GULF WAR ILLNESS

Pyridostigmine bromide and stress interact to impact immune function, cholinergic neurochemistry and behavior in a rat model of Gulf War Illness.

Macht VA[1], Woodruff JL[2], Maissy ES[3], Grillo CA[2], Wilson MA[4], Fadel JR[3], Reagan LP[5].

Brain Behav Immun. **2019 Apr 3**. pii: S0889-1591(18)30567-1. doi: 10.1016/j.bbi.2019.04.015. PMID: 30953774. [Epub ahead of print]

Gulf War Illness (GWI) is characterized by a constellation of symptoms that include cognitive dysfunction. While the causes for GWI remain unknown, prophylactic use of the acetylcholinesterase inhibitor pyridostigmine bromide (PB) in combination with the stress of deployment has been proposed to be among the causes of the cognitive dysfunction in GWI. Mechanistically, clinical studies suggest that altered immune function may be an underlying factor in the neurochemical and neurobehavioral complications of GWI. Accordingly, the goal of this study was to determine how responses to an immune challenge (lipopolysaccharide; LPS) or stress impacts inflammation, acetylcholine (ACh) neurochemistry and behavior in an experimental model of GWI. Rats with a history of PB treatment exhibited potentiated increases in C-reactive protein levels in response to a submaximal LPS challenge compared to control rats, indicating that prior treatment with this cholinesterase inhibitor leads to exacerbated inflammatory responses to a subsequent immune challenge. ACh responses to LPS administration were decreased in the hippocampus, but not prefrontal cortex (PFC), in rats with a prior history of PB treatment or stress exposure. Additionally, ACh release in response to acute immobilization stress was attenuated in the PFC and hippocampus in these groups. These attenuated cholinergic responses were accompanied by impairments in contextual and cue-based fear learning. The results of this study suggest that stress and LPS challenges adversely affect central ACh neurochemistry in a rodent model of GWI and support the hypothesis that dysregulated immune responses are mechanistically linked to the neurological complications of GWI.

CHRONIC FATIGUE SYNDROME

Evidence of Clinical Pathology Abnormalities in People with Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS) from an Analytic Cross-Sectional Study.

Nacul L[1], de Barros B[2], Kingdon CC[3], Cliff JM[4], Clark TG[5,6], Mudie K[7], Dockrell HM[8], Lacerda EM[9].

Diagnostics (Basel). **2019 Apr 10**;9(2). pii: E41. doi: 10.3390/diagnostics9020041. PMID: 30974900.

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating disease presenting with extreme fatigue, post-exertional malaise, and other symptoms. In the absence of a diagnostic biomarker, ME/CFS is diagnosed clinically, although laboratory tests are routinely used to exclude alternative diagnoses. In this analytical cross-sectional study, we aimed to explore potential haematological and biochemical markers for ME/CFS, and disease severity. We reviewed laboratory test results from 272 people with ME/CFS and 136 healthy controls participating in the UK ME/CFS Biobank (UKMEB). After corrections for multiple comparisons, most results were within the normal range, but people with severe ME/CFS presented with lower median values ($p < 0.001$) of serum creatine kinase (CK; median = 54 U/L), compared to healthy controls (HCs; median = 101.5 U/L) and non-severe ME/CFS (median = 84 U/L). The differences in CK concentrations persisted after adjusting for sex, age, body mass index, muscle mass, disease duration, and activity levels (odds ratio (OR) for being a severe case = 0.05 (95% confidence interval (CI) = 0.02-0.15) compared to controls, and OR = 0.16 (95% CI = 0.07-0.40), compared to mild cases). This is the first report that serum CK concentrations are markedly reduced in severe ME/CFS, and these results suggest that serum CK merits further investigation as a biomarker for severe ME/CFS.

CHRONIC FATIGUE SYNDROME (Continued)

Chronotropic Intolerance: An Overlooked Determinant of Symptoms and Activity Limitation in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome?

Davenport TE[1,2], Lehnen M[1], Stevens SR[2], VanNess JM[2,3], Stevens J[2], Snell CR[2].

Front Pediatr. **2019 Mar 22**;7:82. doi: 10.3389/fped.2019.00082. PMCID: PMC6439478. eCollection 2019.

Post-exertional malaise (PEM) is the hallmark clinical feature of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). PEM involves a constellation of substantially disabling signs and symptoms that occur in response to physical, mental, emotional, and spiritual over-exertion. Because PEM occurs in response to over-exertion, physiological measurements obtained during standardized exertional paradigms hold promise to contribute greatly to our understanding of the cardiovascular, pulmonary, and metabolic states underlying PEM. In turn, information from standardized exertional paradigms can inform patho-etiologic studies and analeptic management strategies in people with ME/CFS. Several studies have been published that describe physiologic responses to exercise in people with ME/CFS, using maximal cardiopulmonary testing (CPET) as a standardized physiologic stressor. In both non-disabled people and people with a wide range of health conditions, the relationship between exercise heart rate (HR) and exercise workload during maximal CPET are repeatable and demonstrate a positive linear relationship. However, smaller or reduced increases in heart rate during CPET are consistently observed in ME/CFS. This blunted rise in heart rate is called chronotropic intolerance (CI). CI reflects an inability to appropriately increase cardiac output because of smaller than expected increases in heart rate. The purposes of this review are to (1) define CI and discuss its applications to clinical populations; (2) summarize existing data regarding heart rate responses to exercise obtained during maximal CPET in people with ME/CFS that have been published in the peer-reviewed literature through systematic review and meta-analysis; and (3) discuss how trends related to CI in ME/CFS observed in the literature should influence future patho-etiological research designs and clinical practice.

