GULF WAR ILLNESS

Monosodium luminol reinstates redox homeostasis, improves cognition, mood and neurogenesis, and alleviates neuro- and systemic inflammation in a model of Gulf War Illness.

Shetty AK[1], Attaluri S[2], Kodali M[2], Shuai B[2], Shetty GA[2], Upadhya D[2], Hattiangady B[2], Madhu LN[2], Upadhya R[2], Bates A[2], Rao X[2].

Redox Biol. **2019 Nov 18**;28:1013. doi: 10.1016/j.redox.2019.101389. PMID: 31778892. [Epub ahead of print]

Enduring brain dysfunction is amid the highly manifested symptoms in veterans with Gulf War Illness (GWI). Animal studies have established that lasting brain dysfunction in GWI is concomitant with augmented oxidative stress, inflammation, and declined neurogenesis in the brain, and systemic inflammation. We hypothesize that drugs capable of restoring redox homeostasis in GWI will improve cognitive and mood function with modulation of neuroinflammation and neurogenesis. We examined the efficacy of monosodium luminol-GVT (MSL), a drug that promotes redox homeostasis, for improving cognitive and mood function in GWI rats. Young rats were exposed to GWI-related chemicals and moderate restraint stress for four weeks. Four months later, GWI rats received different doses of MSL or vehicle for eight weeks. Behavioral analyses in the last three weeks of treatment revealed that GWI rats receiving higher doses of MSL displayed better cognitive and mood function associated with reinstatement of redox homeostasis. Such restoration was evident from the normalized expression of multiple genes encoding proteins involved in combating oxidative stress in the brain and the return of several oxidative stress markers to control levels in the brain and the circulating blood. Sustained redox homeostasis by MSL also resulted in antiinflammatory and pro-neurogenic effects, which were apparent from reduced densities of hypertrophied astrocytes and activated microglia, and increased neurogenesis with augmented neural stem cell proliferation. Moreover, MSL treatment normalized the concentration of multiple proinflammatory markers in the circulating blood. Thus, MSL treatment reinstated redox homeostasis in an animal model of GWI, which resulted in alleviation of both brain and systemic inflammation, improved neurogenesis, and better cognitive and mood function.

CHRONIC FATIGUE SYNDROME

Identification of actin network proteins, talin-1 and filamin-A, in circulating extracellular vesicles as blood biomarkers for human myalgic encephalomyelitis/ chronic fatigue syndrome.

Eguchi A[1], Fukuda S[2], Kuratsune H[3], Nojima J[4], Nakatomi Y[5], Watanabe Y[6], Feldstein AE[7].

Brain Behav Immun. **2019 Nov 20**. pii: S0889-1591(19)30762-7. doi: 10.1016/j.bbi.2019.11.015. PMID: 31759091. [Epub]

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a serious, debilitating disorder with a wide spectrum of symptoms, including pain, depression, and neurocognitive deterioration. Over 17 million people around the world have ME/CFS, predominantly women with peak onset at 30-50 years. Given the wide spectrum of symptoms and unclear etiology, specific biomarkers for diagnosis and stratification of ME/CFS are lacking. Here we show that actin network proteins in circulating extracellular vesicles (EVs) offer specific non-invasive biomarkers for ME/CFS. We found that circulating EVs were significantly increased in ME/CFS patients correlating to C-reactive protein, as well as biological antioxidant potential. Area under the receiver operating characteristic curve for circulating EVs was 0.80, allowing correct diagnosis in 90-94% of ME/CFS cases. From two independent proteomic analyses using circulating EVs from ME/CFS, healthy controls, idiopathic chronic fatigue, and depression, proteins identified from ME/CFS patients are involved in focal adhesion, actin skeletal regulation, PI3K-Akt signaling pathway, and Epstein-Barr virus infection. In particular, talin-1, filamin-A, and 14-3-3 family proteins were the most abundant proteins, representing highly specific ME/CFS biomarkers. Our results identified circulating EV number and EV-specific proteins as novel biomarkers for diagnosing ME/CFS, providing important information on the pathogenic mechanisms of ME/CFS.

HEADACHE and MIGRAINE

Effect of Ubrogepant vs Placebo on Pain and the Most Bothersome Associated Symptom in the Acute Treatment of Migraine: The ACHIEVE II Randomized Clinical Trial.

Lipton RB[1], Dodick DW[2], Ailani J[3], Lu K[4], Finnegan M[4], Szegedi A[4], Trugman JM[4].

JAMA. **2019 Nov 19**;322(19):1887-1898. doi: 10.1001/jama.2019.16711. PMID: 31742631.

Importance: Ubrogepant is an oral calcitonin gene-related peptide receptor antagonist under investigation for acute treatment of migraine.

Objective: To evaluate the efficacy and tolerability of ubrogepant compared with placebo for acute treatment of a single migraine attack.

Design, Setting, and Participants: Phase 3, multicenter, randomized, double-blind, placebo-controlled, single-attack, clinical trial (ACHIEVE II) conducted in the United States (99 primary care and research clinics; August 26, 2016-February 26, 2018). Participants were adults with migraine with or without aura experiencing 2 to 8 migraine attacks per month.

