GULF WAR ILLNESS

The Effects of Tai Chi Mind-Body Approach on the Mechanisms of Gulf War Illness: an Umbrella Review.

Reid KF[1], Bannuru RR[2], Wang C[2], Mori DL[3], Niles BL[4].

Integr Med Res. 2019 Sep;8(3):167-172. doi: 10.1016/j.imr.2019.05.003. PMCID: PMC6600798. PMID: 31304089. Epub **2019 May 30**.

Gulf War illness (GWI) is a chronic and multisymptom disorder affecting military veterans deployed to the 1991 Persian Gulf War. It is characterized by a range of acute and chronic symptoms, including but not limited to, fatigue, sleep disturbances, psychological problems, cognitive deficits, widespread pain, and respiratory and gastrointestinal difficulties. The prevalence of many of these chronic symptoms affecting Gulf War veterans occur at markedly elevated rates compared to nondeployed contemporary veterans. To date, no effective treatments for GWI have been identified. The overarching goal of this umbrella review was to critically evaluate the evidence for the potential of Tai Chi mind-body exercise to benefit and alleviate GWI symptomology. Based on the most prevalent GWI chronic symptoms and case definitions established by the Centers for Disease Control and Prevention and the Kansas Gulf War Veterans Health Initiative Program, we reviewed and summarized the evidence from 7 published systematic reviews and meta-analyses. Our findings suggest that Tai Chi may have the potential for distinct therapeutic benefits on the major prevalent symptoms of GWI. Future clinical trials are warranted to examine the feasibility, efficacy, durability and potential mechanisms of Tai Chi for improving health outcomes and relieving symptomology in GWI.

Sex Differences in Gulf War Illness: A Reanalysis of Data From the CDC Air Force Study Using CDC and Modified Kansas Case Definitions.

Heboyan V[1], Krengel MH, Sullivan K, Iobst S, Klimas N, Wilson C, Coughlin SS.

J Occup Environ Med. **2019 Jul;**61(7):610-616. doi: 10.1097/JOM.0000000000001620. PMID: 31090678.

OBJECTIVE: Estimate and compare the prevalence of Gulf War Illness (GWI) in male and female Gulf War veterans using Centers for Disease Control and Prevention (CDC) and modified Kansas case definitions.

METHODS: Data from the landmark CDC Air Force Study of GW Air Force veterans is used.

RESULTS: Nearly half of the deployed veterans met the GWI CDC case definition compared with 14% of non-deployed veterans. Only 29% met the definition using the modified Kansas criteria compared with 8% of non-deployed veterans. Deployed veterans and female veterans exhibited significantly higher GWI risk. Female GW veterans had higher rates of severe and mild-to-moderate cases of GWI.

CONCLUSION: Results suggest increased GWI rates based on CDC and modified Kansas criteria among deployed and female veterans. Further research is needed to examine the chronic health outcomes of female GW veterans independently.

CHRONIC FATIGUE SYNDROME

Post-Exertional Malaise Is Associated with Hypermetabolism, Hypoacetylation and Purine Metabolism Deregulation in ME/CFS Cases.

McGregor NR[1], Armstrong CW[2], Lewis DP[3], Gooley PR[2].

Diagnostics (Basel). **2019 Jul 4;**9(3). pii: E70. doi: 10.3390/diagnostics9030070. PMID: 31277442

Post-exertional malaise (PEM) is a cardinal predictive symptom in the definition of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). If the cases overexert themselves they have what is termed "payback" resulting in a worsening of symptoms or relapse which can last for days, weeks or even months. The aim was to assess the changes in biochemistry associated with the cases self-reported PEM scores over a 7-day period and the frequency of reporting over a 12-month period. Forty-seven ME/CFS cases and age/sex-matched controls had a clinical examination, completed questionnaires; were subjected to standard serum biochemistry; had their serum and urine metabolomes analyzed in an observational study. Thirty-five of the 46 ME/CFS cases reported PEM in the last 7-days and these were allocated to the PEM group. The principal biochemical change related to the 7-day severity of PEM was the fall in the purine metabolite, hypoxanthine. This decrease correlated with alterations in the glucose:lactate ratio highly suggestive of a glycolytic anomaly. Increased excretion of urine metabolites within the 7-day response period indicated a hypermetabolic event was occurring. Increases in urine excretion of methylhistidine (muscle protein degradation), mannitol (intestinal barrier deregulation) and acetate were noted with the hypermetabolic event. These data indicate hypoacetylation was occurring, which may also be related to deregulation of multiple cytoplasmic enzymes and DNA histone regulation. These findings suggest the primary events associated with PEM were due to hypoacetylation and metabolite loss during the acute PEM response.

