

GULF WAR ILLNESS

[Rates of Chronic Medical Conditions in 1991 Gulf War Veterans Compared to the General Population.](#)

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Int J Environ Res Public Health. **2019 Mar 16**;16(6). pii: E949. doi: 10.3390/ijerph16060949. PMID: 30884809.

Prevalence of nine chronic medical conditions in the population-based Ft. Devens Cohort (FDC) of GW veterans were compared with the population-based 2013–2014 National Health and Nutrition Examination Survey (NHANES) cohort. Excess prevalence was calculated as the difference in prevalence estimates from the Ft. Devens and NHANES cohorts; and confidence intervals and *p*-values are based on the standard errors for the two prevalence estimates. FDC males were at increased risk for reporting seven chronic medical conditions compared with NHANES males. FDC females were at decreased risk for high blood pressure and increased risk for diabetes when compared with NHANES females. FDC veterans reporting war-related chemical weapons exposure showed higher risk of high blood pressure; diabetes; arthritis and chronic bronchitis while those reporting taking anti-nerve gas pills had increased risk of heart attack and diabetes. GW veterans are at higher risk of chronic conditions than the general population and these risks are associated with self-reported toxicant exposures.

CHRONIC FATIGUE SYNDROME

[Network structure underpinning \(dys\)homeostasis in chronic fatigue syndrome: Preliminary findings.](#)

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PLoS One. **2019 Mar 25**;14(3):e0213724. doi: 10.1371/journal.pone.0213724. PMID: 30908516. eCollection 2019.

INTRODUCTION: A large body of evidence has established a pattern of altered functioning in the immune system, autonomic nervous system and hypothalamic pituitary adrenal axis in chronic fatigue syndrome. However, the relationship between components within and between these systems is unclear. In this paper we investigated the underlying network structure of the autonomic system in patients and controls, and a larger network comprising all three systems in patients alone.

METHODS: In a sample of patients and controls we took several measures of autonomic nervous system output during 10 minutes of supine rest covering tests of blood pressure variability, heart rate variability and cardiac output. Awakening salivary cortisol was measured on each of two days with participants receiving 0.5mg dexamethasone during the afternoon of the first day. Basal plasma cytokine levels and the in vitro cytokine response to dexamethasone were also measured. Symptom outcome measures used were the fatigue impact scale and cognitive failures questionnaire. Mutual information criteria were used to construct networks describing the dependency amongst variables. Data from 42 patients and 9 controls were used in constructing autonomic networks, and 15 patients in constructing the combined network.

RESULTS: The autonomic network in patients showed a more uneven distribution of information, with two distinct modules emerging dominated by systolic blood pressure during active stand and end diastolic volume and stroke volume respectively. The combined network revealed strong links between elements of each of the three regulatory systems, characterised by three higher modules the centres of which were systolic blood pressure during active stand, stroke volume and ejection fraction respectively.

CONCLUSIONS: CFS is a complex condition affecting physiological systems. It is important that novel analytical techniques are used to understand the abnormalities that lead to CFS. The underlying network structure of the autonomic system is significantly different to that of controls, with a small number of individual nodes being highly influential. The combined network suggests links across regulatory systems which shows how alterations in single nodes might spread throughout the network to produce alterations in other, even distant, nodes. Replication in a larger cohort is warranted.

CHRONIC FATIGUE SYNDROME (Continued)

[Whole blood human transcriptome and virome analysis of ME/CFS patients experiencing post-exertional malaise following cardiopulmonary exercise testing.](#)

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PLoS One. **2019 Mar 21**;14(3):e0212193. doi: 10.1371/journal.pone.0212193. PMID: 30897114. eCollection 2019.

Myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) is a syndrome of unknown etiology characterized by profound fatigue exacerbated by physical activity, also known as post-exertional malaise (PEM). Previously, we did not detect evidence of immune dysregulation or virus reactivation outside of PEM periods. Here we sought to determine whether cardiopulmonary exercise stress testing of ME/CFS patients could trigger such changes. ME/CFS patients (n = 14) and matched sedentary controls (n = 11) were subjected to cardiopulmonary exercise on 2 consecutive days and followed up to 7 days post-exercise, and longitudinal whole blood samples analyzed by RNA-seq. Although ME/CFS patients showed significant worsening of symptoms following exercise versus controls, with 8 of 14 ME/CFS patients showing reduced oxygen consumption ([Formula: see text]) on day 2, transcriptome analysis yielded only 6 differentially expressed gene (DEG) candidates when comparing ME/CFS patients to controls across all time points. None of the DEGs were related to immune signaling, and no DEGs were found in ME/CFS patients before and after exercise. Virome composition (P = 0.746 by chi-square test) and number of viral reads (P = 0.098 by paired t-test) were not significantly associated with PEM. These observations do not support transcriptionally-mediated immune cell dysregulation or viral reactivation in ME/CFS patients during symptomatic PEM episodes.