Interventions: Ubrogepant 50 mg (n = 562), ubrogepant 25 mg (n = 561), or placebo (n = 563) for a migraine attack of moderate or severe pain intensity.

Main Outcomes and Measures: Co-primary efficacy outcomes were pain freedom and absence of the participant-designated most bothersome migraine-associated symptom (among photophobia, phonophobia, and nausea) at 2 hours after taking the medication.

Results: Among 1686 randomized participants, 1465 received study treatment (safety population; mean age, 41.5 years; 90% female); 1355 of 1465 (92.5%) were evaluable for efficacy. Pain freedom at 2 hours was reported by 101 of 464 participants (21.8%) in the ubrogepant 50-mg group, 90 of 435 (20.7%) in the ubrogepant 25-mg group, and 65 of 456 (14.3%) in the placebo group (absolute difference for 50 mg vs placebo, 7.5%; 95% CI, 2.6%-12.5%; P = .01; 25 mg vs placebo, 6.4%; 95% CI, 1.5%-11.5%; P = .03). Absence of the most bothersome associated symptom at 2 hours was reported by 180 of 463 participants (38.9%) in the ubrogepant 50-mg group, 148 of 434 (34.1%) in the ubrogepant 25-mg group, and 125 of 456 (27.4%) in the placebo group (absolute difference for 50 mg vs placebo, 11.5%; 95% CI, 5.4%-17.5%; P = .01; 25 mg vs placebo, 6.7%; 95% CI, 0.6%-12.7%; P = .07). The most common adverse events within 48 hours of any dose were nausea (50 mg, 10 of 488 [2.0%]; 25 mg, 12 of 478 [2.5%]; and placebo, 10 of 499 [2.0%]) and dizziness (50 mg, 7 of 488 [1.4%]; 25 mg, 10 of 478 [2.1%]; placebo, 8 of 499 [1.6%]).

Conclusions and Relevance: Among adults with migraine, acute treatment with ubrogepant compared with placebo led to significantly greater rates of pain freedom at 2 hours with 50-mg and 25-mg doses, and absence of the most bothersome migraine-associated symptom at 2 hours only with the 50-mg dose. Further research is needed to assess the effectiveness of ubrogepant against other acute treatments for migraine and to evaluate the long-term safety of ubrogepant among unselected patient populations.

Trial Registration: ClinicalTrials.gov Identifier: NCT02867709.

Making Better Dose Decisions: Using Exposure-Response Modeling to Integrate Efficacy Outcome of Two Phase 2b Clinical Trials of Ubrogepant for Migraine Treatment.

Li CC[1,2], Voss T[1], Kowalski K[3,4], Yang B[3,5], Jan Kleijn H[6], Jones CJ[1], Bosch R[1,7], Michelson D[1], DeAngelis M[1], Xu Y[1], Xie I[1], Kothare PA[1].

Clin Transl Sci. **2019 Nov 23**. doi: 10.1111/cts.12730. PMID: 31758661. [Epub ahead of print]

Ubrogepant (MK-1602) is a novel, oral, calcitonin gene-related peptide receptor antagonist in clinical development with positive Phase III outcomes for acute treatment of migraine. This paper describes the population exposure-response (E-R) modeling and simulations which were used to inform the Phase III dose-selection rationale, based on approximately 800 participants pooled across two Phase IIb randomized dose-finding clinical trials. The E-R model describes the placebo and ubrogepant treatment effects based on migraine pain endpoints (2-hour pain relief and 2-hour pain freedom) at various dose levels. Sensitivity analyses were conducted to evaluate various assumptions of placebo response in light of the high placebo response observed in one Phase II trial. A population PK model describing the effect of formulations was included in the E-R simulation framework to assess potential dose implications of a formulation switch from Phase II to Phase III. Model-based simulations predict that a dose of 25 mg or higher is likely to achieve significantly better efficacy than placebo with desirable efficacy levels. The understanding of E-R helped support the dose selection for the Phase III clinical trials.

HEADACHE and MIGRAINE (Continued)

Effects of fremanezumab on the use of acute headache medication and associated symptoms of migraine in patients with episodic migraine.

Brandes JL[1], Kudrow D[2], Yeung PP[3], Sakai F[4], Aycardi E[3], Blankenbiller T[3], Grozinski-Wolff M[3], Yang R[3], Ma Y[3].

Cephalalgia. **2019 Nov 21**:333102419885905. doi: 10.1177/0333102419885905. PMID: 31752521. [Epub ahead of print]

BACKGROUND: Fremanezumab, a fully humanized monoclonal antibody targeting calcitonin gene-related peptide, has demonstrated efficacy for the preventive treatment of migraine in adults.

OBJECTIVE: To evaluate the effect of fremanezumab treatment on acute headache medication use and migraine-associated symptoms in patients with episodic migraine.

