, the NIS database is highly dependent on the selection and report accuracy of the appropriate diagnostic ICD codes. These estimates could be imprecise from over or underestimation of the number of patients with chronic pain with comorbid depression.

CONCLUSIONS: These findings from the present investigation suggest that depression in patients with chronic pain remained stable from 2011 to 2015, with the majority of patients identified as women, white, and ages 45 to 65 years.

High frequency medical cannabis use is associated with worse pain among individuals with chronic pain.

Boehnke KF[1], Scott JR[2], Litinas E[3], Sisley S[4], Williams DA[2], Clauw DJ[2].

J Pain. **2019 Sep 24**. pii: S1526-5900(19)30814-4. doi: 10.1016/j.jpain.2019.09.006. PMID: 31560957. [Epub ahead of print]

Cannabis is widely used for chronic pain. However, there is some evidence of an inverse dose-response relationship between cannabis effects and pain relief which may negatively affect analgesic outcomes. In this cross-sectional survey, we examined whether daily cannabis use frequency was associated with pain severity and interference, quality of life measures relevant to pain (e.g., anxiety and depressive symptoms), and cannabis use preferences (administration routes, cannabinoid ratio). Our analysis included 989 adults who used cannabis every day for chronic pain. Participant use was designated as light, moderate, and heavy (1-2, 3-4, and 5 or more cannabis uses per day, respectively). The sample was also sub-grouped by self-reported medical only use (designated MED, n=531, 54%) vs. medical use concomitant with a past-year history of recreational use (designated MEDREC, n=458, 46%). In the whole sample, increased frequency of use was significantly associated with worse pain intensity and interference, and worse negative affect, although high frequency users also reported improved positive affect. Subgroup analyses showed that these effects were driven by MED participants. Heavy MED participant consumption patterns showed greater preference for smoking, vaporizing, and high THC products. In contrast, light MED participants had greater preference for tinctures and high CBD products. Selection bias, our focus on chronic pain, and our cross-sectional design likely limit the generalizability our results. Our findings suggest that lower daily cannabis use frequency is associated with better clinical profile as well as lower risk cannabis use behaviors among MED participants. Future longitudinal studies are needed to examine how high frequency of cannabis use interacts with potential therapeutic benefits. PERSPECTIVE: Our findings suggest that lower daily cannabis use frequency is associated with better clinical profile as well as safer use behaviors (e.g., preference for CBD and non-inhalation administration routes). These trends highlight the need for developing cannabis use guidelines for clinicians to better protect patients using cannabis.

CHRONIC PAIN (Continued)

Application of ICD-11 among individuals with chronic pain: A post hoc analysis of the Stanford Self-Management Program.

Hornemann C[1], Schröder A[1], Ørnbøl E[1], Christensen NB[1], Høeg MD[1], Mehlsen M[2], Frostholm L[1].

Eur J Pain. **2019 Sep 25**. doi: 10.1002/ejp.1486. PMID: 31556212. [Epub ahead of print]

BACKGROUND: Chronic primary pain (CPP) is one of seven diagnostic groups within the proposed classification of chronic pain in ICD-11. Our aims were to apply the proposed ICD-11 criteria in a large cohort of chronic pain patients participating in the Chronic Pain Self-Management Program (CPSMP) and further investigate whether participants with CPP differed from participants with chronic secondary pain (CSP) regarding health, health expenditure, and the effect of participating in the CPSMP.

METHODS: A secondary analysis of a randomized, controlled trial on the effect of the CPSMP. Four examiners categorized participants' pain according to ICD-11 using register-based medical diagnoses and patients' self-reported symptoms. Afterwards, differences between CPP and CSP were examined.

RESULTS: Out of 394 participants, 312 were successfully classified into CPP (n=164) or CSP (n=148) whereas 76 had a mixed pain condition. Participants with CPP were younger, more likely to be women, and had a longer pain duration compared to participants with CSP. Participants with CPP reported worse health-related quality of life on the SF-36 Mental Component Summary and subscales of vitality, social functioning, and bodily pain. Participants with CSP had more physical comorbidities and higher total health expenditure. None of the groups benefitted from the CPSMP.