HEADACHE and MIGRAINE

Two randomized migraine studies of galcanezumab: Effects on patient functioning and disability.

Ford JH[1], Ayer DW[2], Zhang Q[2], Carter JN[2], Leroux E[2], Skljarevski V[2], Aurora SK[2], Tockhorn-Heidenreich A[2], Lipton RB[2].

Neurology. **2019 Jul 3**. pii: 10.1212/WNL.0000000000007856. doi: 10.1212/WNL.0000000000007856. PMID: 31270220. [Epub ahead of print]

OBJECTIVE: To evaluate changes from baseline in patient-reported outcomes for measures of functioning and disability among patients with migraine treated with galcanezumab or placebo.

METHODS: Patients with episodic migraine (4-14 monthly migraine headache days) were treated with either galcanezumab (Evaluation of LY2951742 in the Prevention of Episodic Migraine [EVOLVE]-1: 120 mg n = 210, 240 mg n = 208; EVOLVE-2: 120 mg n = 226, 240 mg n = 220) or placebo (EVOLVE-1 n = 425; EVOLVE-2 n = 450) during 6 months of treatment. Migraine-Specific Quality of Life Questionnaire v2.1 (MSQv2.1) measured the effect of migraine on patient functioning (physical and emotional) in 3 domains, and the Migraine Disability Assessment (MIDAS) quantified headache-related disability associated with missed or reduced productivity at work or home and social events. Both were collected at baseline and during the treatment period (MSQv2.1 = monthly; MIDAS = months 3 and 6 only).

RESULTS: Differences in MSQv2.1 total score least squares (LS) mean change from baseline (month 4-6) for galcanezumab (120 and 240 mg, respectively) were superior to placebo (EVOLVE-1 = 7.3 and 6.7 [both $p < 0.001$]; EVOLVE-2 = 8.5 and 7.3 [both $p < 0.001$]). Differences were similar for all domain scores ($p < 0.001$ for both galcanezumab doses compared with placebo), were observed as early as month 1, and were sustained for 6 months for most domains. Differences of MIDAS LS mean change from baseline (month 6) for galcanezumab (120 and 240 mg, respectively) compared with placebo were: EVOLVE-1 = -6.3 ($p < 0.001$) and -5.2 ($p = 0.002$); EVOLVE-2 = -9.2 and -8.2 (both $p < 0.001$).

CONCLUSIONS: Patients with episodic migraine treated with galcanezumab reported significant and clinically meaningful improvements in daily functioning and decreased disability compared with patients who received placebo.

CLASSIFICATION OF EVIDENCE: This study provides Class II evidence that for patients with migraine, galcanezumab (120 mg or 240 mg) given once monthly improved functioning and reduced disability.

HEADACHE and MIGRAINE (Continued)

Sustained responses to lasmiditan: Results from post-hoc analyses of two Phase 3 randomized clinical trials for acute treatment of migraine.

Doty EG[1], Krege JH[2], Jin L[3], Raskin J [2], Halker Singh RB[4], Kalidas K[5].

Cephalalgia. **2019 Jul 3**:333102419859313. doi: 10.1177/0333102419859313. PMID: 31266353. [Epub ahead of print]

BACKGROUND: Sustained pain freedom is an important attribute of acute migraine therapies for patients and physicians. Here we report efficacy of the centrally penetrant, highly selective, 5-HT_{1F} agonist lasmiditan on sustained pain freedom and other outcomes at 24 and 48 hours post-dose.

