GULF WAR ILLNESS

Dysbiosis-Associated Enteric Glial Cell Immune-Activation and Redox Imbalance Modulate Tight Junction Protein Expression in Gulf War Illness Pathology.

Kimono D[1], Sarkar S[1], Albadrani M[1], Seth R[1], Bose D[1], Mondal A[1], Li Y[2], Kar AN[3], Nagarkatti M[4], Nagarkatti P[4], Sullivan K[5], Janulewicz P[5], Lasley S[6], Horner R[7], Klimas N[8], Chatterjee S[1].

Front Physiol. **2019 Oct 14**;10:1229. doi: 10.3389/fphys.2019.01229. PMCID: PMC6802578. PMID: 31680990.

About 14% of veterans who suffer from Gulf war illness (GWI) complain of some form of gastrointestinal disorder but with no significant markers of clinical pathology. Our previous studies have shown that exposure to GW chemicals resulted in altered microbiome which was associated with damage associated molecular pattern (DAMP) release followed by neuro and gastrointestinal inflammation with loss of gut barrier integrity. Enteric glial cells (EGC) are emerging as important regulators of the gastrointestinal tract and have been observed to change to a reactive phenotype in several functional gastrointestinal disorders such as IBS and IBD. This study is aimed at investigating the role of dysbiosis associated EGC immune-activation and redox instability in contributing to observed gastrointestinal barrier integrity loss in GWI via altered tight junction protein expression. Using a mouse model of GWI and *in vitro* studies with cultured EGC and use of antibiotics to ensure gut decontamination we show that exposure to GW chemicals caused dysbiosis associated change in EGCs. EGCs changed to a reactive phenotype characterized by activation of TLR4-S100β/RAGE-iNOS pathway causing release of nitric oxide and activation of NOX2 since gut sterility with antibiotics prevented this change. The resulting peroxynitrite generation led to increased oxidative stress that triggered inflammation as shown by increased NLRP-3 inflammasome activation and increased cell death. Activated EGCs *in vivo* and *in vitro* were associated with decrease in tight junction protein occludin and selective water channel aquaporin-3 with a concomitant increase in Claudin-2. The tight junction protein levels were restored following a parallel treatment of GWI mice with a TLR4 inhibitor SsnB and butyric acid that are known to decrease the immunoactivation of EGCs. Our study demonstrates that immune-redox mechanisms in EGC are important players in the pathology in GWI and may be possible therapeutic targets for improving outcomes in GWI symptom persistence.

CHRONIC FATIGUE SYNDROME

A logistic regression analysis of risk factors in ME/CFS pathogenesis.

Lacerda EM[1], Geraghty K[2], Kingdon CC[3], Palla L[3], Nacul L[3].

BMC Neurol. **2019 Nov 7**;19(1):275. doi: 10.1186/s12883-019-1468-2. PMID: 31699051.

BACKGROUND: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a complex disease, whose exact cause remains unclear. A wide range of risk factors has been proposed that helps understanding potential disease pathogenesis. However, there is little consistency for many risk factor associations, thus we undertook an exploratory study of risk factors using data from the UK ME/CFS Biobank participants. We report on risk factor associations in ME/CFS compared with multiple sclerosis participants and healthy controls.

METHODS: This was a cross-sectional study of 269 people with ME/CFS, including 214 with mild/moderate and 55 with severe symptoms, 74 people with multiple sclerosis (MS), and 134 healthy controls, who were recruited from primary and secondary health services. Data were collected from participants using a standardised written questionnaire. Data analyses consisted of univariate and multivariable regression analysis (by levels of proximity to disease onset).

RESULTS: A history of frequent colds (OR = 8.26, P <= 0.001) and infections (OR = 25.5, P = 0.015) before onset were the strongest factors associated with a higher risk of ME/CFS compared to healthy controls. Being single (OR = 4.41, P <= 0.001), having lower income (OR = 3.71, P <= 0.001), and a family history of anxiety is associated with a higher risk of ME/CFS compared to healthy controls only (OR = 3.77, P < 0.001). History of frequent colds (OR = 6.31, P < 0.001) and infections before disease onset (OR = 5.12, P = 0.005), being single (OR = 3.66, P = 0.003) and having lower income (OR = 3.48, P = 0.001), are associated with a higher risk of ME/CFS than MS. Severe ME/CFS cases were associated with lower age of ME/CFS onset (OR = 0.63, P = 0.022) and a family history of neurological illness (OR = 6.1, P = 0.001).

CONCLUSIONS: Notable differences in risk profiles were found between ME/CFS and healthy controls, ME/CFS and MS, and mild-moderate and severe ME/CFS. However, we found some commensurate overlap in risk associations between all cohorts. The most notable difference between ME/CFS and MS in our study is a history of recent infection prior to disease onset. Even recognising that our results are limited by the choice of factors we selected to investigate, our findings are consistent with the increasing body of evidence that has been published about the potential role of infections in the pathogenesis of ME/CFS, including common colds/flu.

CHRONIC FATIGUE SYNDROME (Continued)

The longitudinal effects of seated isometric yoga on blood biomarkers, autonomic functions, and psychological parameters of patients with chronic fatigue syndrome: a pilot study.

Oka T[1,2], Tanahashi T[1], Lkhagvasuren B[1,3], Yamada Y[2].

Biopsychosoc Med. **2019 Nov 5**;13:28. doi: 10.1186/s13030-019-0168-x. PMCID: PMC6836361. PMID: 31709006.

Background: In a previous randomized controlled trial, we found that practicing seated isometric yoga regularly for 2 months improved the fatigue of patients with chronic fatigue syndrome (CFS) who are resistant to conventional therapy. The aim of this pilot study was to investigate the possible mechanisms behind this finding by comparing blood biomarkers, autonomic nervous function, and psychological indices before versus after an intervention period of seated isometric yoga practice.