CONCLUSIONS: We successfully applied the new classification of chronic pain in ICD-11 on the basis of ICD-10 medical diagnoses and symptom self-report. Participants with CPP differed significantly from participants with CSP on baseline characteristics, self-reported health measures, and total health expenditure. The CPSMP was not effective in any of the groups.

Mindfulness-oriented recovery enhancement reduces opioid misuse risk via analgesic and positive psychological mechanisms: A randomized controlled trial.

Garland EL[1], Hanley AW[1], Riquino MR[1], Reese SE[1], Baker AK[1], Salas K[1], Yack BP[1], Bedford CE[1], Bryan MA[1], Atchley R[1], Nakamura Y[2], Froeliger B[3], Howard MO[4].

J Consult Clin Psychol. **2019 Oct**;87(10):927-940. doi: 10.1037/ccp0000390. PMID: 31556669.

OBJECTIVE: Despite the heightened urgency of the current prescription opioid crisis, few psychotherapies have been evaluated for chronic pain patients receiving long-term opioid analgesics. Current psychological pain treatments focus primarily on ameliorating negative affective processes, yet basic science suggests that risk for opioid misuse is linked with a dearth of positive affect. Interventions that modulate positive psychological processes may produce therapeutic benefits among patients with opioid-treated chronic pain. The aim of this study was to conduct a theory-driven mechanistic analysis of proximal outcome data from a Stage 2 randomized controlled trial of Mindfulness-Oriented Recovery Enhancement (MORE), an integrative intervention designed to promote positive psychological health.

METHOD: Patients with opioid-treated chronic pain (N = 95; age = 56.8 ± 11.7; 66% female) were randomized to 8 weeks of therapist-led MORE or support group (SG) interventions. A latent positive psychological health variable comprised of positive affect, meaning in life, and self-transcendence measures was examined as a mediator of the effect of MORE on changes in pain severity at posttreatment and opioid misuse risk by 3-month follow-up.

RESULTS: Participants in MORE reported significantly greater reductions in pain severity by posttreatment ($p = .03$) and opioid misuse risk by 3-month follow-up ($p = .03$) and significantly greater increases in positive psychological health ($p < .001$) than SG participants. Increases in positive psychological health mediated the effect of MORE on pain severity by posttreatment ($p = .048$), which in turn predicted decreases in opioid misuse risk by follow-up ($p = .02$).

CONCLUSIONS: Targeting positive psychological mechanisms via MORE and other psychological interventions may reduce opioid misuse risk among chronic pain patients receiving long-term opioid therapy. (PsycINFO Database Record (c) 2019 APA, all rights reserved).

TRIAL REGISTRATION: ClinicalTrials.gov NCT03298269.

IRRITABLE BOWEL SYNDROME

Clostridium butyricum alleviates intestinal low-grade inflammation in TNBS-induced irritable bowel syndrome in mice by regulating functional status of lamina propria dendritic cells.

Zhao Q[1], Yang WR[2], Wang XH[3], Li GQ[3], Xu LQ[1], Cui X[1], Liu Y[4], Zuo XL[5].

World J Gastroenterol. **2019 Sep 28**;25(36):5469-5482. doi: 10.3748/wjg.v25.i36.5469. PMCID: PMC6767978. PMID: 31576093.

BACKGROUND: Irritable bowel syndrome (IBS) is one of the most common functional gastroenterological diseases characterized by abnormal visceral sensitivity and low-grade inflammation. The role of *Clostridium butyricum* (*C. butyricum*) in reducing intestinal low-grade inflammation *via* immune pathways has been well defined. However, the detailed mechanisms of the effects of *C. butyricum* on intestinal mucosal immunity, especially on immune cells of the lamina propria, remain unclear. Dendritic cells (DCs), which are important immune cells, secrete proinflammatory cytokines (IL-1β, IL-6, and others) and express T cell immuno-globulin and mucin domain-3 (TIM3), promoting proliferation and activation of DCs, and mediating Th1 and Th17 inflammatory responses.