METHODS: In the Phase 3 HALO trial, patients with episodic migraine were randomized to receive subcutaneous fremanezumab monthly (225 mg at baseline, weeks 4 and 8), fremanezumab quarterly (675 mg at baseline, placebo at weeks 4 and 8), or placebo over a 12-week period. The secondary endpoint was change from baseline in the monthly number of days with use of any acute headache mediation or migraine-specific acute headache medication; exploratory endpoints were change from baseline in the monthly number of days with nausea or vomiting, photophobia, or phonophobia.

RESULTS: Of 875 patients randomized, 865 were included in the analysis (monthly, n = 287; quarterly, n = 288; placebo, n = 290). Baseline mean ± standard deviation days with: Any acute headache medication use (monthly: 7.7 ± 3.4; quarterly: 7.8 ± 3.7; placebo: 7.7 ± 3.6), migraine-specific acute headache medication use (6.1 ± 3.1; 6.6 ± 3.1; 7.1 ± 3.0), nausea or vomiting (4.5 ± 3.6; 4.9 ± 3.7; 4.5 ± 3.3) and photophobia and phonophobia (5.5 ± 4.1; 6.3 ± 4.1; 6.0 ± 3.9) were similar among treatment arms. Fremanezumab reduced the number of days of acute headache medication use ([least-squares mean change vs. placebo] monthly: -1.4 [95% confidence interval: -1.84, -0.89], $p < 0.001$; quarterly: -1.3 [-1.76, -0.82], $p < 0.001$) and migraine-specific acute headache medication use (monthly: -2.2 [-2.80, -1.56], $p < 0.001$; quarterly: -2.2 [-2.81, -1.58], $p < 0.001$) compared with placebo. Fremanezumab also reduced nausea or vomiting, photophobia, and phonophobia compared with placebo.

CONCLUSIONS: Fremanezumab reduced the need for acute headache medications, including migraine-specific medications, while treating migraine-associated symptoms in patients with episodic migraine.

TRIAL REGISTRATION: Clinicaltrials.gov NCT02629861.

Evaluation of simple inflammatory blood parameters in patients with migraine.

Yazar HO[1], Yazar T[2], Aygün A[3], Kaygisiz Ş[4], Kirbaş D[5].

Ir J Med Sci. **2019 Nov 22**. doi: 10.1007/s11845-019-02136-y. PMID: 31758522. [Epub ahead of print]

AIM: This study aimed to identify the serum neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), platelet/lymphocyte ratio (PLR), and C-reactive protein (CRP)/albumin (CAR) ratios among patients with diagnosis of migraine according to migraine subtypes (attack/attack-free period, migraine with or without aura, episodic/chronic migraine, family history/no family history) and to collect data to investigate the role of inflammation and oxidative stress in etiology.

METHOD: The study was completed with 235 patients with migraine diagnosis classified according to the International Classification of Headache Disorders-2013(ICHD) classification and 166 healthy controls. Patients with migraine were assessed during the attack by emergency medicine specialists in the emergency room and in attack-free periods in neurology clinics by neurology specialists.

RESULTS: Of patients with migraine, 77.02% were female and 22.98% were male. The neutrophil, NLR, PLR, and MLR levels were higher than the control group ($p < 0.05$). The serum CRP, neutrophil, NLR, MLR, and CAR levels were higher, and albumin and lymphocyte levels were lower during migraine attack periods ($p < 0.05$). Migraines with aura were observed to have higher serum NLR levels compared to the aura-free patients ($p < 0.05$). Migraine patients with positive family history were found to have higher NLR levels compared to patients without a family history ($p < 0.05$).

CONCLUSION: Although non-specific, serum NLR, MLR, PLR, and CAR levels may be potential biomarkers associated with migraine subtypes with different clinical features such as migraine attack period, migraine with aura, and patients with family history of migraine. Elevated inflammatory markers may indicate the severity of disease.

HEADACHE and MIGRAINE (Continued)

Wearing Off Effect of OnabotulinumtoxinA Near the End of Treatment Cycle for Chronic Migraine: A 4-Year Clinical Experience.

Khan FA[1,2,3], Mohammed AE[4], Poongkunran M[1], Chimakurthy A[1], Pepper M[1,2].

Headache. **2019 Nov 22**. doi: 10.1111/head.13713. PMID: 31758548. [Epub ahead of print]

INTRODUCTION: The injection interval for onabotulinumtoxinA (BoNTA) in the management of chronic migraine (CM) is 12 weeks (78-84 days). The aim of this study was to review patient-reported wearing off effect (WOE) of the therapeutic benefit of BoNTA near the end of the treatment cycle. We intended to describe the demographics of patients at baseline and compare groups of patients with multiple episodes of WOE.

METHODS: We conducted a retrospective review of patients with CM who received uninterrupted BoNTA therapy from January 2014 to March 2018. The data from patient-reported WOE (worsening headache variables and neck pain) that occurred during the 4 weeks (28 days) prior to the scheduled re-injection of BoNTA for treatment cycles with injection interval ≤13 weeks and without obvious confounding factors were reviewed.