Methods: Fifteen patients with CFS who did not show satisfactory improvements after at least 6 months of conventional therapy practiced seated isometric yoga (biweekly 20-min sessions with a yoga instructor and daily practice at home) for 2 months. The longitudinal effects of seated isometric yoga on fatigue, blood biomarkers, autonomic function, and psychological state were investigated by comparing the following parameters before and after the intervention period: Fatigue severity was assessed by the Chalder fatigue scale (FS) score. Levels of the blood biomarkers cortisol, DHEA-S, TNF-α, IL-6, prolactin, carnitine, TGF-β1, BDNF, MHPG, HVA, and α-MSH were measured. The autonomic nervous functions assessed were heart rate (HR) and HR variability. Psychological indices included the 20-item Toronto Alexithymia Scale (TAS-20) and the Hospital Anxiety and Depression Scale (HADS).

Results: Practicing seated isometric yoga for 2 months resulted in significant reductions in the Chalder FS ($P = 0.002$) and HADS-depression ($P = 0.02$) scores. No significant changes were observed in any other parameter evaluated. The change in Chalder FS score was not correlated with the change in HADS-depression score. However, this change was positively correlated with changes in the serum TNF-α levels ($P = 0.048$), the high frequency component of HR variability ($P = 0.042$), and TAS-20 scores ($P = 0.001$).

Conclusions: Regular practice of seated isometric yoga for 2 months reduced the fatigue and depressive symptom scores of patients with CFS without affecting any other parameters we investigated. This study failed to identify the markers responsible for the longitudinal fatigue-relieving effect of seated isometric yoga. However, considering that the reduced fatigue was associated with decreased serum TNF-α level and TAS-20 scores, fatigue improvement might be related to reduced inflammation and improved alexithymia in these patients.

Trial registration: University Hospital Medical Information Network (UMIN CTR) UMIN000009646. Registered Dec 27, 2012.

Autonomic markers, chronic fatigue syndrome, and post-exertion states.

Friedberg F[1].

J Psychosom Res. **2019 Oct 30**:109845. doi: 10.1016/j.jpsychores.2019.109845. PMID: 31706455. [Epub ahead of print]

Article Introduction (no abstract): A large body of evidence suggests that autonomic imbalance, i.e., hyperactive sympathetic nervous system and hypoactive parasympathetic nervous system, is associated with a number of pathological conditions and diseases, and may be a final common pathway to increased morbidity and mortality [1]. Heart rate variability (HRV), a measure of inter-beat interval fluctuations and more broadly of parasympathetic (vagal) activity has been successfully used to index autonomic imbalances [1]. HRV provides a conveniently assessed, non-invasive window onto the autonomic system. It should be noted that HRV is an indirect measure of autonomic output, as it measures the end organ response to the autonomic nervous system. Reduced HRV is associated with autonomic impairments that precede changes in the heart rate (HR) itself or other physiological measures of distress [2]. In addition to HRV, other cardiac measures including HR and time-to-recovery of resting HR after exposure to a stressor provide valid indices of centrally-mediated vagal inhibition of sympatho-excitatory circuits [3].

In chronic fatigue syndrome (CFS), several studies have found abnormalities in autonomic function, i.e., HR and HRV, in comparison to healthy controls [4]. Current evidence points to chronic sympathetic hyper-arousal (particularly reduced HRV) in patients with CFS that persists even during sleep [5].…

[View full text and references for this article in the Journal of Psychometric Research.]

HEADACHE and MIGRAINE

Long-term tolerability and nonvascular safety of erenumab, a novel calcitonin gene-related peptide receptor antagonist for prevention of migraine: A pooled analysis of four placebo-controlled trials with long-term extensions.

Ashina M[1], Kudrow D[2], Reuter U[3], Dolezil D[4], Silberstein S[5], Tepper SJ[6], Xue F[7], Picard H[7], Zhang F[7], Wang A[7], Zhou Y[8], Hong F[9], Klatt J[9], Mikol DD[7].

Cephalalgia. **2019 Nov 10**:333102419888222. doi: 10.1177/0333102419888222. PMID: 31707815. [Epub ahead of print]

BACKGROUND: Efficacy and safety of erenumab have been evaluated in a comprehensive clinical development program resulting in approval for migraine prevention in over 40 countries to date.

METHODS: This integrated safety analysis included four double-blind randomized trials and their extensions (up to three-plus years). Safety endpoints included exposure-adjusted patient incidences of adverse events, serious adverse events, and anti-erenumab antibodies.

RESULTS: In all, 2375 of the patients randomized across the four studies received at least one dose of erenumab (70 mg or 140 mg), with cumulative exposure of 2641.2 patient-years. Exposure-adjusted adverse event rates during the double-blind treatment phase were similar to placebo, with the exception of injection-site reactions (17.1 vs. 10.8 per 100 patient-years), constipation (7.0 vs. 3.8 per 100 patient-years), and muscle spasm (2.3 vs. 1.2 per 100 patient-years). During the long-term extensions, adverse events reported were similar to those observed during the double-blind treatment phase, and rates of injection site reactions, constipation, and muscle spasm were reported at lower rates than in the double-blind treatment phase. There were two deaths reported, both confounded by pre-existing conditions.

CONCLUSIONS: This pooled safety analysis revealed a favorable and stable adverse event profile over time for erenumab with more than three years of exposure.

TRIAL REGISTRATION: ClinicalTrials.gov NCT01952574, NCT02483585, NCT02456740, NCT02066415, and NCT02174861.

Rapid Onset of Effect of Galcanezumab for the Prevention of Episodic Migraine: Analysis of the EVOLVE Studies.

Detke HC[1], Millen BA[1], Zhang Q[1], Samaan K[1], Ailani J[2], Dodick DW[3], Aurora SK[1].

Headache. **2019 Nov 11**. doi: 10.1111/head.13691. PMID: 31710104. [Epub ahead of print]

OBJECTIVE: To evaluate onset of effect of galcanezumab in patients with episodic migraine.