AIM: To investigate the role of DCs in the development of IBS in a rat model and to understand the regulation of DCs after *C. butyricum* intervention.

METHODS: An IBS animal model was established using C57BL/6 mice, and *C. butyricum* was continuously administered *via* the intragastric route to simulate different intestinal immune states. Intestinal visceral hypersensitivity and histopathology were assessed using the abdominal withdrawal reflex (AWR) test and hematoxylin & eosin (H&E) staining, respectively. The expression of proinflammatory cytokines (IL-1β and IL-6) and TIM3 was analyzed by Western blot analysis and real-time PCR. Flow cytometry was applied to analyze the quantity, function, and membrane molecule TIM3 of the lamina propria dendritic cells (LPDCs). The regulatory effect of *C. butyricum* was verified in bone marrow-derived dendritic cells by *in vitro* experiments.

RESULTS: The secretion of proinflammatory cytokines (IL-1β and IL-6) in mice with IBS was significantly increased compared with that of the control group, which suggested that the intestinal mucosa in mice with IBS was in a low-grade inflammatory state. The expression of CD11C+CD80+ and CD11c+TIM3+ in intestinal LPDCs in mice with IBS increased significantly. Meanwhile, the cytokines (IL-1β and IL-6) were significantly reduced after the intervention with probiotic *C. butyricum*. The amount and function of LPDCs and the TIM3 on the surface of the LPDCs were decreased with the alleviation of the intestinal inflammatory response.

CONCLUSION: The results suggest that *C. butyricum* regulates the amount and functional status of LPDCs in the intestinal mucosa of mice with IBS, and therefore modulates the local immune response in the intestine.

OTHER RESEARCH OF INTEREST

Use of technology to increase physical activity in female veterans and soldiers aged 19-64 years.

Riordan JK[1], Alexander S, Montgomery IS.

J Am Assoc Nurse Pract. **2019 Oct**;31(10):575-582. doi: 10.1097/JXX.0000000000000277. PMID: 31567835.

BACKGROUND AND PURPOSE: Heart disease is the leading cause of mortality for American women, claiming 289,753 lives annually. Research has show that female veterans are more sedentary after separating from service and that mobile apps can assist in increasing physical activity. The purposes of this study were to: 1) implement a mobile application to increase physical activity, 2) compare the exercise data, and 3) determine the sustainability of using a mobile application in female active duty soldiers, military retirees, and veterans with prior service.

METHODS: A convenience sample of 30 participants, aged 19-64 years, was recruited from the Womack Army Medical Center, Fort Bragg, North Carolina. Active duty soldiers, retired military, and family members are eligible for care at Womack. Six of the participants with prior military service are spouses of active duty and retired military and were included in the sample. The participants documented the type of physical activity and amount of time exercised over 12 weeks using the closed discussion group. Clinically significant differences were demonstrated in individual averages of minutes exercised per week in the group of veterans ($n = 4$; $Z = -0.944$, $p = .345$, $r = 0.3$) and active duty group ($n = 5$; $Z = -1.826$, $p = .068$, $r = 0.65$).

CONCLUSIONS: The study did not demonstrate a statistically significant increase in physical activity using technology.

IMPLICATIONS FOR PRACTICE: Mobile technology provides nurse practitioners with tools to empower patients. The use of technology to increase physical activity is relatively new and continues to evolve.

OTHER RESEARCH OF INTEREST (Continued)

A Longitudinal Investigation of Military Sexual Trauma and Perinatal Depression.

Gross GM[1,2], Kroll-Desrosiers A[3], Mattocks K[3,4].

J Womens Health (Larchmt). **2019 Sep 27**. doi: 10.1089/jwh.2018.7628. PMID: 31560602. [Epub ahead of print]

Introduction: Military sexual trauma (MST), which includes sexual harassment or assault while in the military, is prevalent among women Veterans and associated with depression and suicide. Little is known about women Veterans' perinatal mental health, including the potential role of MST. This is the first study to investigate the impact of MST on risk of depression and suicidal ideation (SI) during and after pregnancy.