RESULTS: We identified 98 eligible patients and analyzed 471 treatment cycles. Forty-three unique patients reported at least 1 occurrence of WOE. About 24/43 patients reported 1 WOE event and 19/43 patients reported ≥2 WOE events. Between the 2 groups, anxiety disorder and opioid use for headache were statistically significantly different. In the former group, the median interquartile range (IQR) dose of BoNTA was 165 (155, 175) units and the median IQR duration of the antinociceptive effect of BoNTA was 66.5 (63, 71.5) days. In the latter group, the median IQR dose of BoNTA was 167 (155, 173.3) units and the median IQR duration of the antinociceptive effect of BoNTA was 65.3 (62.5, 68.8) days. Up to 32% of these patients reported an increase in the use of abortive therapies to manage the symptoms of WOE.

DISCUSSION: The primary goal of BoNTA in the treatment of CM is to mitigate the development of central sensitization. Since the 12-week injection paradigm may not provide sustained antinociceptive effect in all patients, it may account for the failure of response to BoNTA. Repeated occurrences of the WOE can potentially lead to medication overuse and impact quality of life.

A causal role for TRESK loss of function in migraine mechanisms.

Pettingill P[1], Weir GA[1,2], Wei T[1], Wu Y[1], Flower G[1], Lalic T[1], Handel A[3], Duggal G[1], Chintawar S[1], Cheung J[1], Arunasalam K[1], Couper E[4], Haupt LM[5], Griffiths LR[5], Bassett A[6], Cowley SA[4], Cader MZ[1].

Brain. **2019 Nov 19**. pii: awz342. doi: 10.1093/brain/awz342. PMID: 31742594. [Epub ahead of print]

The two-pore potassium channel, TRESK has been implicated in nociception and pain disorders. We have for the first time investigated TRESK function in human nociceptive neurons using induced pluripotent stem cell-based models. Nociceptors from migraine patients with the F139WfsX2 mutation show loss of functional TRESK at the membrane, with a corresponding significant increase in neuronal excitability. Furthermore, using CRISPR-Cas9 engineering to correct the F139WfsX2 mutation, we show a reversal of the heightened neuronal excitability, linking the phenotype to the mutation. In contrast we find no change in excitability in induced pluripotent stem cell derived nociceptors with the C110R mutation and preserved TRESK current; thereby confirming that only the frameshift mutation is associated with loss of function and a migraine relevant cellular phenotype. We then demonstrate the importance of TRESK to pain states by showing that the TRESK activator, cloxyquin, can reduce the spontaneous firing of nociceptors in an in vitro human pain model. Using the chronic nitroglycerine rodent migraine model, we demonstrate that mice lacking TRESK develop exaggerated nitroglycerine-induced mechanical and thermal hyperalgesia, and furthermore, show that cloxyquin conversely is able to prevent sensitization. Collectively, our findings provide evidence for a role of TRESK in migraine pathogenesis and its suitability as a therapeutic target.

CHRONIC PAIN

Infertility and Health-Related Quality of Life in United States Women Veterans.

Mancuso AC[1], Summers KM[1], Mengeling MA[2,3,4], Torner JC[5], Ryan GL[1], Sadler AG[3,6].

J Womens Health (Larchmt). **2019 Nov 22**. doi: 10.1089/jwh.2019.7798. PMID: 31755818. [Epub ahead of print]

Background: To assess associations between infertility and health-related quality of life and medical comorbidities in U.S. women Veterans.

Materials and Methods: This cross-sectional observational study involved computer-assisted telephone interviews of Veterans Administration-enrolled women between ages 21 and 52 years. Patients were analyzed in two groups by self-reported history of infertility. Outcomes included health-related quality of life as measured by the short-form 12-item interview (SF-12) physical and mental component summary (PCS and MCS) scores, depression, post-traumatic stress disorder (PTSD), eating disorders, fibromyalgia, other chronic pain, cardiovascular disease risk factors, and cancer. Age-adjusted *p*-values and adjusted odds ratios (AORs) were calculated using individual multivariate regression models to control for significant confounding covariates.

Results: Of the 996 women veterans included, 179 (18.0%) reported a history of infertility. Infertility was associated with worse perceived physical health as determined by the SF-12 PCS [beta coefficient (B) -3.23 (-5.18 to -1.28)] and fibromyalgia [AOR 1.97 (1.22 to 3.19)]. Infertility was also associated with higher rates of depression, other chronic pain, and cancer, which remained significant after adjusting for age ($p = 0.021$, $p = 0.016$, and $p = 0.045$, respectively); however, no association for all was seen after adjustment for other significant covariates. There was no difference in Veterans' mental health using the SF-12 MCS, nor differences seen in PTSD or eating disorder rates, or in cardiovascular risk factors.

Conclusions: This novel investigation in U.S. women Veterans found worse physical health-related quality of life and increased rates of fibromyalgia among women reporting a history of infertility, adding to the growing literature on infertility as a marker for overall poorer health.

Graded chronic pain scale revised: mild, bothersome, and high impact chronic pain.

Von Korff M[1], DeBar LL[1], Krebs EE[2], Kerns RD[3], Deyo RA[4], Keefe FJ[5].