STUDY DESIGN AND METHODS: Data from the similarly designed, Phase 3, double-blind studies SAMURAI (NCT02439320) and SPARTAN (NCT02605174) were pooled to more precisely estimate efficacy effects in these post-hoc analyses. In both studies, inclusion criteria were 3-8 migraine attacks per month and Migraine Disability Assessment Score of ≥ 11 (at least moderate disability). Patients were randomized equally to lasmiditan 200 mg, 100 mg, 50 mg (50 mg only in SPARTAN), or to placebo. The study drug was to be taken within 4 hours of onset of pain for non-improving headache of at least moderate severity. Sustained pain freedom was defined as being pain free at 2 hours and at the given time point (24 or 48 hours) post-dose without use of additional study drug or migraine medications. Sustained responses were assessed similarly for most bothersome symptom-free, total migraine-free, and disability-free outcomes. For comparisons with previously published data on other acute medications, an additional endpoint of modified sustained pain freedom at 24 hours was defined as being pain free at 2 hours and no moderate-to-severe headache at 24 hours post-dose without use of additional study drug or migraine medications.

RESULTS: Significantly higher proportions of patients treated with lasmiditan versus placebo achieved headache pain freedom at 2 hours post-dose: 200 mg: 35.6%; 100 mg: 29.9%; 50 mg: 28.6%; placebo: 18.3% (all $p < 0.001$). Sustained pain freedom was significantly higher in patients treated with lasmiditan versus placebo at 24 hours: 200 mg: 21.2%; 100 mg: 16.9%; 50 mg: 17.4%; placebo: 10.3% (all $p < 0.01$); and at 48 hours: 200 mg: 18.4%; 100 mg: 15.2%; 50 mg: 14.9%; placebo: 9.6% (all $p < 0.05$). Similar sustained benefits of lasmiditan versus placebo at 24 and 48 hours were noted for most bothersome symptom-free, total migraine-free and disability-free responses. Modified sustained pain freedom at 24 hours was also observed in significantly higher proportions of lasmiditan-treated patients versus placebo: 200 mg: 27.0%; 100 mg: 21.7%; 50 mg: 21.7%; placebo: 12.9% (all $p < 0.01$).

CONCLUSION: Sustained responses at 24 and 48 hours were noted in significantly more patients treated with lasmiditan versus placebo for several efficacy outcomes including pain freedom, most bothersome symptom-free, total migraine-free and disability-free responses.

CLINICALTRIALS.GOV IDENTIFIER NUMBERS: SAMURAI: NCT02439320; SPARTAN: NCT02605174.

HEADACHE and MIGRAINE (Continued)

Observational, open-label, non-randomized study on the efficacy of onabotulinumtoxinA in the treatment of nummular headache: The pre-numabot study.

García-Azorín D[1], Trigo-López J[1], Sierra Á[1], Blanco-García L[2], Martínez-Pías E[1], Martínez B[1], Talavera B[1], Guerrero ÁL[1,3,4].

Cephalalgia. **2019 Jul 4**:333102419863023. doi: 10.1177/0333102419863023. PMID: 31272194. [Epub ahead of print]

BACKGROUND: Nummular headache is a primary headache characterised by superficial, coin-shaped pain. Superficial sensory fibre dysfunction might be involved in its pathophysiology. Considering the mechanism of action of onabotulinumtoxinA, it could be a reasonable option in treatment of nummular headache. The aim of the study was to evaluate the efficacy and tolerability of onabotulinumtoxinA in a series of nummular headache patients.

PATIENTS AND METHODS: This was an observational, prospective, non-randomized and open-label study. Nummular headache patients with at least 10 headache days in three preceding months were included. They were administered 25 units of onabotulinumtoxinA. The primary endpoint was the decrease of headache days per month, evaluated between weeks 20 to 24, compared with baseline. The secondary endpoints included reduction of intense headache days and acute treatment days evaluated between weeks 20-24 and weeks 8-12, compared with baseline. The 30%, 50% and 75% responder rates were determined, and tolerability described.

RESULTS: We included 53 patients, 67.9% females, with a median age of 54 years. Preventive treatment had been used previously in 60.4% of patients. The median diameter of the nummular headache was 5 cm. At baseline, the number of headache days per month was 24.5 (7.3); the number of intense headache days was 12.5 (10.1), and the number of acute treatment days was 12.8 (7.8). After onabotulinumtoxinA, the mean number of headache days per month decreased to 6.9 (9.3) between weeks 20 and 24 ($p < 0.001$). Secondary endpoints concerning intense headache days per month and acute treatment days per month were also statistically significant ($p < 0.001$). The 50% responder rate, evaluated between weeks 20 and 24, was 77.4% and the 75% responder rate was 52.8%. Concerning tolerability, 26 patients (49.1%) experienced an adverse event (AE), the commonest being injection-site pain in 12 cases (22.6%). There were no moderate or severe AEs.