Therapeutic Effect and Metabolic Mechanism of A Selenium-Polysaccharide from *Ziyang* Green Tea on Chronic Fatigue Syndrome.

Shao C[1,2], Song J[3], Zhao S[4], Jiang H[5], Wang B[6], Chi A[7].

Polymers (Basel). **2018 Nov 15**;10(11). pii: E1269. doi: 10.3390/polym10111269. PMCID: PMC6401680. PMID: 30961194.

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

Ziyang green tea was considered a medicine food homology plant to improve chronic fatigue Ssyndrome (CFS) in China. The aim of this research was to study the therapeutic effect of selenium-polysaccharides (Se-TP) from *Ziyang* green tea on CFS and explore its metabolic mechanism. A CFS-rats model was established in the present research and Se-TP was administrated to evaluate the therapeutic effect on CFS. Some serum metabolites including blood urea nitrogen (BUN), blood lactate acid (BLA), corticosterone (CORT), and aldosterone (ALD) were checked. Urine metabolites were analyzed via gas chromatography-mass spectrometry (GC-MS). Multivariate statistical analysis was also used to check the data. The results selected biomarkers that were entered into the MetPA database to analyze their corresponding metabolic pathways. The results demonstrated that Se-TP markedly improved the level of BUN and CORT in CFS rats. A total of eight differential metabolites were detected in GC-MS analysis, which were benzoic acid, itaconic acid, glutaric acid, 4-acetamidobutyric acid, creatine, 2-hydroxy-3-isopropylbutanedioic acid, l-dopa, and 21-hydroxypregnenolone. These differential metabolites were entered into the MetPA database to search for the corresponding metabolic pathways and three related metabolic pathways were screened out. The first pathway was steroid hormone biosynthesis. The second was tyrosine metabolism, and the third was arginine-proline metabolism. The 21-hydroxypregnenolone level of rats in the CFS group markedly increased after the Se-TP administration. In conclusion, Se-TP treatments on CFS rats improved their condition. Its metabolic mechanism was closely related to that which regulates the steroid hormone biosynthesis.

HEADACHE and MIGRAINE

Safety and Tolerability of Fremanezumab for the Prevention of Migraine: A Pooled Analysis of Phases 2b and 3 Clinical Trials.

Silberstein SD[1], McAllister P[2], Ning X[3], Faulhaber N[4] , Lang N[4], Yeung P[3], Schiemann J[3], Aycardi E[3], Cohen JM[3], Janka L[3], Yang R[3].

Headache. **2019 Apr 12**. doi: 10.1111/head.13534. PMID: 30977520. [Epub ahead of print]

OBJECTIVE: Presentation of pooled analysis of safety data for fremanezumab in patients with chronic (CM) or episodic migraine (EM) from 4 placebo-controlled phase 2b and phase 3 studies.

BACKGROUND: There is a need for an effective, safe, and well-tolerated preventive therapy that specifically targets the pathophysiology of migraine to reduce the frequency and severity of migraine attacks in patients with CM or EM who experience 4 or more migraine days per month. Fremanezumab is a fully humanized monoclonal antibody that targets calcitonin gene-related peptide, a neuropeptide involved in the pathophysiology of migraine.

DESIGN/METHODS: The 4 placebo-controlled phases 2b and 3 studies included in this analysis were 16-week, multicenter, randomized, double-blind, placebo-controlled, and parallel-group studies consisting of a screening visit, a 28-day pretreatment baseline period, and a 12-week treatment period with a final evaluation 4 weeks after the final dose of the study drug. Safety endpoints included adverse events (AEs) and immunogenicity.

RESULTS: A total of 2566 patients were randomized across all studies (fremanezumab, n = 1704; placebo, n = 862), and 2563 patients were treated. Common reasons for study discontinuation were withdrawal by patient (n = 78), patient lost to follow-up (n = 60), and AE (n = 50). The mean (standard deviation) duration of exposure was 83.8 (13.6) days for the patients who received fremanezumab, with a total exposure of 390.4 patient years and maximum exposure of 181 days. AEs were mostly mild to moderate in severity and were reported among 48-69% of patients in all treatment groups, and most were injection site reactions (pain, induration, and erythema). Two deaths occurred (chronic obstructive pulmonary disease and intentional overdose of diphenhydramine), both of which were deemed unrelated to study drug by the investigators and sponsor. Cardiovascular adverse events, abnormal liver function tests, and hypersensitivity were uncommon and occurred at similar rates between the placebo and fremanezumab groups.

CONCLUSIONS: Fremanezumab is a generally safe and well-tolerated preventive therapy for migraine in adults.

Decreased grey matter volume in mTBI patients with post-traumatic headache compared to headache-free mTBI patients and healthy controls: a longitudinal MRI study.

Burrowes SAB[1,2,3], Rhodes CS[4], Meeker TJ[2], Greenspan JD[2,3], Gullapalli RP[4], Seminowicz DA[5,6].