BACKGROUND: Galcanezumab is a monoclonal antibody that binds to calcitonin gene-related peptide and is indicated for preventive treatment of migraine.

DESIGN/METHODS: Data on the primary outcome measure were analyzed from 2 previously published double-blind, Phase 3 studies (EVOLVE-1 [N = 858] and EVOLVE-2 [N = 915]) wherein adult patients with episodic migraine were randomized to receive monthly subcutaneous injections of galcanezumab 120 mg (with 240-mg loading dose) or 240 mg or placebo for up to 6 months. Monthly onset of effect was defined as the earliest month at which galcanezumab achieved and subsequently maintained statistical superiority to placebo on the mean change from baseline in the number of monthly migraine headache days (MHDs). If onset occurred in Month 1, weekly onset was evaluated and defined as the earliest week at which galcanezumab statistically separated from placebo and maintained statistical separation for remaining weeks in that month. Day of onset of effect was also analyzed, as were monthly and weekly onset, for occurrence of ≥50% reduction from baseline in number of MHDs.

RESULTS: For both studies, change from baseline in monthly MHDs showed a statistically significant separation of galcanezumab from placebo at Month 1 and each subsequent month (each P < .001). Analysis of the first month for both studies indicated onset of effect in the first week, with galcanezumab-treated patients having significantly higher odds of having fewer MHDs in the first week (odds ratio [95% confidence interval] for EVOLVE-1, 2.71 [2.00, 3.66], and for EVOLVE-2, 2.88 [2.16, 3.86]; both P < .001) and each subsequent week compared with placebo-treated patients (P ≤ .004). Daily analysis showed onset of effect at Day 1 (first day after injection day). Galcanezumab also demonstrated superiority to placebo on occurrence of ≥50% reduction in MHDs starting at Week 1 (percentage of patients with 50% response in galcanezumab group vs placebo group for EVOLVE-1, 54.3% vs 32.4% [P < .001], and for EVOLVE-2, 59.4% vs 38.0% [P < .001]).

CONCLUSION: Rapid onset of preventive effect on the first day after injection of galcanezumab was confirmed in both studies of episodic migraine.

HEADACHE and MIGRAINE (Continued)

Efficacy of Galcanezumab in Patients with Episodic Migraine and a History of Preventive Treatment Failure: Results from Two Global Randomized Clinical Trials.

Ruff DD[1], Ford JH[1], Tockhorn-Heidenreich A[2], Stauffer VL[1], Govindan S[3], Aurora SK[1], Terwindt GM[4], Goadsby PJ[5].

Eur J Neurol. **2019 Nov 6**. doi: 10.1111/ene.14114. PMID: 31692188. [Epub ahead of print]

BACKGROUND: Efficacy of galcanezumab, a monoclonal antibody for migraine prevention, has been demonstrated in two pivotal trials in patients with episodic migraine.

METHODS: EVOLVE-1&-2 were identical Phase 3, randomised, double-blind, placebo-controlled studies in patients with episodic migraine. Mean migraine headache days/month at baseline was 9. Patients were randomized 2:1:1 to monthly injections of placebo, galcanezumab 120mg/240mg during the 6-month double-blind treatment period. Key efficacy outcomes were assessed in subgroups among patients for whom, previously, for efficacy and/or safety/tolerability reasons: i) one or more (≥1) preventives failed, ii) two or more (≥2) preventives failed, and iii) preventives were never used, or used but not failed (no prior failure).

RESULTS: In integrated analysis of EVOLVE studies, galcanezumab 120mg/240mg versus placebo led to larger overall mean (SE) reductions in monthly migraine headache days across 6 months in patients with prior preventive failures (p<0.001): ≥1 failure: 120mg: -4.0(0.4); 240mg: -4.2(0.5); placebo: -1.3(0.4); ≥2 failures: 120mg: -3.1(0.7); 240mg: -3.8(0.8); placebo: -0.5(0.6). Similar results were observed among patients with no prior failure, but placebo response was larger: 120mg: -4.7(0.2); 240mg: -4.5(0.2); placebo: -3.0(0.2) (p<0.001 vs. placebo). Significant improvements were observed with galcanezumab versus placebo for ≥50% and ≥75% reduction in monthly migraine headache days.

CONCLUSION: In patients with episodic migraine treated with galcanezumab, those with ≥1 or ≥2 prior preventive failure had significant larger improvements, versus placebo, in efficacy outcomes. Similar results were observed in patients with no prior failure, with larger placebo response.

Migraine progression in subgroups of migraine based on comorbidities: Results of the CaMEO Study.

Lipton RB[1], Fanning KM[2], Buse DC[2], Martin VT[2], Hohaia LB[2], Adams AM[2], Reed ML[2], Goadsby PJ[2].

Neurology. **2019 Nov 5**. pii: 10.1212/WNL.0000000000008589. doi: 10.1212/WNL.0000000000008589. PMID: 31690685. [Epub]

OBJECTIVE: To test the hypothesis that statistically defined subgroups of migraine (based on constellations of comorbidities and concomitant conditions; henceforth comorbidities), previously identified using Chronic Migraine Epidemiology and Outcomes (CaMEO) Study data, differ in prognosis, as measured by rates of progression from episodic migraine (EM) to chronic migraine (CM).

METHODS: The onset of CM was assessed up to 4 times over 12 months in individuals with EM and ≥1 comorbidity at baseline, based on constellations of comorbidities (comorbidity classes). The "fewest comorbidities" class served as reference. Individuals completing ≥1 follow-up survey from the web-based CaMEO Study were included. Covariates included sociodemographic variables and headache characteristics. Sex, income, cutaneous allodynia, and medication overuse were modeled as binary variables; age, body mass index, headache-related disability (Migraine Disability Assessment [MIDAS]), and Migraine Symptom Severity Scale as continuous variables. CM onset was assessed using discrete time analysis.