CONCLUSION: It was found that after injecting onabotulinumtoxinA, the number of headache days per month was reduced in nummular headache patients. The number of intense headache days per month and acute treatment days were also lowered. No serious adverse events occurred during treatment.

Impact of chronic migraine attacks and their severity on the endogenous μ-opioid neurotransmission in the limbic system.

Jassar H[1], Nascimento TD[2], Kaciroti N[3], DosSantos MF[2], Danciu T[4], Koeppe RA[5], Smith YR[6], Bigal ME[7], Porreca F[8], Casey KL[9], Zubieta JK[10], DaSilva AF[11].

Neuroimage Clin. **2019 Jun 18**;23:101905. doi: 10.1016/j.nicl.2019.101905. PMID: 31279240. [Epub ahead of print]

OBJECTIVE: To evaluate, in vivo, the impact of ongoing chronic migraine (CM) attacks on the endogenous μ-opioid neurotransmission.

BACKGROUND: CM is associated with cognitive-emotional dysfunction. CM is commonly associated with frequent acute medication use, including opioids.

METHODS: We scanned 15 migraine patients during the spontaneous headache attack (ictal phase): 7 individuals with CM and 8 with episodic migraine (EM), as well as 7 healthy controls (HC), using positron emission tomography (PET) with the selective μ-opioid receptor (μOR) radiotracer [^{11}C]carfentanil. Migraineurs were scanned in two paradigms, one with thermal pain threshold challenge applied to the site of the headache, and one without thermal challenge. Multivariable analysis was performed between the μ-opioid receptor availability and the clinical data.

RESULTS: μOR availability, measured with [^{11}C]carfentanil nondisplaceable binding potential (BP_{ND}), in the left thalamus (P-value = 0.005) and left caudate (P-value = 0.003) were decreased in CM patients with thermal pain threshold during the ictal phase relative to HC. Lower μOR BP_{ND} in the right parahippocampal region (P-value = 0.001) and right amygdala (P-value = 0.002) were seen in CM relative to EM patients. Lower μOR BP_{ND} values indicate either a decrease in μOR concentration or an increase in endogenous μ-opioid release in CM patients. In the right amygdala, 71% of the overall variance in μOR BP_{ND} levels was explained by the type of migraine (CM vs. EM: partial-R^2 = 0.47, P-value<0.001, Cohen's effect size d = 2.6SD), the severity of the attack (pain area and intensity number summation [P.A.I.N.S.]: partial-R^2 = 0.16, P-value = 0.031), and the thermal pain threshold (allodynia: partial-R^2 = 0.08).

CONCLUSIONS: Increased endogenous μ-opioid receptor-mediated neurotransmission is seen in the limbic system of CM patients, especially in right amygdala, which is highly modulated by the attack frequency, pain severity, and sensitivity. This study demonstrates for the first time the negative impact of chronification and exacerbation of headache attacks on the endogenous μ-opioid mechanisms of migraine patients. ClinicalTrials.gov identifier: NCT03004313.

CHRONIC PAIN

Exploring the Meaning of Cognitive Behavioral Therapy for Insomnia for Patients with Chronic Pain.

Koffel E[1,2], Amundson E[1,3], Wisdom JP[4].

Pain Med. **2019 Jul 4**. pii: pnz144. doi: 10.1093/pm/pnz144. PMID: 31271434. [Epub ahead of print]

OBJECTIVE: Insomnia is one of the most common, persistent, and distressing symptoms associated with chronic pain. Cognitive behavioral therapy for insomnia (CBT-I) is the firstline treatment for insomnia, but patient preferences and perspectives about CBT-I within the context of chronic pain are unknown. The current qualitative study sought to understand the experience of CBT-I among patients with chronic pain, including aspects of CBT-I that were found to be difficult (e.g., pain as a specific barrier to adherence/dropout), changes in sleep and pain functioning after CBT-I, and aspects of CBT-I that were appreciated.

DESIGN: Qualitative semistructured interviews.

METHODS: We conducted individual semistructured interviews with 17 veterans with chronic pain and insomnia who had recently participated in CBT-I, as well as their CBT-I therapists, and used thematic analysis to identify conceptual themes.