Brain Imaging Behav. **2019 Apr 12**. doi: 10.1007/s11682-019-00095-7. PMID: 30980274. [Epub ahead of print]

Traumatic brain injury (TBI) occurs in 1.7 million people annually and many patients go on to develop persistent disorders including post-traumatic headache (PTH). PTH is considered chronic if it continues past 3 months. In this study we aimed to identify changes in cerebral grey matter volume (GMV) associated with PTH in mild TBI patients. 50 mTBI patients (31 Non-PTH; 19 PTH) underwent MRI scans: within 10 days post-injury, 1 month, 6 months and 18 months. PTH was assessed at visit 4 by a post-TBI headache questionnaire. Healthy controls (n = 21) were scanned twice 6 months apart. Compared to non-PTH, PTH patients had decreased GMV across two large clusters described as the right anterior-parietal (p = 0.012) and left temporal-opercular (p = 0.027). Compared to healthy controls non-PTH patients had decreased GMV in the left thalamus (p = 0.047); PTH patients had decreased GMV in several extensive clusters: left temporal-opercular (p = 0.003), temporal-parietal (p = 0.041), superior frontal gyrus (p = 0.008) and right middle frontal/superior frontal gyrus (0.004) and anterior-parietal (p = 0.003). Differences between PTH and non-PTH patients were most striking at early time points. These early changes may be associated with an increased risk of PTH. Patients with these changes should be monitored for chronic PTH.

HEADACHE and MIGRAINE (Continued)

The Impact of Spinal Manipulation on Migraine Pain and Disability: A Systematic Review and Meta-Analysis.

Rist PM[1], Hernandez A[1,2], Bernstein C[3,4], Kowalski M[3], Osypiuk K[1,2], Vining R[5], Long CR[5], Goertz C[6], Song R[7], Wayne PM[1,2].

Headache. **2019 Apr**;59(4):532-542. doi: 10.1111/head.13501. PMCID: PMC6461372. PMID: 30973196. Epub 2019 Mar 14.

BACKGROUND: Several small studies have suggested that spinal manipulation may be an effective treatment for reducing migraine pain and disability. We performed a systematic review and meta-analysis of published randomized clinical trials (RCTs) to evaluate the evidence regarding spinal manipulation as an alternative or integrative therapy in reducing migraine pain and disability.

METHODS: PubMed and the Cochrane Library databases were searched for clinical trials that evaluated spinal manipulation and migraine-related outcomes through April 2017. Search terms included: migraine, spinal manipulation, manual therapy, chiropractic, and osteopathic. Meta-analytic methods were employed to estimate the effect sizes (Hedges' g) and heterogeneity (I^2) for migraine days, pain, and disability. The methodological quality of retrieved studies was examined following the Cochrane Risk of Bias Tool.

RESULTS: Our search identified 6 RCTs (pooled n = 677; range of n = 42-218) eligible for meta-analysis. Intervention duration ranged from 2 to 6 months; outcomes included measures of migraine days (primary outcome), migraine pain/intensity, and migraine disability. Methodological quality varied across the studies. For example, some studies received high or unclear bias scores for methodological features such as compliance, blinding, and completeness of outcome data. Due to high levels of heterogeneity when all 6 studies were included in the meta-analysis, the 1 RCT performed only among chronic migraineurs was excluded. Heterogeneity across the remaining studies was low. We observed that spinal manipulation reduced migraine days with an overall small effect size (Hedges' g = -0.35, 95% CI: -0.53, -0.16, P < .001) as well as migraine pain/intensity.

CONCLUSIONS: Spinal manipulation may be an effective therapeutic technique to reduce migraine days and pain/intensity. However, given the limitations to studies included in this meta-analysis, we consider these results to be preliminary. Methodologically rigorous, large-scale RCTs are warranted to better inform the evidence base for spinal manipulation as a treatment for migraine.

Acute withdrawal and botulinum toxin A in chronic migraine with medication overuse: a double-blind randomized controlled trial.

Pijpers JA[1], Kies DA[1,2], Louter MA[1,3], van Zwet EW[4], Ferrari MD[1], Terwindt GM[1].

Brain. **2019 Apr 14**. pii: awz052. doi: 10.1093/brain/awz052. PMID: 30982843. [Epub ahead of print]

Botulinum toxin A (BTA) is widely used as treatment of chronic migraine. Efficacy in studies, however, was only modest and likely influenced by unblinding due to BTA-induced removal of forehead wrinkles. Moreover, most study participants were overusing acute headache medications and might have benefitted from withdrawal. We assessed in a double blind, placebo-controlled, randomized clinical trial whether add-on therapy with BTA enhances efficacy of acute withdrawal. Participants were enrolled between December 2012 and February 2015, with follow-up to January 2016, in a single academic hospital in the Netherlands. A total of 179 participants, male and female, aged 18-65, diagnosed with chronic migraine and overuse of acute headache medication were included. All participants were instructed to withdraw acutely from all medication for a 12-week period, in an outpatient setting. In addition, they were randomly assigned (1:1) to 31 injections with BTA (155 units) or placebo (saline); to prevent unblinding, placebo-treated participants received low doses of BTA (17.5 units in total) in the forehead, along with saline injections outside the forehead region. Primary endpoint was percentage change in monthly headache days from baseline to the last 4 weeks of double-blind treatment (Weeks 9-12). Among 179 randomized patients, 90 received BTA and 89 received placebo, and 175 (98%) completed the double-blind phase. All 179 patients were included in the intention-to-treat analyses. BTA did not reduce monthly headache days versus placebo (-26.9% versus -20.5%; difference -6.4%; 95% confidence interval: -15.2 to 2.4; P = 0.15). Absolute changes in migraine days at 12 weeks for BTA versus placebo were -6.2 versus -7.0 (difference: 0.8; 95% confidence interval: -1.0 to 2.7; P = 0.38). Other secondary endpoints, including measures for disability and quality of life, did also not differ. Withdrawal was well tolerated and blinding was successful. Thus, in patients with chronic migraine and medication overuse, BTA does not afford any additional benefit over acute withdrawal alone. Acute withdrawal should be tried first before initiating more expensive treatment with BTA.