RESULTS: In the final sociodemographic model, all comorbidity classes had significantly elevated hazard ratios (HRs) for risk of progression to CM from EM, relative to fewest comorbidities. HRs for CM onset ranged from 5.34 (95% confidence interval [CI] 3.89-7.33; $p \leq 0.001$) for most comorbidities to 1.53 (95% CI 1.17-2.01; $p < 0.05$) for the respiratory class. After adjusting for headache covariates independently, each comorbidity class significantly predicted CM onset, although HRs were attenuated.

CONCLUSIONS: Subgroups of migraine identified by comorbidity classes at cross-section predicted progression from EM (with ≥1 comorbidity at baseline) to CM. The relationship of comorbidity group to CM onset remained after adjusting for indicators of migraine severity, such as MIDAS.

CLINICALTRIALSGOV IDENTIFIER: NCT01648530.

HEADACHE and MIGRAINE (Continued)

Novelty in Inflammation and Immunomodulation in Migraine.

Cavestro C[1], Ferrero M[1], Mandrino S[1], Di Tavi M[1], Rota E[2].

Curr Pharm Des. **2019**;25(27):2919-2936. doi: 10.2174/1381612825666190709204107. PMID: 31686633.

BACKGROUND: Migraine is a diffuse and disabling disease. Its pathophysiology is complex and involves both central and peripheral dysfunctions.

OBJECTIVE: This review will discuss the pathogenesis of migraine from the origin of the neuro-inflammatory theory, to the modern pathophysiological model and the latest therapies.

METHODS: PUBMED and EMBASE (up to May 2019) were searched for: migraine, inflammation, immunomodulation. An additional search was carried out from the bibliography of previous review articles.

RESULTS: Migraine was thought to be mainly a vascular disorder, according to the so-called "vascular theory". Based on animal models, a new hypothesis called "the neuro-inflammatory" was conceived at the end of the 20th century. The growing knowledge about the trigeminovascular system and its role in the inflammatory-pain pathway, allowed to identify other specific neurotransmitters, such as the Calcitonin Gene-Related Peptide and Pituitary Adenylate Cyclase-Activating Peptide. Evidence was provided that the inflammatory-pain system could become sensitised and, due to this sensitisation, the pain could also perpetuate, even in the absence of any triggers of the migraine attack. At last, brain immune cells modification during cortical spreading depression in migraine was demonstrated, along with the existence and function of the glymphatic system. The better comprehension of the immune system abnormalities allowed the development of new immunomodulating drugs: the monoclonal antibodies against the CGRP or the CGRP receptor. Moreover, new insights into the molecular mechanism of CGRP, and the function of C-fibres and Aδ-fibres, highlighted the mechanism of action of Botulinum Toxin type A in the treatment of chronic migraine.

CHRONIC PAIN

Mobile Neurofeedback for Pain Management in Veterans with TBI and PTSD.

Elbogen EB[1,2], Alsobrooks A[2], Battles S[2], Molloy K[2], Dennis PA[1,2], Beckham JC[1,2], McLean SA[3], Keith JR[4], Russoniello C[5].

Pain Med. **2019 Nov 7**. pii: pnz269. doi: 10.1093/pm/pnz269. PMID: 31697371. [Epub ahead of print]

OBJECTIVE: Chronic pain is common in military veterans with traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD). Neurofeedback, or electroencephalograph (EEG) biofeedback, has been associated with lower pain but requires frequent travel to a clinic. The current study examined feasibility and explored effectiveness of neurofeedback delivered with a portable EEG headset linked to an application on a mobile device.

DESIGN: Open-label, single-arm clinical trial.

SETTING: Home, outside of clinic.

SUBJECTS: N = 41 veterans with chronic pain, TBI, and PTSD.

METHOD: Veterans were instructed to perform "mobile neurofeedback" on their own for three months. Clinical research staff conducted two home visits and two phone calls to provide technical assistance and troubleshoot difficulties.

RESULTS: N = 36 veterans returned for follow-up at three months (88% retention). During this time, subjects completed a mean of 33.09 neurofeedback sessions (10 minutes each). Analyses revealed that veterans reported lower pain intensity, pain interference, depression, PTSD symptoms, anger, sleep disturbance, and suicidal ideation after the three-month intervention compared with baseline. Comparing pain ratings before and after individual neurofeedback sessions, veterans reported reduced pain intensity 67% of the time immediately following mobile neurofeedback. There were no serious adverse events reported.

CONCLUSIONS: This preliminary study found that veterans with chronic pain, TBI, and PTSD were able to use neurofeedback with mobile devices independently after modest training and support. While a double-blind randomized controlled trial is needed for confirmation, the results show promise of a portable, technology-based neuromodulatory approach for pain management with minimal side effects.

CHRONIC PAIN (Continued)

The natural course of chronic pain in a general population: Stability and change in an eight-wave longitudinal study over four years (the HUNT pain study).

Glette M[1], Stiles TC[2], Borchgrevink PC[3], Landmark T[3].

J Pain. **2019 Nov 4**. pii: S1526-5900(19)30845-4. doi: 10.1016/j.jpain.2019.10.008. PMID: 31698134. [Epub ahead of print]

Epidemiological studies have to a little extent addressed the potential fluctuations of chronic pain over time, and there is a lack of information about the long-term course of pain using repeated measurements. We wanted to identify different trajectories of pain during eight waves of follow-up over four years among individuals in the general population reporting pain lasting at least six months at baseline. Secondarily, we wanted to investigate whether biopsychosocial factors at baseline were associated with the different pain trajectories. Longitudinal Latent Class Analysis (LLCA) was performed to classify 1905 random participants from a larger population-based study (HUNT3) into groups based on their longitudinal pain severity reporting. A five-class solution gave the best fit. The terms chosen to describe the pain trajectories were: "fluctuating" (n = 586 [31 %]), "persistent mild" (n = 449 [24 %]), "persistent moderate" (n = 414 [22 %]), "persistent severe" (n = 251 [13 %]), and "gradual improvement" (n = 205 [11 %]). In a multinomial logistic regression model using "gradual improvement" as the reference category, the "persistent moderate", "persistent severe", and "fluctuating" pain groups were associated with chronic widespread pain (CWP), elevated levels of catastrophizing, and poorer mental health. The "persistent mild" group was associated with sleep difficulties only. This study finds that although most individuals have a stable pain course, individuals in the largest distinct trajectory reports pain that fluctuate between mild and moderate levels, thus fluctuating under and above the chronic pain definition using moderate pain or more as a criterion. Perspective: When examining the long-term course of chronic pain in the general population, five trajectories emerge. Although most individuals have stable pain, the largest distinct trajectory fluctuated under and above the chronic pain cut-off, using moderate pain or more as a criterion. A dichotomous categorization of chronic pain may be overly simplistic.