Pain. **2019 Nov 20**. doi: 10.1097/j.pain.0000000000001758. PMID: 31764390. [Epub ahead of print]

Drawing on advances in chronic pain metrics, a simplified Graded Chronic Pain Scale Revised (GCPS-R) was developed to differentiate mild, bothersome and high impact chronic pain. GCPS-R was validated among adult enrollees of two health plans (N=2021). In this population, the prevalence of chronic pain (pain present most or every day, prior 3 months) was 40.5%: 15.4% with mild chronic pain (lower pain intensity and interference); 10.1% bothersome chronic pain (moderate to severe pain intensity with lower life activities interference); and 15.0% high impact chronic pain (sustained pain-related activity limitations). Persons with mild chronic pain versus those without chronic pain showed small differences on ten health status indicators (unfavorable health perceptions, activity limitations, receiving long-term opioid therapy), with non-significant differences for 7 of 10 indicators. Persons with bothersome versus mild chronic pain differed significantly on 6 of 10 indicators (e.g., negative pain coping beliefs, psychological distress, unfavorable health perceptions and pain-related interference with overall activities). Persons with high impact chronic pain differed significantly from those with mild chronic pain on all 10 indicators. Persons with high impact chronic pain, relative to those with bothersome chronic pain, were more likely to have substantial activity limitations (significant differences for 4 of 5 disability indicators) and more often received long-term opioid therapy. GCPS-R strongly predicted five activity limitation indicators with area under receiver operating characteristic curve coefficients of 0.76 to 0.89. We conclude that the 5 item GCPS-R and its scoring rules provide a brief, simple and valid method for assessing chronic pain.

CHRONIC PAIN (Continued)

New procedure of high-frequency repetitive transcranial magnetic stimulation for central neuropathic pain: a placebo-controlled randomized cross-over study.

Quesada C[1,2], Pommier B[1,3], Fauchon C[1], Bradley C[4], Créac'h C[1,5,2], Murat M[1], Vassal F[1,3], Peyron R[1,5,2].

Pain. **2019 Nov 20**. doi: 10.1097/j.pain.0000000000001760. PMID: 31764387. [Epub ahead of print]

Repetitive transcranial magnetic stimulation (rTMS) is a procedure increasingly used to treat patients with central neuropathic pain (CNP), but its efficacy is still under debate. Patients with medically refractory chronic CNP were included in two randomized phases (active/sham), separated by a wash-out period of 8 weeks. Each phase consisted of 4 consecutive rTMS sessions and a final evaluation session, all separated from one another by 3 weeks. High-frequency (20Hz) rTMS was delivered over the primary motor cortex (M1) contralateral to the patient's pain using a neuronavigated robotic system. Patients and clinicians assessing outcomes were blinded to treatment allocation during the trial. The primary outcome measured the percentage of pain relief (%R) from baseline. Secondary outcomes were VAS score, Neuropathic Pain Symptom Inventory (NPSI), analgesic drug consumption and quality of life (EQ-5D). Thirty-six patients performed the entire study with no adverse effects. The analgesic effect for the main criterion (%R) was significantly higher in the active (33.8% CI: [23.88-43.74]) than in the sham phase (13.02% CI: [6.64-19.76]). This was also the case for the secondary outcome VAS (-19.34% CI: [14.31-25.27] vs. -4.83% CI: [1.96-8.18]). No difference was observed for quality of life or analgesic drug consumption. Seventeen patients (47%) were identified as responders but no significant interaction was found between clinical and technical factors considered here and the analgesic response. These results provide strong evidence that 3-weeks spaced high-frequency rTMS of M1 results in a sustained analgesic effect and support the clinical interest of this stimulation paradigm to treat refractory chronic pain.

IRRITABLE BOWEL SYNDROME

Breath Test Gas Patterns in Inflammatory Bowel Disease with Concomitant Irritable Bowel Syndrome-Like Symptoms: A Controlled Large-Scale Database Linkage Analysis.

Gu P[1], Patel D[2], Lakhoo K[2], Ko J[2], Liu X[3], Chang B[4], Pan D[5], Lentz G[6], Sonesen M[6], Estiandan R[6], Lin E[3], Pimentel M[3], Rezaie A[3].

Dig Dis Sci. **2019 Nov 21**. doi: 10.1007/s10620-019-05967-y. PMID: 31754993. [Epub ahead of print]

INTRODUCTION: Breath testing (BT) has gained interest for diagnosing small intestinal bacterial overgrowth (SIBO) in IBD patients with irritable bowel syndrome (IBS) overlap. We aim to characterize the rate of SIBO and BT gas patterns in IBD patients with IBS-like symptoms compared to non-IBD patients.

METHODS: A database of 14,847 consecutive lactulose BTs was developed from patients with IBS-like symptoms between November 2005 and October 2013. BTs were classified as normal, H_2 predominant, CH_4 predominant, and flatline based on criteria established from the literature. BT data linkage with electronic health records and chart review identified IBD patients along with disease phenotype, location, severity, and antibiotic response. Poisson loglinear model evaluated differences in gas patterns between the two groups.