CHRONIC PAIN

The Role of Nonpharmacological Approaches to Pain Management: Proceedings of a Workshop.

Forum on Neuroscience and Nervous System Disorders; Global Forum on Innovation in Health Professional Education; Board on Health Sciences Policy; Board on Global Health; Health and Medicine Division; The National Academies of Sciences, Engineering, and Medicine.

Rapporteurs: Lisa Bain, Sheena M. Posey Norris, and Clare Stroud.

Washington (DC): National Academies Press (US); **April 12, 2019.** doi: https://doi.org/10.17226/25406.

Publication Online: (PDF format).

On December 4–5, 2018 the Forum on Neuroscience and Nervous System Disorders and Global Forum on Innovation in Health Professional Education hosted a public workshop that brought together experts and key stakeholders from government, academia, industry, health professional societies, and disease-focused organizations to discuss nonpharmacological treatments and integrative health models for pain management, and their role within the broad landscape of approaches to chronic pain management. This Proceedings of a Workshop highlights presentations that discussed the state of evidence on the effectiveness of nonpharmacological treatments and integrative health models for pain management, multimodal approaches, and research gaps and key questions for further research. The Proceedings also summarizes workshop discussions that examined health professions' current approaches for educating students, trainees, and practicing clinicians on nonpharmacological pain management as well as the policies that would enable broader dissemination and implementation of evidence-based nonpharmacological approaches, when appropriate.

Research Priorities in Post-acute and Long-term Care: Results of a Stakeholder Needs Assessment.

Drake C[1], Wald HL[2], Eber LB[3], Trojanowski JI[4], Nearing KA[5], Boxer RS[6].

J Am Med Dir Assoc. **2019 Apr 11**. pii: S1525-8610(19)30244-0. doi: 10.1016/j.jamda.2019.02.018. PMID: 30982714. [Epub ahead of print]

OBJECTIVES: Conduct a needs assessment among post-acute and long-term care (PA-LTC) stakeholder groups to identify (1) research topics of highest priority and (2) perspectives on research, including concerns/barriers to conducting research in the PA-LTC setting.

DESIGN: Mixed methods multistakeholder engagement process. Needs assessment conducted with tailored strategies per stakeholder group: interview, survey, and focus group.

SETTING AND PARTICIPANTS: Four stakeholder groups—medical directors/providers (n = 89), administrative leadership (n = 5), frontline staff (n = 17), and family members of residents and residents themselves (n = 11)—were recruited from the Colorado PA-LTC community through an academic-community partnership between the University of Colorado and Colorado Medical Directors Association.

MAIN OUTCOME(S): Stakeholder perspectives on research and high priority PA-LTC research topics.

RESULTS: Research priorities common across stakeholder groups included polypharmacy (overuse of medication generally and overuse of antibiotics specifically), care transitions, mental health (including dementia, Alzheimer's disease, behaviors), chronic pain, urinary tract infection, and quality of life issues. Providers specifically prioritized heart failure, Parkinson's, and other chronic illnesses. Administrators and directors of nurses emphasized hospitalizations. Staff prioritized medication/therapy compliance. Families/residents prioritized neurologic disease. Concerns included staff burden, consenting process, privacy, and family involvement.

CONCLUSIONS/IMPLICATIONS: PA-LTC patients have a lot to offer as participants and decision makers in research, frontline staff are enthusiastic about participation, family members want to be involved, and providers value research findings in their practice but need a more supportive environment to produce and participate in research.

CHRONIC PAIN (Continued)

Impact of Abuse Deterrent Formulations of Opioids in Patients With Chronic Pain in the United States: A Cost-Effectiveness Model.

Kumar VM[1], Agboola F[2], Synnott PG[2], Segel C[2], Webb M[3], Ollendorf DA[4], Banken R[5], Chapman RH[2].

Value Health. **2019 Apr**;22(4):416-422. doi: 10.1016/j.jval.2018.12.005. PMID: 30975392. Epub 2019 Mar 21.

OBJECTIVE: Opioid abuse is a significant public health problem in the United States. We evaluate the clinical effectiveness and economic impact of abuse-deterrent formulations (ADF) of opioids relative to non-ADF opioids in preventing abuse.