A Prospective Six-Month Study of Chronic Pain Sufferers: A Novel OTC Neuromodulation Therapy.

Staelin R[1], Koneru SN[2], Rawe IM[2].

Pain Res Manag. **2019 Sep 30**;2019:3154194. doi: 10.1155/2019/3154194. PMCID: PMC6800946. PMID: 31687056.

Objective: To assess the durability of treatment over various chronic pain conditions of an emerging, nonprescription electromagnetic neuromodulation device that uses pulsed shortwave therapy.

Methods: A 6-month prospective study, involving 240 chronic pain sufferers, 94% of whom reported using pain pills and 98% reported using pain therapies prior to entering the study. Their average baseline pain was 8.2 VAS points before treatment; they had a pain duration of 6.5 years, and they were positive responders to pulsed shortwave therapy in an initial 7-day trial. Prospective assessments were obtained at intervals of 3, 4, and 6 months following a retrospective 7-day assessment. Longitudinal analyses were conducted to determine pain relief trends after the initial 7-day device use.

Results: Seven days after initial treatment, the average pain was reduced to 2.9, a 65% pain reduction for the study subjects. At the 6-month measurement, the average pain was 3.3, a 60% pain reduction from baseline. Only 17% of the subjects saw their pain level increase although this new level was still lower than baseline pain. Pain relief translated into improved quality of life and reduced medication use for the majority of the subjects. There were no significant adverse side effects reported over the 6 months of use.

Conclusion: Ninety-seven percent of the recruited subjects, all of whom had previously reported clinically significant pain relief using the 7-day PSWT device, sustained this relief for 6 months by using the device on an as-needed basis.

CHRONIC PAIN (Continued)

CSF levels of apolipoprotein C1 and autotaxin found to associate with neuropathic pain and fibromyalgia.

Lind AL[1], Just D[2], Mikus M[2], Fredolini C[2], Ioannou M[2], Gerdle B[3], Ghafouri B[3], Bäckryd E[3], Tanum L[4], Gordh T[1], Månberg A[2].

J Pain Res. **2019 Oct 15**;12:2875-2889. doi: 10.2147/JPR.S215348. PMCID: PMC6800548. PMID: 31686904. eCollection 2019.

Objective: Neuropathic pain and fibromyalgia are two common and poorly understood chronic pain conditions that lack satisfactory treatments, cause substantial suffering and societal costs. Today, there are no biological markers on which to base chronic pain diagnoses, treatment choices or to understand the pathophysiology of pain for the individual patient. This study aimed to investigate cerebrospinal fluid (CSF) protein profiles potentially associated with fibromyalgia and neuropathic pain.

Methods: CSF samples were collected from 25 patients with neuropathic pain (two independent sets, n=14 patients for discovery, and n=11 for verification), 40 patients with fibromyalgia and 134 controls without neurological disease from two different populations. CSF protein profiling of 55 proteins was performed using antibody suspension bead array technology.

Results: We found increased levels of apolipoprotein C1 (APOC1) in CSF of neuropathic pain patients compared to controls and there was a trend for increased levels also in fibromyalgia patients. In addition, levels of ectonucleotide pyrophosphatase family member 2 (ENPP2, also referred to as autotaxin) were increased in the CSF of fibromyalgia patients compared to all other groups including patients with neuropathic pain.

Conclusion: The increased levels of APOC1 and ENPP2 found in neuropathic pain and fibromyalgia patients may shed light on the underlying mechanisms of these conditions. Further investigation is required to elucidate their role in maintaining pain and other main symptoms of these disorders.

IRRITABLE BOWEL SYNDROME

Lactose and Fructo-oligosaccharides Increase Visceral Sensitivity in Mice via Glycation Processes, Increasing Mast Cell Density in Colonic Mucosa.

Kamphuis JBJ[1], Guiard B[2], Leveque M[1], Olier M[1], Jouanin I[3], Yvon S[1], Tondereau V[1], Rivière P[1], Guéraud F[4], Chevolleau S[3], Noguer-Meireles MH[3], Martin JF[3], Debrauwer L[3], Eutamène H[5], Theodorou V[1].

Gastroenterology. **2019 Nov 9**. pii: S0016-5085(19)41528-X. doi: 10.1053/j.gastro.2019.10.037. PMID: 31711923. [Epub]

BACKGROUND & AIMS: Irritable bowel syndrome (IBS) is characterized by abdominal pain, bloating, and erratic bowel habits. A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) can reduce symptoms of IBS, possibly by reducing microbial fermentation products. We investigated whether ingestion of FODMAPs can induce IBS-like visceral hypersensitivity mediated by fermentation products of intestinal microbes in mice.

METHODS: C57Bl/6 mice were gavaged with lactose, with or without the antiglycation agent pyridoxamine, or saline (controls) daily for 3 weeks. A separate group of mice were fed a diet containing fructo-oligosaccharides, with or without pyridoxamine in drinking water, or a normal chow diet (controls) for 6 weeks. Feces were collected and analyzed by16S ribosomal RNA gene sequencing and bacterial community analyses. Abdominal sensitivity was measured by electromyography and mechanical von Frey filament assays. Colon tissues were collected from some mice and analyzed by histology and immunofluorescence to quantify mast cells and expression of advanced glycosylation end-product specific receptor (AGER).