RESULTS: After excluding patients with repeat breath tests, we identified 486 IBD and 10,505 non-IBD patients with at least one BT. Positive BT was present in 57% (n = 264) of IBD patients. Crohn's disease (odds ratio (OR) 0.21, [95% confidence interval (CI) 0.11-0.38]) and ulcerative colitis (OR 0.39, [95% CI 0.22-0.70]) patients were less likely to produce excess CH_4. IBD patients were more likely to have flatline BT (OR 1.82, [95% CI 1.20-2.77]). In IBD patients with SIBO, 57% improved symptomatically with antibiotics.

CONCLUSION: In a cohort of IBD patients with IBS-like symptoms, a high rate of patients had positive BT and symptomatic improvement with antibiotics. In IBD, methanogenesis is suppressed and flatline BT is more frequent, suggesting excess hydrogenotrophic bacteria. These findings suggest methanogenic and hydrogenotrophic microorganisms as potential targets for microbiome-driven biomarkers and therapies.

IRRITABLE BOWEL SYNDROME (Continued)

A meta-analysis on small intestinal bacterial overgrowth in patients with different subtypes of irritable bowel syndrome.

Ghoshal UC[1], Nehra A[1], Mathur A[1], Rai S[1].

J Gastroenterol Hepatol. **2019 Nov 21**. doi: 10.1111/jgh.14938. PMID: 31750966. [Epub ahead of print]

BACKGROUND: Enteric microbiota is increasingly being recognized as an important factor in the pathogenesis of irritable bowel syndrome (IBS). The reported prevalence of small intestinal bacterial overgrowth (SIBO) in subjects with IBS is highly variable, and there is no consensus on the role of SIBO in different subtypes of IBS, and indications and methods of testing.

METHODS: A comprehensive literature search was performed for studies applying tests for SIBO in subjects with IBS. After applying prospectively decided exclusion criteria, the eligible papers were examined using a meta-analysis approach for the prevalence of SIBO in subjects with IBS using different tests. The odds ratios of SIBO among subjects with IBS as compared with healthy controls using different tests were calculated.

RESULTS: Of the available studies (22, 17, 5, and 3 using lactulose and glucose hydrogen breath tests [LHBT and GHBT], jejunal aspirate culture, and more than one tests, respectively) meeting the inclusion criteria, 36.7% (95% confidence interval [CI] 24.2-44.6) had a positive test for SIBO. Patients with IBS were 2.6 (95% CI 1.3-6.9) and 8.3 (95% CI 3.0-5.9) times more likely to have a positive test for SIBO as compared with healthy controls using GHBT and jejunal aspirate culture, respectively. Patients with diarrhea-predominant IBS were more likely to have positive GHBT as compared with the other subtypes.

CONCLUSIONS: Patients with IBS were more likely to have SIBO as compared with healthy subjects using GHBT and jejunal aspirate culture but not using LHBT. Patients with diarrhea-predominant IBS more often have SIBO.

Allergies and Irritable Bowel Syndrome.

Talley NJ[1].

Gastroenterol Hepatol (N Y). **2019 Nov**;15(11):619-621. PMCID: PMC6883730. PMID: 31802988.

G&H: What is currently understood about the connection between allergies and irritable bowel syndrome?

NT: Epidemiologic studies suggest an etiopathogenic link between atopic diseases, such as asthma and eczema, and functional gastrointestinal disorders, particularly irritable bowel syndrome (IBS) and functional dyspepsia. These studies build on the previously recognized relationship between asthma and gastroesophageal reflux disease, the latter of which overlaps with IBS and functional dyspepsia. Supporting an atopic disease process is emerging evidence that food antigens (eg, wheat proteins) may drive small intestinal pathologic alterations such as increased intestinal permeability and tissue eosinophilia in patients with IBS and functional dyspepsia. The immune system may play a critical role in functional gastrointestinal disorders, as further demonstrated by circulating small intestinal homing T cells and the release of cytokines in both IBS and functional dyspepsia that may influence the brain (ie, immune-driven gut-brain disorders). Interestingly, there is an increased risk of autoimmune diseases in patients with functional gastrointestinal disorders. This finding has been replicated in 2 large epidemiologic studies and further supports the concept that a subset of patients with IBS or functional dyspepsia has immune activation.

[View full text and references for this question and answer article in Gastroenterology & Hepatology.]

OTHER RESEARCH OF INTEREST (Continued)

Chronic Exposure to Solvents Among Construction Painters: Reductions in Exposure and Neurobehavioral Health Effects.

Fiedler N[1], Weisel C, Nwankwo C, Kipen H, Lange G, Ohman-Strickland P, Laumbach R.

J Occup Environ Med. **2018 Dec**;60(12):e663-e670. doi: 10.1097/JOM.0000000000001470. PMCID: PMC6289817. PMID: 30308619.

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

OBJECTIVE: The aim of this study was to assess the neurobehavioral effects of lifetime solvent exposure by comparing the performance of painters and demographically comparable controls.

METHODS: Performance of exposed painters (N=133) was compared with unexposed tapers, glaziers, or carpenters (N=78) on the following domains: motor/perceptual speed, visual contrast, attention, working memory/planning, and visual and verbal memory. Lifetime exposure was estimated with questionnaires, field measurements, and paint composition.