METHODS: We developed a cost-effectiveness model simulating 2 cohorts of 100 000 noncancer, chronic-pain patients newly prescribed either ADF or non-ADF extended-release (ER) opioids and followed them over 5 years, tracking new events of opioid abuse and opioid-related overdose deaths in addition to tracking 5-year cumulative costs of therapeutic use and abuse of ADF and non-ADF opioids. Patients in each cohort entered the model for therapeutic opioid use from where they could continue in that pathway, discontinue opioid use, or abuse opioids or die of opioid overdose-related or unrelated causes. In addition, one-way sensitivity and scenario analysis were conducted.

RESULTS: Over a 5-year time period, using ADF opioids prevented an additional 2300 new cases of opioid abuse at an additional cost of approximately $535 million to the healthcare sector. Threshold analyses showed that a 40% decrease in ADF opioid costs was required to attain cost neutrality between the 2 cohorts, whereas a 100% effectiveness in abuse reduction still did not result in cost neutrality. A 43% decrease in diversion with ADFs relative to non-ADFs was required to attain cost neutrality. Including a societal perspective produced results directionally similar to the base-case analysis findings.

CONCLUSION: ADF opioids have the potential to prevent new cases of opioid abuse, but at substantially higher costs to the health system.

Outcomes Associated with Treatment of Chronic Pain with Tapentadol Compared with Morphine and Oxycodone: A UK Primary Care Observational Study.

Morgan CL[1], Jenkins-Jones S[2], Currie C[2], Baxter G[3].

Adv Ther. **2019 Apr 8**. doi: 10.1007/s12325-019-00932-7. PMID: 30963513. [Epub ahead of print]

INTRODUCTION: This study compared adverse outcomes and resource use for patients with a diagnosis of pain treated with tapentadol prolonged-release (PR) versus those treated with morphine controlled-release (CR) and oxycodone CR.

METHODS: Data were sourced from the Clinical Practice Research Datalink (CPRD), a database derived from UK primary care. Patients prescribed tapentadol PR between May 2011 and December 2016 were selected and matched to two groups of controls treated with either morphine CR or oxycodone CR on gender, age, pain duration, pain site, pain aetiology, Charlson index and prior analgesia. Times to first adverse event (constipation or nausea/vomiting) were compared within a Cox proportional hazards model. Rates of primary care contacts, accident and emergency contacts and, for a subset of patients linked to Hospital Episode Statistics (HES), inpatient admissions and outpatient contacts were compared using incidence rate ratios (IRRs) derived from Poisson regression.

RESULTS: A total of 1907 patients prescribed tapentadol PR were identified and 1791 (93.9%) had a pain diagnosis. Of these 1246 (65.3%) were matched to morphine controls and 829 (43.4%) to oxycodone controls. Compared to controls, gastrointestinal adverse events with tapentadol PR treatment were reduced; aHR = 0.532 (0.402-0.703; $p < 0.001$) versus morphine CR and 0.517 (0.363-0.735; $p < 0.001$) versus oxycodone CR. Compared with morphine CR, primary care contacts [IRR = 0.831 (0.802-0.861)], accident and emergency attendance [0.739 (0.572-0.951)], outpatient contacts [0.917 (0.851-0.989)] and inpatients contacts [0.789 (0.664-0.938)] were reduced. For oxycodone, the respective figures were 0.735 (0.703-0.768), 0.971 (0.699-1.352), 0.877 (0.799-0.962) and 0.748 (0.601-0.932).

CONCLUSION: Tapentadol PR was associated with significantly fewer adverse gastrointestinal events than morphine CR and oxycodone CR in patients with a diagnosis of pain. There was also significantly reduced primary and secondary care resource use. As with all observational studies, potential bias due to residual confounding and confounding by indication should be considered.

FUNDING: Grünenthal Ltd.

CHRONIC PAIN (Continued)

Health-related quality of life change in patients treated at a multidisciplinary pain clinic.

Vartiainen P[1], Heiskanen T[1], Sintonen H[2], Roine RP[3], Kalso E[1].

Eur J Pain. **2019 Apr 13**. doi: 10.1002/ejp.1398. PMID: 30980782. [Epub ahead of print]

BACKGROUND: Multidisciplinary pain management (MPM) is a generally-accepted method for treating chronic pain, but heterogeneous outcome measures provide only limited conclusions concerning its effectiveness. Therefore, further studies on the effectiveness of MPM are needed to identify subgroups of patients who benefit, or do not benefit, from these interventions. Our aim was to analyze health-related quality of life (HRQoL) changes after MPM and to identify factors associated with treatment outcomes.

METHODS: We carried out a real-world observational follow-up study of chronic pain patients referred to a tertiary multidisciplinary outpatient pain clinic to describe, using the validated HRQoL instrument 15D, the HRQoL change after MPM, and to identify factors associated with this change. 1043 patients responded to the 15D HRQoL questionnaire at baseline and 12 months after the start of treatment. Background data were collected from the pre-admission questionnaire of the pain clinic.

RESULTS: 53% of the patients reported a clinically important improvement and, of these, 81% had a major improvement. 35% reported a clinically important deterioration, and 12% had no change in HRQoL. Binary logistic regression analysis revealed that major improvement was positively associated with shorter duration of pain (<3 years), worse baseline HRQoL, higher education levels, and being employed.

CONCLUSIONS: The majority of the patients reported significant HRQoL improvement after multidisciplinary pain management. Better understanding of the factors associated with treatment outcomes is needed to meet the needs of those who had unfavourable outcomes.

Remission From Suicidal Ideation Among Those in Chronic Pain: What Factors Are Associated With Resilience?