RESULTS: Results revealed that patients and CBT-I therapists found changing sleep habits during CBT-I challenging due to anxiety and temporary increases in fatigue, but did not identify major pain-related barriers to adhering to CBT-I recommendations; patients experienced better sleep, mood, energy, and socialization after CBT-I despite minimal changes in pain intensity; and patients highly valued CBT-I as a personalized treatment for sleep and strongly recommended it for other patients with chronic pain.

CONCLUSIONS: Findings of improved sleep and functional outcomes support efforts to incorporate CBT-I into chronic pain treatment, including educating patients and providers about the strong feasibility of improving sleep and quality of life despite ongoing pain.

Genetic contribution in low back pain: a prospective genetic association study.

Margarit C[1,2], Roca R[2], Inda MD[2], Muriel J[2], Ballester P[2], Moreu R[3], Conte AL[4], Nuñez A[5], Morales D[5], Peiró A[1,2,3] .

Pain Pract. **2019 Jul 3**. doi: 10.1111/papr.12816. PMID: 31269327. [Epub ahead of print]

OBJECTIVES: Chronic pain is one of the commonest reasons individuals seek medical attention. It is a major issue because of the wide inter-individual variability in the analgesic response. This might be partly explained by the presence of variants in genes encoding molecules involved in pharmacodynamics and pharmacokinetics. The aim was to analyze opioid effectiveness in chronic low-back pain (CLBP) relief after opioid titration, unveiling the impact of pharmacogenetics.

METHODS: The study included 231 opioid-naïve patients from the Spine Unit; age 63±14 years, 64% female, 29±6 Kg/m^2, VAS pain intensity 73±16 mm. Clinical data were collected at baseline, 3 months after opioid titration and after 2-4 years of follow-up concerning pain (intensity and relief), quality of life, disability, comorbidities and drug prescription (opioid dose, rotations and adverse events). The genotype influence of OPRM1, COMT, UGT2B7, ABCB1, KCNJ6, and CYP3A5*3A in analgesic response was analyzed by RT-PCR genotyping.

RESULTS: Patients with the COMT G472A-AA genotype (rs4680) and KCNJ6 A1032G-A allele (rs2070995) CLBP responded differently to opioid titration, with higher pain intensity requiring higher dosing. Furthermore, GG- genotypes of A118G (OPRM1, rs1799971) and A854G (UGT2B7, rs776746) influenced the neuropathic component. After opioid titration, CLBP intensity, neuropathic component, low-back pain disability, anxiety and depression significantly decreased, while quality of life increased.

CONCLUSION: Single-nucleotide polymorphisms in genes involved in pain transmission and opioid metabolism might predispose to exaggerated sensitivity and differences in the opioid analgesic effect in CLBP patients. We encourage clinical trials for their clinical application in chronic pain management.

CHRONIC PAIN (Continued)

Differences in the miRNA signatures of chronic musculoskeletal pain patients from neuropathic or nociceptive origins.

Dayer CF[1,2], Luthi F[1,3,4], Le Carré J[1,2], Vuistiner P[1,2], Terrier P[1,2,5], Benaim C[4], Giacobino JP[1], Léger B[1,2].

PLoS One. **2019 Jul 5**;14(7):e0219311. doi: 10.1371/journal.pone.0219311. PMID: 31276478. eCollection 2019.

BACKGROUND: The quality of life for millions of people worldwide is affected by chronic pain. In addition to the effect of chronic pain on well-being, chronic pain has also been associated with poor health conditions and increased mortality. Due to its multifactorial origin, the classification of pain types remains challenging. MicroRNAs (miRNA) are small molecules that regulate gene expression. They are released into the bloodstream in a stable manner under normal and pathological conditions and have been described as potential biomarkers. In the present study, we aimed to investigate whether pain may induce an aberrant, specific dysregulation of miRNA expression, depending on the origin of the pain.

METHODS AND FINDINGS: To do so, we measured the expression changes of 184 circulating miRNAs (c-miRNAs) in the plasma samples of patients with different origins of chronic musculoskeletal pain. After statistical analyses, we identified seven c-miRNA candidates that were differentially expressed depending on the nociceptive or neuropathic origin of the pain. We then developed a two c-miRNA signature (hsa-miR-320a and hsa-miR-98-5p) that was able to correctly classify the pain type of 70% of the patients from the validation set.