RESULTS: Mice gavaged with lactose or fed fructo-oligosaccharides had increased abdominal sensitivity compared with controls, associated with increased numbers of mast cells in colon and expression of the receptor for AGER in proximal colon epithelium. These effects were prevented by administration of pyridoxamine. Lactose and/or pyridoxamine did not induce significant alterations in the composition of the fecal microbiota. Mass spectrometric analysis of carbonyl compounds in fecal samples identified signatures associated with mice given lactose or fructo-oligosaccharides vs controls.

CONCLUSIONS: We found that oral administration of lactose or fructo-oligosaccharides to mice increases abdominal sensitivity, associated with increased numbers of mast cells in colon and expression of AGER; these can be prevented with an antiglycation agent. Lactose and/or pyridoxamine did not produce alterations in fecal microbiota of mice. Our findings indicate that preventing glycation reactions might reduce abdominal pain in patients with IBS with sensitivity to FODMAPs.

IRRITABLE BOWEL SYNDROME (Continued)

Biofeedback for treatment of irritable bowel syndrome.

Goldenberg JZ[1,2], Brignall M[3], Hamilton M[4], Beardsley J[4], Batson RD[5], Hawrelak J[6,7], Lichtenstein B[4], Johnston BC[8].

Cochrane Database Syst Rev. **2019 Nov 12**;2019(11). doi: 10.1002/14651858.CD012530.pub2. PMCID: PMC6848969. PMID: 31713856.

BACKGROUND: Irritable bowel syndrome (IBS) is a prevalent condition that currently lacks highly effective therapies for its management. Biofeedback has been proposed as a therapy that may help individuals learn to exert conscious control over sympatho-vagal balance as an indirect method of symptom management.

OBJECTIVES: Our primary objective was to assess the efficacy and safety of biofeedback-based interventions for IBS in adults and children.

SEARCH METHODS: We searched the Cochrane Inflammatory Bowel Disease (IBD) Group Specialized Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Allied and Complementary Medicine Database (AMED) from inception to 24 July 2019. We also searched reference lists from published trials, trial registries, device manufacturers, conference proceedings, theses, and dissertations.

SELECTION CRITERIA: We judged randomized controlled trials to be eligible for inclusion if they met the Association for Applied Psychophysiology and Biofeedback definition of biofeedback, and if they compared a biofeedback intervention to an active, sham, or no-treatment control for the management of IBS.

DATA COLLECTION AND ANALYSIS: Two authors independently screened trials for inclusion, extracted data, and assessed risk of bias. Primary outcomes were IBS global or clinical improvement scores and overall quality of life measures. Secondary outcome measures were adverse events, assessments of stool frequency and consistency, changes in abdominal pain, depression, and anxiety. For dichotomous outcomes, we calculated the risk ratio (RR) and 95% confidence interval (CI). For continuous outcomes, we calculated the mean difference (MD) and 95% CI. We used GRADE criteria to assess the overall certainty of the evidence.

MAIN RESULTS: We identified eight randomized trials with a total of 300 adult participants for our analysis. We did not identify any trials in children. Four trials assessed thermal biofeedback. One trial assessed rectosigmoidal biofeedback. Two trials assessed heart rate variability biofeedback. Two trials assessed electrocutaneous biofeedback. Comparators were: no treatment (symptom monitoring group; three studies), attention control (pseudomeditation; two studies), relaxation control (one study), counseling (two studies), hypnotherapy (one study), standard therapy (one study), and sham biofeedback (one study). We judged all trials to have a high or unclear risk of bias. **Global/Clinical improvement:** The clinical benefit of biofeedback plus standard therapy compared to standard therapy alone was uncertain (RR 4.20, 95% CI 1.40 to 12.58; 1 study, 20 participants; very low-certainty evidence). The same study also compared biofeedback plus standard therapy to sham biofeedback plus standard therapy. The clinical benefit in the biofeedback group was uncertain (RR 2.33, 95% CI 1.13 to 4.80; 1 study, 20 participants; very low-certainty evidence). The clinical benefit of heart rate biofeedback compared to hypnotherapy was uncertain when measured with the IBS severity scoring system (IBS-SSS) (MD -58.80, 95% CI -109.11 to -8.49; 1 study, 61 participants; low-certainty evidence). Compared to counseling, the effect of heart rate biofeedback was unclear when measured with a composite symptom reduction score (MD 7.03, 95% CI -51.07 to 65.13; 1 study, 29 participants; low-certainty evidence) and when evaluated for clinical response (50% improvement) (RR 1.09, 95% CI 0.48 to 2.45; 1 study, 29 participants; low-certainty evidence). The clinical benefit of thermal biofeedback used in a multi-component psychological intervention (MCPI) compared to no treatment was uncertain when measured with a composite clinical symptom reduction score (MD 30.34, 95% CI 8.47 to 52.21; 3 studies, 101 participants; very low-certainty evidence), and when evaluated as clinical response (50% improvement) (RR 2.12, 95% CI 1.24 to 3.62; 3 studies, 101 participants; very low-certainty evidence). Compared to attention control, the effects of thermal biofeedback within an MCPI were unclear when measured with a composite clinical symptom reduction score (MD 4.02, 95% CI -21.41 to 29.45; 2 studies, 80 participants; very low-certainty evidence) and when evaluated as clinical response (50% improvement) (RR 1.10, 95% CI 0.72 to 1.69, 2 studies, 80 participants; very low-certainty evidence). **Quality of life:** A single trial used overall quality of life as an outcome measure, and reported that both the biofeedback and cognitive therapy groups improved after treatment. The trial did not note any between-group differences, and did not report any outcome data. **Adverse events:** Only one of the eight trials explicitly reported adverse events. This study reported no adverse events in either the biofeedback or cognitive therapy groups (RD 0.00, 95% CI -0.12 to 0.12; 29 participants; low-certainty evidence).