Fuller-Thomson E[1], Kotchapaw LD[2].

J Pain. **2019 Apr 9**. pii: S1526-5900(19)30696-0. doi: 10.1016/j.jpain.2019.02.096. PMID: 30979638. [Epub ahead of print]

Although there have been many studies on the link between chronic pain and suicidality, surprisingly little research has focused on resilience and recovery among those in chronic and disabling pain who have had suicidal thoughts. The objectives of this study were to identify the prevalence and correlates of recovery from suicidal thoughts among those in chronic pain. A secondary analysis of a nationally representative sample of Canadians in chronic and disabling pain who had ever had serious suicidal thoughts (N = 635) was conducted to identify the prevalence and characteristics of those who are no longer considering suicide. Data were drawn from the Canadian Community Health Survey-Mental Health. Three in five Canadians in chronic pain (63%) who had seriously considered suicide at some point in their life had been free of these thoughts in the past year. Those free of suicidal ideation were significantly more likely to be older, women, white, better educated, with a confidant, and to use spirituality to cope, but less likely to have low household incomes, difficulties meeting basic expenses, and a history of depression and anxiety disorders. PERSPECTIVE: Almost two-thirds of formerly suicidal Canadians with chronic pain were free from suicidal thoughts in the past year. These findings provide a hopeful message of resilience and recovery in the context of disabling pain and help to improve targeted outreach to those most at risk for unremitting suicidality.

IRRITABLE BOWEL SYNDROME

Efficacy of Fecal Microbiota Transplantation in Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis.

Xu D[1], Chen VL[1], Steiner CA[1], Berinstein JA[1], Eswaran S[1], Waljee AK[1], Higgins PDR[1], Owyang C[1].

Am J Gastroenterol. **2019 Mar 20**. doi: 10.14309/ajg.0000000000000198. PMID: 30908299. [Epub ahead of print]

OBJECTIVES: Irritable bowel syndrome (IBS) is a common gastrointestinal condition with a heterogeneous pathophysiology. An altered gut microbiome has been identified in some IBS patients, and fecal microbiota transplantation (FMT) has been suggested to treat IBS. We performed meta-analyses and systematic review of available randomized controlled trials (RCTs) to evaluate the efficacy of FMT in IBS.

METHODS: We performed a systematic literature search of MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Web of Science. Selection criteria included RCTs of FMT vs placebo using FMT excipients or autologous FMT in IBS. Meta-analyses were conducted to evaluate the summary relative risk (RR) and 95% confidence intervals (CIs) of combined studies for primary outcome of improvement in global IBS symptoms as measured by accepted integrative symptom questionnaires or dichotomous responses to questions of overall symptom improvement.

RESULTS: Among 742 citations identified, 7 were deemed to be potentially relevant, of which 4 studies involving 254 participants met eligibility. No significant difference in global improvement of IBS symptoms was observed at 12 weeks in FMT vs placebo (RR = 0.93; 95% CI 0.48-1.79). Heterogeneity among studies was significant (I = 79%). Subgroup analyses revealed benefits of single-dose FMT using colonoscopy and nasojejunal tubes in comparison with autologous FMT for placebo treatment (number needed to treat = 5, RR = 1.59; 95% CI 1.06-2.39; I = 0%) and a reduction in likelihood of improvement of multiple-dose capsule FMT RCTs (number needed to harm = 3, RR = 0.54; 95% CI 0.34-0.85; I = 13%). Placebo response was 33.7% in nonoral FMT RCTs and 67.8% in capsule FMT RCTs. The Grading of Recommendations Assessment, Development and Evaluation quality of the body of evidence was very low.

CONCLUSIONS: Current evidence from RCTs does not suggest a benefit of FMT for global IBS symptoms. There remain questions regarding the efficacy of FMT in IBS as well as the lack of a clean explanation on the discrepant results among RCTs in subgroup analyses.

Noneffectiveness of electroacupuncture for comorbid generalized anxiety disorder and irritable bowel syndrome.

Mak DPA[1], Chung CHV[2], Suet Ying Y[1], Tse YK[3], Wong YSS[2], Ju Y[3], Hung SS[3], Leung KC[3], You HSJ[4], Lui R[5], Wong SH[5], Leung NWO[1], Lam CWL[1], Lee S[1], Wu CJ[5].

J Gastroenterol Hepatol. **2019 Mar 19**. doi: 10.1111/jgh.14667. PMID: 30891824. [Epub ahead of print]

BACKGROUND AND AIM: Comorbid generalized anxiety disorder and irritable bowel syndrome are common and therapeutically challenging. We aimed to assess the effectiveness of electroacupuncture in relieving anxiety and bowel symptoms in Chinese adults with this form of comorbidity.

METHODS: In a single-blind randomized sham-controlled trial, subjects with comorbid generalized anxiety disorder and irritable bowel syndrome were randomly assigned to receive 10 weekly sessions of electroacupuncture or sham electroacupuncture. Patients were assessed at baseline, immediately after intervention and at 6-week follow-up. Primary outcome was anxiety (7-item Patient Health Questionnaire section for anxiety). Secondary outcomes included bowel symptoms (bowel symptoms questionnaire), depressive symptoms (9-item Patient Health Questionnaire), somatic symptoms (15-item Patient Health Questionnaire) and health-related quality of life (Euroqol-5 dimensions).