RESULTS: After controlling for confounders, lifetime solvent exposure did not predict reduction in performance for overall domains of function. Lifetime solvent exposures predicted subtle alterations for individual tests of verbal learning, motor coordination, and visuospatial accuracy.

CONCLUSION: Concentrations of solvents in paints have steadily declined during the working lifetime of subjects in this study. Although reduced performance was observed on individual tests, these alterations were not consistent across tests and unlikely to be of clinical significance.

How safe are our studies? Analysis of adverse events in Bayer First-in-Human trials from 2006 to 2016 .

Jung D, Boettcher MF, Wensing G.

Int J Clin Pharmacol Ther. **2019 Nov 20**. doi: 10.5414/CP203390. PMID: 31746730. [Epub ahead of print]

PURPOSE: In regard to the current scientific discussion, this analysis aims to broaden the database for a risk evaluation of First-in-Human (FiH) trials with healthy volunteers.

MATERIALS AND METHODS: Study documents of each FiH study conducted between 2006 and 2016 for Bayer Clinical Pharmacology Cardiovascular were reviewed for inclusion. Study types, treatments, dose steps, study population, number, incidence, and intensity of treatment-emergent adverse events (AEs) were cumulatively analyzed using descriptive statistics. A comparison to a previous similar analysis (period 2000 - 2005) was made.

RESULTS: 22 out of 25 studies were included (20 small molecules, 2 biologics) investigating drugs for cardiovascular (9), hematological (7), pulmonary (3), kidney (2), and metabolic (1) diseases. The mean age of subjects was 34.2 years. 1,250 subjects received treatment (950 active, 300 placebo). 952 AEs occurred (0.76 AEs/treatment, 0.85 AEs/active treatment, 0.49 AEs/placebo treatment). 88.2% (840/952) of AEs were mild, 11.3% (108/952) moderate, and 0.4% (4/952) were severe. 0.4% (5/1250) of subjects had active drug- or procedure-related serious AEs. The most frequent AE was headache (12.9% (123/952)), the mostly affected system organ class was CNS (14.4% of all subjects). The relative risk for an AE was significantly higher under active drug compared to placebo (1.24, 95% LCL >1). The incidence of AEs increased with higher dose steps. A higher incidence of AEs (active and placebo) in recent compared to previous studies was observed.

CONCLUSION: The risk of severe harm for healthy participants was low. The risk to experience any AE was higher under active drug compared to placebo. A trend change towards more frequent reporting of AEs in the recent studies was observed.

OTHER RESEARCH OF INTEREST (Continued)

Proton-pump inhibitor use is associated with a broad spectrum of neurological adverse events including impaired hearing, vision, and memory.

Makunts T[1], Alpatty S[1], Lee KC[1], Atayee RS[1], Abagyan R[2].

Sci Rep. **2019 Nov 21**;9(1):17280. doi: 10.1038/s41598-019-53622-3. PMID: 31754136.

Proton-pump inhibitors, PPIs, are considered effective therapy for stomach acid suppression due to their irreversible inhibition of the hydrogen/potassium pump in the gastric parietal cells. They are widely prescribed and are considered safe for over-the-counter use. Recent studies have shown an association between PPI use and Alzheimer dementia, while others have disputed that connection. We analyzed over ten million United States Food and Drug Administration Adverse Event Reporting System reports, including over forty thousand reports containing PPIs, and provided evidence of increased propensity for memory impairment among PPI reports when compared to histamine-2 receptor antagonist control group. Furthermore, we found significant associations of PPI use with a wide range of neurological adverse reactions including, migraine, several peripheral neuropathies, and visual and auditory neurosensory abnormalities.

Update: Interim Guidance for Health Care Providers for Managing Patients with Suspected E-cigarette, or Vaping, Product Use-Associated Lung Injury - United States, November 2019.

Jatlaoui TC, Wiltz JL, Kabbani S, Siegel DA, Koppaka R, Montandon M, Adkins SH, Weissman DN, Koumans EH, O'Hegarty M, O'Sullivan MC, Ritchey MD, Chatham-Stephens K, Kiernan EA, Layer M, Reagan-Steiner S, Legha JK, Shealy K, King BA, Jones CM, Baldwin GT, Rose DA, Delaney LJ, Briss P, Evans ME; Lung Injury Response Clinical Working Group.

Collaborators: (9): Aberegg S[1], Calfee CS[2], Callahan SJ[3], Esper A[4], Griffiths A[5], Harris D[6], Hayes D Jr[7], Rao DR[8], Smith LS[9].

MMWR Morb Mortal Wkly Rep. **2019 Nov 22**;68(46):1081-1086. doi: 10.15585/mmwr.mm6846e2. PMID: 31751322.