CONCLUSIONS: In conclusion, circulating miRNAs are promising biomarkers to identify and characterize the chronic pain type and to further improve its clinical management.

IRRITABLE BOWEL SYNDROME

Effectiveness of mesalazine to treat irritable bowel syndrome: A meta-analysis.

Zhang FM[1], Li S, Ding L, Xiang SH, Zhu HT, Yu JH, Xu GQ.

Medicine (Baltimore). **2019 Jul**;98(28):e16297. doi: 10.1097/MD.0000000000016297. PMCID: PMC6641673. PMID: 31305414.

AIM: Accumulating evidence has explored the effect of mesalazine on irritable bowel syndrome (IBS). However, these studies remain inconsistent. Thus, a meta-analysis was conducted to estimate the role of mesalazine on IBS.

METHODS: PubMed, Medline, Embase, Web of Science, and the Cochrane Library Database were searched for all relevant randomized, controlled, blinded trials on mesalazine in patients with IBS between January 1980 and October 2018. All statistical analyses were performed using Revman 5.3 software. A fixed-effects model was adopted, 95% confidence intervals for SMD was calculated. Heterogeneity was evaluated by χ test and I statistic.

RESULTS: Five studies involving 387 participants were finally included in this meta-analysis. The results showed that the SMD for clinical efficacy on abdominal pain in IBS patients treated with mesalazine in comparison to placebo was 0.19 (95% CI=-0.01 to 0.39, P=.06), which was statistically non-significant but clinically important. For beneficial effect of abdominal bloating, the SMD was 0.05 (95% CI=-0.20 to 0.30, P=.70), which was statistically non-significant. In regard to clinical efficacy on defecation frequency per day, the results revealed that the SMD was 0.29 (95% CI=-0.14 to 0.73, P=.18), which was statistically non-significant but clinically important. As for beneficial effect of general well-being, we found that the SMD was 0.41 (95% CI=-0.75 to 1.58, P=.49), which was statistically non-significant. With respect to stool consistency, the SMD was 0.01 (95% CI=-0.31 to 0.33, P=.96), which was statistically non-significant. For the effect of defecation urgency severity in IBS patients treated with mesalazine in comparison to placebo, we detected a surprising result with an SMD of 0.54 (95% CI=0.05-1.04, P=.03), which was statistically significant. There was no significant difference between mesalazine group and placebo group on total mucosal immune cell counts of the patients with IBS with an SMD of -1.64 (95% CI=-6.17 to 2.89, P=.48) and there was also no significant difference in adverse reactions between two groups with an SMD of 1.05 (95% CI=0.76-1.46 P=.77).

CONCLUSION: Mesalazine is not superior to placebo in relieving clinical symptoms of abdominal pain, abdominal bloating, and general well-being of IBS and has no advantage of reducing defecation frequency per day and immune cell infiltration and improving stool consistency though without adverse reactions of mesalazine compared with placebo. For defecation urgency severity, placebo is even superior to mesalazine for IBS patients. Thus, mesalazine might be a cost burden to patients without providing good effectiveness. In view of the small sample size of the current study and the differences in every experimental designs, this study has high heterogeneity and requires subsequent verification.

IRRITABLE BOWEL SYNDROME (Continued)

Pathophysiology of the irritable bowel syndrome - Reflections of today.

Hellström PM[1].

Best Pract Res Clin Gastroenterol. **2019 Jun - Aug**;40-41:101620. doi: 10.1016/j.bpg.2019.05.007. PMID: 31594651. Epub 2019 May 24.

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

Irritable bowel syndrome (IBS) is a chronic gastrointestinal symptom complex defined by abdominal pain and disturbed bowel habits over 3 months within a period of 6 months, in absence of any identifiable organic pathology. Over the years, speculations of the pathophysiology of IBS has moved from elusive central nervous symptoms impinging on psychosomatic disease, to objective signs of intestinal fermentation with abdominal bloating and intestinal dysmotility. The specific subgroup of post-infectious IBS is of special interest since it opens the possibility of dysbiosis as the pivotal point for development of IBS in association with traveler's diarrhea or antibiotic treatment with ensuing dysbiosis and abdominal symptoms that may resolve over decades. The undefined disease mechanisms that take place within the gut seem responsible for the gut-brain signaling leading to activation of brain centers that drive the clinical picture of IBS, further modulated by the patient's social background and previous lifetime events.