RESULTS: Eighty subjects, 40 in each arm, were randomized. All but 2 in the sham group completed 10 weekly sessions. There was no significant difference in the proportion of patients experiencing significant (≥ 50%) reduction of anxiety symptoms between the two groups immediately after intervention (32.4% vs 21.6%, P = 0.06) and at 6-week follow-up (25.7% in electroacupuncture vs 27% in sham, P = 0.65). Anxiety, depressive, bowel symptom severity did not differ significantly between electroacupuncture and sham groups.

CONCLUSIONS: Findings failed to support the effectiveness of electroacupuncture for comorbid generalized anxiety disorder and irritable bowel syndrome. Further studies are needed to identify effective acupuncture treatment protocols for such comorbidity.

OTHER RESEARCH OF INTEREST

Bidirectional association between migraine and fibromyalgia: retrospective cohort analyses of two populations.

Penn IW[1,2], Chuang E[3], Chuang TY[4], Lin CL[5], Kao CH[6,7,8].

BMJ Open. **2019 Apr 8**;9(4):e026581. doi: 10.1136/bmjopen-2018-026581. PMID: 30962236.

OBJECTIVE: Fibromyalgia (FM) and migraine are common pain disorders that tend to coexist. This study determined whether these two conditions exhibited any mutual influences.

SETTING: Cohort study.

PARTICIPANTS: A retrospective, longitudinal cohort study was conducted using data obtained from a nationwide healthcare database. This study had two arms. Arm 1 comprised 33 216 patients with FM and arm 2 consisted of 7420 patients with migraine; all of these patients were diagnosed between 2000 and 2010. Using the aforementioned database, control subjects who had neither FM nor migraine and were matched with the FM and migraine patients by sex, age and index date of diagnosis were recruited. Each control cohort was four times the size of the corresponding study cohort. Follow-up for the control and study cohorts was conducted until the end of 2011.

RESULTS: The incidence rates of FM and migraine were calculated in arms 1 and 2, respectively. The overall incidence of migraine was greater in the FM cohort than in the corresponding control cohort (4.39 vs 2.07 per 1000 person-years (PY)); crude HR=2.12, 95% CI=1.96 to 2.30; adjusted HR (aHR)=1.89, 95% CI=1.75 to 2.05). After adjustment for sex, age and comorbidities, the overall incidence of FM in the migraine cohort was 1.57 times greater than that in the corresponding control cohort (7.01 vs 4.49 per 1000 PY; aHR=1.52, 95% CI=1.39 to 1.65).

CONCLUSIONS: The present study revealed a bidirectional link between FM and migraine.

A Randomized and Controlled Crossover Study Investigating the Improvement of Walking and Posture Functions in Chronic Stroke Patients Using HAL Exoskeleton - The HALESTRO Study (HAL-Exoskeleton STROke Study).

Sczesny-Kaiser M[1], Trost R[1], Aach M[2], Schildhauer TA[3], Schwenkreis P[1], Tegenthoff M[1].

Front Neurosci. **2019 Mar 29**;13:259. doi: 10.3389/fnins.2019.00259. PMCID: PMC6450263. PMID: 30983953. eCollection 2019.

Background: The exoskeleton HAL (hybrid assistive limb) has proven to improve walking functions in spinal cord injury and chronic stroke patients when using it for body-weight supported treadmill training (BWSTT). Compared with other robotic devices, it offers the possibility to initiate movements actively. Previous studies on stroke patients did not compare HAL-BWSTT with conventional physiotherapy (CPT). Therefore, we performed a crossover clinical trial comparing CPT and HAL-BWSTT in chronic stroke patients with hemiparesis, the HALESTRO study. Our hypothesis was that HAL-training would have greater effects on walking and posture functions compared to a mixed-approach CPT.

Methods: A total of 18 chronic stroke patients participated in this study. Treatment consisted of 30 CPT sessions and of 30 sessions of BWSTT with a double leg type HAL exoskeleton successively in a randomized, crossover study design. Primary outcome parameters were walking time and speed in 10-meter walk test (10MWT), time in timed-up-and-go test (TUG) and distance in 6-min walk test (6MWT). Secondary outcome parameters were the functional ambulatory categories (FAC) and the Berg-Balance Scale (BBS). Data were assessed at baseline, at crossover and at the end of the study, all without using and wearing HAL.

Results: Our study demonstrate neither a significant difference in walking parameters nor in functional and balance parameters. When HAL-BWSTT was applied to naïve patients, it led to an improvement in walking parameters and in balance abilities. Pooling all data, we could show a significant effect in 10MWT, 6MWT, FAC and BBS, both therapies sequentially applied over 12 weeks. Thereby, FAC improve from dependent to independent category (3 to 4). One patient dropped out of the study due to intensive fatigue after each training session.

Conclusion: HAL-BWSTT and mixed-approach CPT were effective therapies in chronic stroke patients. However, compared with CPT, HAL training with 30 sessions over 6 weeks was not more effective. The combination of both therapies led to an improvement of walking and balance functions. Robotic rehabilitation of walking disorders alone still lacks the proof of superiority in chronic stroke. Robotic treatment therapies and classical CPT rehabilitation concepts should be applied in an individualized therapy program.