Methods: Bivariate statistical tests between MST harassment and assault, measured by the two standard Veterans Health Administration screening questions, and pre- and postnatal depression and SI, measured by the Edinburgh Postnatal Depression Scale, were examined using longitudinal data from the ongoing Center for Maternal and Infant Outcomes Research in Translation (COMFORT) study. COMFORT includes 620 Veterans interviewed during pregnancy; 452 have been reinterviewed after delivery. Hayes mediation models were employed to examine whether prenatal depression mediated the association between MST and postnatal depression.

Results: MST was associated with higher pre- and postnatal symptoms of depression and SI. Further, prenatal depression mediated the association between MST and postnatal depression (indirect effect [standard error] of harassment on postnatal depression through prenatal depression: 1.11 [0.26], $p < 0.001$; indirect effect [standard error] of assault on postnatal depression through prenatal depression: 1.50 [0.35] $p < 0.001$), even after controlling for demographic variables and prenatal stress.

Conclusions: Women Veterans who have experienced MST may be at higher risk of perinatal depression and SI. Findings highlight the importance of access to mental health care and trauma-informed obstetrical care for these Veterans.

Qualitative methods in implementation research: An introduction.

Hamilton AB[1], Finley EP[2].

Psychiatry Res. **2019 Oct**;280:112516. doi: 10.1016/j.psychres.2019.112516. PMID: 31437661. Epub 2019 Aug 10.

Qualitative methods are a valuable tool in implementation research because they help to answer complex questions such as how and why efforts to implement best practices may succeed or fail, and how patients and providers experience and make decisions in care. This article orients the novice implementation scientist to fundamentals of qualitative methods and their application in implementation research, describing: 1) implementation-related questions that can be addressed by qualitative methods; 2) qualitative methods commonly used in implementation research; 3) basic sampling and data collection procedures; and 4) recommended practices for data analysis and ensuring rigor. To illustrate qualitative methods decision-making, a case example is provided of a study examining implementation of a primary care-based collaborative care management model for women Veterans with anxiety, depression, and PTSD.

Enhancing glycolysis attenuates Parkinson's disease progression in models and clinical databases.

Cai R[1,2], Zhang Y[3], Simmering JE[4], Schultz JL[5], Li Y[2], Fernandez-Carasa I[6], Consiglio A[6,7], Raya A[8,9], Polgreen PM[10], Narayanan NS[11], Yuan Y[1], Chen Z[1], Su W[2], Han Y[1], Zhao C[12], Gao L[2], Ji X[1,2], Welsh MJ[13], Liu L[2,12].

J Clin Invest. **2019 Oct 1**;129(10):4539-4549. doi: 10.1172/JCI129987. PMCID: PMC6763248. PMID: 31524631.

Parkinson's disease (PD) is a common neurodegenerative disease that lacks therapies to prevent progressive neurodegeneration. Impaired energy metabolism and reduced ATP levels are common features of PD. Previous studies revealed that terazosin (TZ) enhances the activity of phosphoglycerate kinase 1 (PGK1), thereby stimulating glycolysis and increasing cellular ATP levels. Therefore, we asked whether enhancement of PGK1 activity would change the course of PD. In toxin-induced and genetic PD models in mice, rats, flies, and induced pluripotent stem cells, TZ increased brain ATP levels and slowed or prevented neuron loss. The drug increased dopamine levels and partially restored motor function. Because TZ is prescribed clinically, we also interrogated 2 distinct human databases. We found slower disease progression, decreased PD-related complications, and a reduced frequency of PD diagnoses in individuals taking TZ and related drugs. These findings suggest that enhancing PGK1 activity and increasing glycolysis may slow neurodegeneration in PD.

OTHER RESEARCH OF INTEREST (Continued)

Association of *a priori* dietary patterns with depressive symptoms: a harmonised meta-analysis of observational studies.