The Rome IV: Irritable bowel syndrome - A functional disorder.

Hellström PM[1], Benno P[2].

Best Pract Res Clin Gastroenterol. **2019 Jun - Aug**;40-41:101634. doi: 10.1016/j.bpg.2019.101634. PMID: 31594650. Epub 2019 Jul 18.

Functional gastrointestinal disorders are the most common disorders encountered in the clinical gastroenterology setting. Over the years the Rome process has generated consensus definitions of functional gastrointestinal disorders, and given diagnostic criteria, based on various symptom patterns, that have evolved over the years. The latest Rome IV consensus was presented in May 2016. This summary points out some of the important changes made from the Rome III 2006 consensus including evaluation of symptoms from the stand-point of basal normative values and disorders of gut-brain interaction, as well as additions of the importance of the microflora. However, we are all aware of the fact that there are limitations, and the Rome consensus does not pick up all patients with functional gastrointestinal disorders. Out of those that seek medical help for their functional gastrointestinal symptoms additional outlines of disease have to be considered and judgements made on the patients' actual symptoms, or rather presentation of their symptoms. The Rome IV consensus is a robust standard for a clinical and research approach to functional gastrointestinal disorders, but might be improved by use of exclusion criteria and additional biochemical biomarkers in order to accurately diagnose those patients who may achieve relief by an extended treatment approach in the clinical setting of gastroenterology. A biopsychosocial approach to the patient is recommended to improve compliance and optimize treatment and outcomes.

Therapeutic potential of an anaerobic cultured human intestinal microbiota, ACHIM, for treatment of IBS.

Benno P[1], Norin E[2], Midtvedt T[2], Hellström PM[3].

Best Pract Res Clin Gastroenterol. **2019 Jun - Aug**;40-41:101607. doi: 10.1016/j.bpg.2019.03.003. PMID: 31594647. Epub 2019 Apr 29.

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

By administering an anaerobic cultivated human intestinal microbiota (ACHIM) via upper gastrointestinal route using endoscopy we aimed to rectify intestinal dysbiosis and simultaneously achieve a treatment response in IBS patients. The study population fulfilled the Rome III IBS criteria and comprised 50 patients. During 10 days, patients recorded the irritable bowel syndrome symptom severity scale (IBS-SSS) along with the Bristol stool scale and number of stools/day. The enrolled patients were categorized as follows: 37 with diarrhea, 5 with constipation and 8 with mixed symptoms. The treatment response showed reduction in a majority of patients, 32 of which with 50-point reduction of IBS-SSS and 21 with a 100-point IBS-SSS reduction. The percentage improvement was 36 (23-49) and 28 (18-38) for women and men respectively. Short-chain fatty acids were not changed. We consider fecal microbiota transplantation in the form of ACHIM as an option for the future therapeutic armamentarium in IBS. REGISTERED TRIAL: www.clinicaltrials.gov NCT02857257.

OTHER RESEARCH OF INTEREST

Gender differences in outcomes following specialized intensive PTSD treatment in the Veterans Health Administration.

Stefanovics EA[1], Rosenheck RA[1].

Psychol Trauma. **2019 Jul 8**. doi: 10.1037/tra0000495. PMID: 31282719. [Epub ahead of print]

OBJECTIVES: Posttraumatic stress disorder (PTSD) among female veterans is a problem of growing importance. Comparison of treatment outcomes and measures of program participation between female and male veterans receiving treatment in specialized intensive Veterans Health Administration (VHA) programs may identify potential gaps in service.

METHOD: National program evaluation data were collected at program entry and 4 months after discharge. The study sample consists of N = 3,370 veterans who were successfully followed up. With adjustment for differences in baseline characteristics outcomes of women and men were compared on changes in PTSD symptoms, substance use, and other outcomes using Cohen's d to evaluate effect sizes. Further analyses examined gender differences in program participation and their effect on differences in outcomes by gender.

RESULTS: Compared to males, females showed greater improvement (i.e., greater reduction) in total PTSD symptom scores ($p < .001$, Cohen's $d = -.29$) and in several subscales including Numbness ($p < .001$, $d = -.34$), Arousal ($p = .01$, $d = -.22$), Reexperiencing Past Traumas ($p < .01$, $d = -.23$), and Irritability ($p = .01$, $d = -.18$), with small to medium effect size differences. These gender-based differences were partially explained by differences in program participation such as greater length of stay among women.