AUTHORS' CONCLUSIONS: There is currently not enough evidence to assess whether biofeedback interventions are effective for controlling symptoms of IBS. Given the positive results reported in small trials to date, biofeedback deserves further study in people with IBS. Future research should include active control groups that use high provider-participant interaction, in an attempt to balance non-specific effects of interventions between groups, and report both commonly used outcome measures (e.g. IBS-SSS) and historical outcome measures (e.g. the composite primary symptom reduction (CPSR) score) to allow for meta-analysis with previous studies. Future studies should be explicit in their reporting of adverse events.

IRRITABLE BOWEL SYNDROME (Continued)

Comparison between the Effects of Acupuncture Relative to Other Controls on Irritable Bowel Syndrome: A Meta-Analysis.

Zheng H[1], Chen R[1], Zhao X[2], Li G[3], Liang Y[3], Zhang H[3], Chi Z[1].

Pain Res Manag. **2019 Nov 11**;2019:2871505. doi: 10.1155/2019/2871505. PMCID: PMC6877908. PMID: 31814859. eCollection 2019.

Background: Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder with recurrent abdominal pain and altered defecation habits. We here attempted to determine the effect of acupuncture on IBS.

Methods: Randomized controlled trials (RCTs) published in CNKI, VIP, Wanfang, PubMed, Cochrane Library, EMBASE, Web of science, and ClinicalTrials.gov till July 17, 2019 were searched. Outcomes were total efficacy rates, overall IBS symptom scores, or global quality of life scores. Standardized mean difference (SMD) with 95% confidence intervals (CI) and risk ratio (RR) with 95% CI were calculated for meta-analysis.

Results: We included 41 RCTs involving 3440 participants for analysis. 8 RCTs compared acupuncture with sham acupuncture, among which 3 trials confirmed the biological effects of acupuncture, especially in treating abdominal pain, discomfort, and stool frequency. No significant difference was found when acupuncture was compared with sham acupuncture, in terms of effects on IBS symptoms and quality of life (SMD = 0.18, 95% CI -0.26~0.63, P=0.42; SMD = -0.10, 95% CI -0.31~0.11, P=0.35), but the pooled efficacy rate data showed a better outcome for true acupuncture (RR = 1.22, 95% CI 1.01~1.47, P=0.04), which was not supported by sensitivity analysis. Acupuncture was more effective relative to western medicine in alleviating IBS symptoms (RR = 1.17, 95% CI 1.12~1.23, I^2 = 0%, P < 0.00001), whose effect might last 3 months. Besides, acupuncture as an adjunct to western medicine, Chinese medications, or tuina was superior over the single latter treatment (RR = 1.68, 95% CI 1.18 to 2.40, P=0.004; 1.19, 1.03 to 1.36, P=0.02; 1.36, 1.08 to 1.72, P=0.009, respectively), with high heterogeneities.

Conclusions: Relative to sham controls, acupuncture showed no superiority for treating IBS, while the advantage over western medicine was significant. Acupuncture could be used as an adjunct in clinical settings to improve efficacy. Future high-quality and large-sample-size studies with adequate quantity-effect design need to be conducted.

Association between irritable bowel syndrome and asthma: a meta-analysis and systematic review.

Deshmukh F[1], Vasudevan A[2], Mengalie E[3].

Ann Gastroenterol. **2019 Nov**-Dec;32(6):570-577. doi: 10.20524/aog.2019.0426. PMCID: PMC6826079. PMID: 31700233.

Background: Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder often seen in outpatient clinics. Diagnosing IBS is often challenging, as it frequently presents with other complicated rheumatological and psychiatric conditions. Asthma has often been associated with gastrointestinal conditions such as gastroesophageal reflux disease and eosinophilic esophagitis. This review and meta-analysis aimed at a better understanding of the association between the conditions.

Methods: A comprehensive literature review was completed using MEDLINE and EMBASE databases through January 2019. Case-control, cross-sectional and cohort studies that evaluated the association between asthma and IBS were divided into 2 groups: the first included studies that identified patients with asthma first and then looked for the presence of IBS. The second group included studies that identified IBS patients first and then looked for the presence of asthma. Random effects meta-analysis was conducted using STATA 15.

Results: The search strategy generated a total of 634 studies and 10 eligible studies (8 case-control and 2 cross-sectional) were selected for meta-analysis. Analysis showed that asthmatics have twice the risk of having IBS (pooled odds ratio [OR] 2.0, 95% confidence interval [CI] 1.5-2.8), and patients with IBS have twice the risk of having asthma (pooled OR 2.2, 95%CI 1.3-3.9).

Conclusions: This study highlights that the risk of asthma is considerably higher in IBS patients and vice versa. Physicians should look out for pulmonary symptoms in IBS patients and consider evaluation with spirometry when necessary. Likewise, asthmatics presenting with gastrointestinal symptoms may need consultation and evaluation for IBS.

IRRITABLE BOWEL SYNDROME (Continued)

Re: A Meta-Analysis of the Clinical Use of Curcumin for Irritable Bowel Syndrome.

Appleton L[1], Day AS[1].

J Clin Med. **2019 Nov 6**;8(11). pii: E1885. doi: 10.3390/jcm8111885. PMCID: PMC6912727. PMID: 31698718.

We read with interest the article by Ng et al. [1] on the use of curcumin in irritable bowel syndrome (IBS). This work systematically reviewed five randomised-controlled trials, and included three for meta-analysis (a total of 326 subjects). The authors concluded that while safe, well tolerated, and beneficial in reducing IBS symptoms, these results were not statistically significant based on the limited evidence available.