CDC, the Food and Drug Administration (FDA), state and local health departments, and public health and clinical stakeholders are investigating a nationwide outbreak of e-cigarette, or vaping, product use-associated lung injury (EVALI) (1). CDC has published recommendations for health care providers regarding EVALI (2-4). Recently, researchers from Utah and New York published proposed diagnosis and treatment algorithms for EVALI (5,6). EVALI remains a diagnosis of exclusion because, at present, no specific test or marker exists for its diagnosis, and evaluation should be guided by clinical judgment. Because patients with EVALI can experience symptoms similar to those associated with influenza or other respiratory infections (e.g., fever, cough, headache, myalgias, or fatigue), it might be difficult to differentiate EVALI from influenza or community-acquired pneumonia on initial assessment; EVALI might also co-occur with respiratory infections. This report summarizes recommendations for health care providers managing patients with suspected or known EVALI when respiratory infections such as influenza are more prevalent in the community than they have been in recent months (7). Recommendations include 1) asking patients with respiratory, gastrointestinal, or constitutional symptoms about the use of e-cigarette, or vaping, products; 2) evaluating those suspected to have EVALI with pulse oximetry and obtaining chest imaging, as clinically indicated; 3) considering outpatient management for clinically stable EVALI patients who meet certain criteria; 4) testing patients for influenza, particularly during influenza season, and administering antimicrobials, including antivirals, in accordance with established guidelines; 5) using caution when considering prescribing corticosteroids for outpatients, because this treatment modality has not been well studied among outpatients, and corticosteroids could worsen respiratory infections; 6) recommending evidence-based treatment strategies, including behavioral counseling, to help patients discontinue using e-cigarette, or vaping, products; and 7) emphasizing the importance of annual influenza vaccination for all persons aged ≥6 months, including patients who use e-cigarette, or vaping products.

OTHER RESEARCH OF INTEREST (Continued)

Oxidative stress in exercise training: the involvement of inflammation and peripheral signals.

Francesca M[1], Tania F[1], Riccardo M[1], Michele M[1], Tania G[1], Pietro M[2], Alessandra M[1].

Free Radic Res. **2019 Nov 24**:1-301. doi: 10.1080/10715762.2019.1697438. PMID: 31762356. [Epub ahead of print]

The evidence about the health benefits of regular physical activity is well established. Exercise intensity is a significant variable and structured high-intensity interval training (HIIT) has been demonstrated to improve both whole-body and skeletal muscle metabolic health in different populations. Conversely, fatigue accumulation, if not resolved, leads to overwork, chronic fatigue syndrome (CFS), overtraining syndrome up to alterations of endocrine function, immune, systemic inflammation, and organic diseases with health threat. In response to temporary increases in stress during training, some athletes are unable to maintain sufficient caloric intake, thus suffering a negative energy balance that causes further stress. The regulation of the energy balance is controlled by the central nervous system through an elaborate interaction of the signaling that involves different tissues such as leptin, adiponectin and ghrelin whose provide important feedback to the hypothalamus to regulate the energy balance. Although exercise-induced reactive oxygen species are required for normal force production in muscle, high levels of ROS appear to promote contractile dysfunction. However, a high level of oxidative stress in may induce a rise in inflammatory markers and a disregulation in expression of adiponectin, leptin and grelin.

Is running associated with a lower risk of all-cause, cardiovascular and cancer mortality, and is the more the better? A systematic review and meta-analysis.

Pedisic Z[1], Shrestha N[2], Kovalchik S[2], Stamatakis E[3,4], Liangruenrom N[2,5], Grgic J[2], Titze S[6], Biddle SJ[7], Bauman AE[4], Oja P[8].

Br J Sports Med. **2019 Nov 4**. pii: bjsports-2018-100493. doi: 10.1136/bjsports-2018-100493. PMID: 31685526. [Epub]

OBJECTIVE: To investigate the association of running participation and the dose of running with the risk of all-cause, cardiovascular and cancer mortality.

DESIGN: Systematic review and meta-analysis.

DATA SOURCES: Journal articles, conference papers and doctoral theses indexed in Academic Search Ultimate, CINAHL, Health Source: Nursing/Academic Edition, MasterFILE Complete, Networked Digital Library of Theses and Dissertations, Open Access Theses and Dissertations, PsycINFO, PubMed/MEDLINE, Scopus, SPORTDiscus and Web of Science.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES: Prospective cohort studies on the association between running or jogging participation and the risk of all-cause, cardiovascular and/or cancer mortality in a non-clinical population of adults were included.

RESULTS: Fourteen studies from six prospective cohorts with a pooled sample of 232 149 participants were included. In total, 25 951 deaths were recorded during 5.5-35 year follow-ups. Our meta-analysis showed that running participation is associated with 27%, 30% and 23% lower risk of all-cause (pooled adjusted hazard ratio (HR)=0.73; 95% confidence interval (CI) 0.68 to 0.79), cardiovascular (HR=0.70; 95% CI 0.49 to 0.98) and cancer (HR=0.77; 95% CI 0.68 to 0.87) mortality, respectively, compared with no running. A meta-regression analysis showed no significant dose-response trends for weekly frequency, weekly duration, pace and the total volume of running.

CONCLUSION: Increased rates of participation in running, regardless of its dose, would probably lead to substantial improvements in population health and longevity. Any amount of running, even just once a week, is better than no running, but higher doses of running may not necessarily be associated with greater mortality benefits.

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