CONCLUSIONS: In spite of the predominantly male environment of these VHA PTSD programs, women experienced greater improvement than men in PTSD symptoms and subscales. The differences were partially explained by positive indicators of program participation. Further studies are needed to better understand these differences. (PsycINFO Database Record (c) 2019 APA, all rights reserved).

Impact of occupational exposure on human microbiota.

Lai PS[1,2,3], Christiani DC[1,2,3].

Curr Opin Allergy Clin Immunol. **2019 Apr**;19(2):86-91. doi: 10.1097/ACI.0000000000000502. PMCID: PMC6395503. PMID: 30507717.

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

PURPOSE OF REVIEW: Recent evidence suggests that environmental exposures change the adult human microbiome. Here, we review recent evidence on the impact of the work microbiome and work-related chemical, metal and particulate exposures on the human microbiome.

RECENT FINDINGS: Prior literature on occupational microbial exposures has focused mainly on the respiratory effects of endotoxin, but a recent study suggests that not all endotoxin is the same; endotoxin from some species is proinflammatory, whereas endotoxin from other species is anti-inflammatory. Work with animals can change the adult human microbiome, likely through colonization. Early studies in military personnel and animal models of gulf war illness show that military exposures change the gut microbiome and increase gut permeability. Heavy metal and particulate matter exposure, which are often elevated in occupational settings, also change the gut microbiome.

SUMMARY: An emerging body of literature shows that work-related exposures can change the human microbiome. The health effects of these changes are currently not well studied. If work exposures lead to disease through alterations in the human microbiome, exposure cessation without addressing changes to the human microbiome may be ineffective for disease prevention and treatment.

OTHER RESEARCH OF INTEREST (Continued)

Clinical characteristics and genetic analyses of 187 patients with undefined autoinflammatory diseases.

Ter Haar NM[1,2], Eijkelboom C[2,3], Cantarini L[4], Papa R[5], Brogan PA[6], Kone-Paut I[7], Modesto C[8], Hofer M[9], Iagaru N[10], Fingerhutová S[11], Insalaco A[12], Licciardi F[13], Uziel Y[14], Jelusic M[15], Nikishina I[16], Nielsen S[17], Papadopoulou-Alataki E[18], Olivieri AN[19], Cimaz R[20], Susic G[21], Stanevica V[22], van Gijn M[23], Vitale A[4], Ruperto N[24], Frenkel J[25], Gattorno M[26].

Ann Rheum Dis. **2019 Jul 5**. pii: annrheumdis-2018-214472. doi: 10.1136/annrheumdis-2018-214472. PMID: 31278138. [Epub ahead of print]

OBJECTIVES: To describe the clinical characteristics, treatment response and genetic findings in a large cohort of patients with undefined systemic autoinflammatory diseases (SAIDs).

METHODS: Clinical and genetic data from patients with undefined SAIDs were extracted from the Eurofever registry, an international web-based registry that retrospectively collects clinical information on patients with autoinflammatory diseases.

RESULTS: This study included 187 patients. Seven patients had a chronic disease course, 180 patients had a recurrent disease course. The median age at disease onset was 4.3 years. Patients had a median of 12 episodes per year, with a median duration of 4 days. Most commonly reported symptoms were arthralgia (n=113), myalgia (n=86), abdominal pain (n=89), fatigue (n=111), malaise (n=104) and mucocutaneous manifestations (n=128). In 24 patients, relatives were affected as well. In 15 patients, genetic variants were found in autoinflammatory genes. Patients with genetic variants more often had affected relatives compared with patients without genetic variants (p=0.005). Most patients responded well to non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, colchicine and anakinra. Complete remission was rarely achieved with NSAIDs alone. Notable patterns were found in patients with distinctive symptoms. Patients with pericarditis (n=11) were older at disease onset (33.8 years) and had fewer episodes per year (3.0/year) compared with other patients. Patients with an intellectual impairment (n=8) were younger at disease onset (2.2 years) and often had relatives affected (28.6%).

CONCLUSION: This study describes the clinical characteristics of a large cohort of patients with undefined SAIDs. Among these, patients with pericarditis and intellectual impairment appear to comprise distinct subsets.

###