IBS is a complex, functional gastrointestinal disorder typically characterized by chronic abdominal pain, altered bowel habit, and abdominal bloat [**2**]. Despite being one of the most common GI disorders, the underlying pathophysiology remains unclear. Traditionally, the aetiology of IBS has focused on altered gut motility, brain–gut interactions, visceral hypersensitivity, and psychosocial distress [**3**]. More recent evidence implicates a range of other factors including changes to gut immune activation, intestinal permeability, alterations in faecal flora, and bacterial dysbiosis [**4**,**5**]. The latter two factors are particularly evident in the development of post-infectious IBS [**6**]. Studies have also highlighted the persistence of low-grade mucosal inflammation at the microscopic and molecular level in patients with IBS, with increased recruitment of enteroendocrine cells [**7**].

Reflecting the various aetiologic factors and the varied clinical presentations (for example, diarrhoea predominant versus constipation predominant IBS), many management options have been considered for IBS. One recent advance in management of IBS has been the use of a diet low in fermentable oligo-, di-, monosaccharides, and Polyols (FODMAPs), which can lead to improvement in symptoms [**8**,**9**,**10**,**11**]. However, this dietary intervention is not universally beneficial. Further, given the lack of definitive therapies for IBS, there is much interest in new possible interventions.

Curcumin, derived from turmeric root (*Curcuma longa*), is known to have numerous actions within the body, including anti-inflammatory, antitumor, and antioxidant effects [**12**,**13**,**14**,**15**,**16**,**17**,**18**,**19**,**20**]. It is believed to modulate cell signalling molecules such as pro-inflammatory cytokines, apoptotic proteins, C-reactive protein, and also inhibits the nuclear factor (NF)-κB intracellular signal transduction pathway [**21**]….

[View full text and references for this editorial in the Journal of Clinical Medicine.]

Use of Treatments for Irritable Bowel Syndrome and Patient Satisfaction Based on the IBS in America Survey.

Rangan V[1], Ballou S[2], Shin A[3], Camilleri M[4]; Beth Israel Deaconess Medical Center GI Motility Working Group[2], Lembo A[2].

Gastroenterology. **2019 Nov 9**. pii: S0016-5085(19)41527-8. doi: 10.1053/j.gastro.2019.10.036. PMID: 31711922. [Epub]

Irritable bowel syndrome (IBS) is a common, chronic, and often debilitating condition, with an estimated prevalence in the general population ranging from 10% to 15%.[1–3] There are many treatment options for individuals with IBS, but there has been limited research on patterns of utilization or satisfaction with specific IBS treatments. This study aimed to better understand treatment utilization and satisfaction among individuals with IBS and to compare treatment recommendations among physicians.

OTHER RESEARCH OF INTEREST

Improving Access to and Equity of Care for People with Serious Illness: Proceedings of a Workshop.

Contributors: National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services; Board on Health Sciences Policy; Roundtable on Quality Care for People with Serious Illness; Laurene Graig, Sylara Marie Cruz, and Joe Alper, Rapporteurs.

National Academies of Sciences, Engineering, and Medicine. **2019**. *Improving Access to and Equity of Care for People with Serious Illness: Proceedings of a Workshop*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25530. PMID: 31525012.

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The Centers for Disease Control and Prevention estimates that approximately 40 million people in the United States suffer from a serious illness that limits their daily activities. These illnesses include heart and lung disease, cancer, diabetes, and Alzheimer's disease and other forms of dementia. However, significant disparities exist across different communities in the quality and access to care for these illnesses. Factors such as race, ethnicity, gender, geography, socioeconomic status, or insurance status exacerbate these complex disparities. It is critical to reevaluate the current models of care delivery across diverse communities and vulnerable populations.

On April 4, 2019, The National Academies of Sciences, Engineering, and Medicine convened a workshop to investigate barriers, policy initiatives, and opportunities for improving access to and equity of care for people living with a serious illness. Discussions explored the current climate of health care and opportunities to improve access to care using organizational, community, patient and family, and clinician perspectives. This publication summarizes the discussions and presentations from the workshop.

Insomnia symptoms and risk of cardiovascular diseases among 0.5 million adults: A 10-year cohort.

Zheng B[1], Yu C[2], Lv J[1], Guo Y[1], Bian Z[1], Zhou M[1], Yang L[1], Chen Y[1], Li X[1], Zou J[1], Ning F[1], Chen J[1], Chen Z[1], Li L[2]; China Kadoorie Biobank Collaborative Group.

Neurology. **2019 Nov 6**. pii: 10.1212/WNL.0000000000008581. doi: 10.1212/WNL.0000000000008581. PMID: 31694922. [Epub]

OBJECTIVE: To examine the associations of individual insomnia symptoms with risks of incident cardio-cerebral vascular diseases (CVD) and possible moderating factors among Chinese adults.

METHODS: The China Kadoorie Biobank is a prospective cohort study that recruited participants from 10 areas across China. Data from 487,200 adults 30 to 79 years of age who were free of stroke, coronary heart disease, and cancer at baseline were analyzed. Three insomnia symptoms were assessed with self-reported difficulties in initiating or maintaining sleep, early morning awakening, and daytime dysfunction for at least 3 d/wk at baseline. Incidences of CVD were followed up through disease registries and national health insurance databases until 2016.

RESULTS: During a median of 9.6 years of follow-up, 130,032 cases of CVD were documented. Cox regressions showed that 3 insomnia symptoms were associated with increased risk of total CVD, with respective adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of 1.09 (95% CI 1.07-1.11), 1.07 (95% CI 1.05-1.09), and 1.13 (95% CI 1.09-1.18). Participants with individual symptoms also had higher risks of ischemic heart disease (IHD; HR 1.13, 1.09, and 1.17) and ischemic stroke but not hemorrhagic stroke. Participants with all 3 symptoms were at an 18%, 22%, or 10% higher risk of CVD, IHD, or ischemic stroke compared to nonsymptomatic adults. Associations between 3 symptoms and CVD incidence were consistently stronger in younger adults or those without baseline hypertension (p for interaction <0.05).

CONCLUSIONS: Individual and coexisting insomnia symptoms are independent risk factors for CVD incidence, especially among young adults or adults who have not developed hypertension.

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