Nicolaou M[1], Colpo M[2], Vermeulen E[1], Elstgeest LEM[3], Cabout M[3], Gibson-Smith D[4], Knuppel A[5], Sini G[2], Schoenaker DAJM[6,7], Mishra GD[6], Lok A[8], Penninx BWJH[4], Bandinelli S[2], Brunner EJ[5], Zwinderman AH[9], Brouwer IA[3], Visser M[3].

Psychol Med. **2019 Aug 14**:1-12. doi: 10.1017/S0033291719001958. PMID: 31409435. [Epub ahead of print]

BACKGROUND: Review findings on the role of dietary patterns in preventing depression are inconsistent, possibly due to variation in assessment of dietary exposure and depression. We studied the association between dietary patterns and depressive symptoms in six population-based cohorts and meta-analysed the findings using a standardised approach that defined dietary exposure, depression assessment and covariates.

METHODS: Included were cross-sectional data from 23 026 participants in six cohorts: InCHIANTI (Italy), LASA, NESDA, HELIUS (the Netherlands), ALSWH (Australia) and Whitehall II (UK). Analysis of incidence was based on three cohorts with repeated measures of depressive symptoms at 5-6 years of follow-up in 10 721 participants: Whitehall II, InCHIANTI, ALSWH. Three a priori dietary patterns, Mediterranean diet score (MDS), Alternative Healthy Eating Index (AHEI-2010), and the Dietary Approaches to Stop Hypertension (DASH) diet were investigated in relation to depressive symptoms. Analyses at the cohort-level adjusted for a fixed set of confounders, meta-analysis used a random-effects model.

RESULTS: Cross-sectional and prospective analyses showed statistically significant inverse associations of the three dietary patterns with depressive symptoms (continuous and dichotomous). In cross-sectional analysis, the association of diet with depressive symptoms using a cut-off yielded an adjusted OR of 0.87 (95% confidence interval 0.84-0.91) for MDS, 0.93 (0.88-0.98) for AHEI-2010, and 0.94 (0.87-1.01) for DASH. Similar associations were observed prospectively: 0.88 (0.80-0.96) for MDS; 0.95 (0.84-1.06) for AHEI-2010; 0.90 (0.84-0.97) for DASH.

CONCLUSION: Population-scale observational evidence indicates that adults following a healthy dietary pattern have fewer depressive symptoms and lower risk of developing depressive symptoms.

Updated CDC Recommendation for Serologic Diagnosis of Lyme Disease.

Mead P[1], Petersen J[1], Hinckley A[1].

MMWR Morb Mortal Wkly Rep. **2019 Aug 16**;68(32):703. doi: 10.15585/mmwr.mm6832a4. PMCID: PMC6818702. PMID: 31415492.

Lyme disease is a tickborne zoonosis for which serologic testing is the principal means of laboratory diagnosis. In 1994, the Association of State and Territorial Public Health Laboratory Directors, CDC, the Food and Drug Administration (FDA), the National Institutes of Health (NIH), the Council of State and Territorial Epidemiologists, and the National Committee for Clinical Laboratory Standards convened the Second National Conference on Serologic Diagnosis of Lyme Disease (1).

The conference proceedings recommended a two-test methodology using a sensitive enzyme immunoassay (EIA) or immunofluorescence assay as a first test, followed by a western immunoblot assay for specimens yielding positive or equivocal results (*1*,*2*). Regarding the development of future tests, the report advised that evaluation of new serologic assays include blind testing against a comprehensive challenge panel, and that new assays should only be recommended if their specificity, sensitivity, and precision equaled or surpassed the performance of tests used in the recommended two-test procedure. To assist serologic test developers, CDC has made available, with support from NIH, a comprehensive panel of sera from patients with various stages of Lyme disease and other conditions, as well as healthy persons (*3*).

On July 29, 2019, FDA cleared several Lyme disease serologic assays with new indications for use based on a modified two-test methodology (*4*). The modified methodology uses a second EIA in place of a western immunoblot assay. Clearance by FDA of the new Lyme disease assays indicates that test performance has been evaluated and is “substantially equivalent to or better than” a legally marketed predicate test.

###