OTHER RESEARCH OF INTEREST (Continued)

Respiratory Health Status of Workers that Exposed to Welding Fumes at Lumut Shipyard.

Ithnin A, Zubir A, Awang N, Mohamad Sulaiman NN.

Pak J Biol Sci. **2019 Jan**;22(3):143-147. doi: 10.3923/pjbs.2019.143.147. PMID: 30972984.

BACKGROUND AND OBJECTIVE: Welding fume exposure has led to the respiratory problems among welders including cough, phlegm, chest illnesses, nausea and fatigue. Inadequate ventilation during welding works causes the situation to worsen. Welding fumes can cause a decrease in lung function among welders. Chronic exposure will lead to other health effects especially COPD (Chronic Obstructive Pulmonary Disease). The objective of this study is to determine the exposure of welding fumes (Cd, Fe, Pb and Zn) towards respiratory health including lung function test (FEV1, FVC, FEV1/FVC, PEFR) of workers in Lumut shipyard, Perak.

MATERIAL AND METHODS: This research study the relationship between exposures of welding fumes towards lung function test among workers in Lumut shipyard, Perak. Lung function test was measured by spirometry among 30 welders and 31 non-welders. The concentration welding fume exposure was measured using OSHA ID-121 method. Sociodemographic data, respiratory symptoms and smoking habit data was analyzed based on the ATS 1987 questionnaire.

RESULTS: The mean concentration for Pb in welding fumes was 2.752 mg m-3 which is above 0.5 mg m-3 PEL-TWA. The FEV1 and FVC readings showed significant different between welders and non-welders ($p = 0.001$). Cough and phlegm symptoms showed significant different between welders and non-welders ($p = 0.001$). Welders had higher prevalence in smoking habit than the non-welders. Chest illnesses symptom showed an association with the smoking habit ($p = 0.01$).

CONCLUSION: There is relationship between welding fumes exposure on lung function test of workers in Lumut shipyard. Pb in welding fumes has high concentration and exceeded PEL-TWA level. The FEV1 and FVC in welders are lower than non-welder due to the fumes exposure. Welders showed higher respiratory symptoms than non-welders. Smoking habit is a contributing factor towards respiratory problem.

The effects of High- versus Moderate-Intensity Exercise on Fatigue in Sarcoidosis.

Grongstad A[1,2], Vøllestad NK[3], Oldervoll LM[4,5], Spruit MA[6,7,8], Edvardsen A[9].

J Clin Med. **2019 Apr 5**;8(4). pii: E460. doi: 10.3390/jcm8040460. PMID: 30959786.

BACKGROUND: Fatigue is a common symptom in patients with sarcoidosis. Despite lacking evidence on whether high-intensity interval training (HIIT) will aggravate fatigue, moderate-intensity exercise is often recommended. This study aimed to investigate whether a single session of HIIT would affect fatigue differently from a single session of moderate-intensity continuous training (MICT).

METHODS: Forty-one patients with pulmonary sarcoidosis were recruited to a cross-over study. All patients completed one treadmill session of HIIT (85% of peak heart rate (HRpeak)) and one of MICT (70% of HRpeak). Fatigue was assessed with the Visual Analogue Scale $0^{-}100$ mm, before (T0), after (T1), and 24 hours after (T2) each exercise session. Paired sample t-test was used to compare changes in fatigue from T0 to T1 and from T0 to T2 between HIIT and MICT.

RESULTS: No statistically significant difference in fatigue levels was found between HIIT and MICT, either at T1 (3.6 (13.5) and 1.4 (13.5)) or at T2 (8.2 (17.0) and 2.1 (17.1)).

CONCLUSIONS: A single session of HIIT did not affect fatigue differently than a single session of MICT. These preliminary findings support the need for further research on the long-term effect of HIIT on fatigue in patients with sarcoidosis.

OTHER RESEARCH OF INTEREST (Continued)

A randomised crossover trial comparing Thai and Swedish massage for fatigue and depleted energy.

MacSween A[1], Lorrimer S[2], van Schaik P[3], Holmes M[4], van Wersch A[3].

J Bodyw Mov Ther. **2018 Jul**;22(3):817-828. doi: 10.1016/j.jbmt.2017.09.014. PMID: 30100318. Epub 2017 Sep 23.

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

BACKGROUND: The aim of this study was to compare the efficacy and social constructions of Thai massage (TM) and Swedish massage (SM) for patients experiencing fatigue or depleted energy.

METHOD: Twenty participants were randomised to receive three once-weekly TM treatments and three once-weekly SM treatments, with crossover after three massages. Symptom checklists were administered at three time points and included Activation-Deactivation Adjective Check List and VAS Scale. Qualitative data were collected through semi-structured interviews and participants' diary entries.

RESULTS: Both massage types enhanced physical, emotional and mental wellbeing through improved sleep, relaxation, relief of stress and relief of muscular tension. TM alone showed specific energising and psychological stimulation results, along with carry-over effect and longer lasting benefits. Ninety-five percent of participants found relief from their initial reason presenting symptoms.

CONCLUSION: TM or SM can relieve symptoms of fatigue or low energy by releasing stress, promoting relaxation, relieving muscular aches and pains and improving energy. SM results in a larger effect in relaxation and improved sleep whereas TM results in a larger effect in energising, rejuvenating and mentally stimulating effects.

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