[Decreased Expression of the CD57 Molecule in T Lymphocytes of Patients with Chronic Fatigue Syndrome.](#)

[Espinosa P](#)¹, [Urria JM](#)^{2,3}.

Mol Neurobiol. **2019 Mar 21**. doi: 10.1007/s12035-019-1549-7. PMID: 30895436. [Epub ahead of print]

The chronic fatigue syndrome (CFS) is characterized by a prolonged incapacitating fatigue, headaches, sleep disturbances, and decreases in cognition, besides alterations in other physiological functions. At present, no specific biological markers have been described in this pathology. In the present study, we analyzed in lymphocytes the CD57 expression for the diagnosis of CFS, evaluating both the percentage of blood lymphocytes expressing CD57 and the average amount of the molecule expressed per cell. The study demonstrated a marked and significant decrease in the expression of CD57 in lymphocytes of CFS patients regarding healthy controls. In T lymphocytes, the decrease was significant both in the percentage of cells expressing CD57 (7.5 ± 1.2 vs 13.3 ± 1.6 , $p = 0.024$) and in a more relevant way in the amount of CD57 molecule expressed per cell (331 ± 59 vs 1003 ± 104 , $p \leq 0.0001$). In non-T lymphocytes, the decrease was significant only in the amount of CD57 expressed per cell (379 ± 114 vs 691 ± 95 , $p = 0.007$). The study of CD57 antigen in blood lymphocytes is a useful marker that could cooperate in the diagnosis of CFS patients. Its decrease in T lymphocytes provides most valuable results than the results in other lymphocyte subpopulations.

[Acceptance and identity change: An interpretative phenomenological analysis of carers' experiences in myalgic encephalopathy/chronic fatigue syndrome.](#)

[Catchpole S](#)¹, [Garip G](#)¹.

J Health Psychol. **2019 Mar 21**:1359105319834678. doi: 10.1177/1359105319834678. PMID: 30895822. [Epub ahead of print]

Myalgic encephalopathy/chronic fatigue syndrome is a debilitating condition and many people rely heavily on family carers. This study explored the caring experiences of seven family carers. Four themes were established: relations with others, role and identity changes, coping with change and uncertainty, and information and support seeking. Caring disrupted multiple areas of carers' lives, including their identities and relationships. Scepticism from others about myalgic encephalopathy/chronic fatigue syndrome was particularly distressing. Acceptance was important for coping and helped some carers achieve positive growth within spousal relationships. Improving support and advice for carers and acknowledging their caring burden could improve their well-being.

CHRONIC FATIGUE SYNDROME (Continued)

[Impact of Polypharmacy on Candidate Biomarker miRNomes for the Diagnosis of Fibromyalgia and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Striking Back on Treatments.](#)

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Pharmaceutics. **2019 Mar 18**;11(3). pii: E126. doi: 10.3390/pharmaceutics11030126. PMID: 30889846.

Fibromyalgia (FM) and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) are diseases of unknown etiology presenting complex and often overlapping symptomatology. Despite promising advances on the study of miRNomes of these diseases, no validated molecular diagnostic biomarker yet exists. Since FM and ME/CFS patient treatments commonly include polypharmacy, it is of concern that biomarker miRNAs are masked by drug interactions. Aiming at discriminating between drug-effects and true disease-associated differential miRNA expression, we evaluated the potential impact of commonly prescribed drugs on disease miRNomes, as reported by the literature. By using the web search tools SM2miR, Pharmaco-miR, and repoDB, we found a list of commonly prescribed drugs that impact FM and ME/CFS miRNomes and therefore could be interfering in the process of biomarker discovery. On another end, disease-associated miRNomes may incline a patient's response to treatment and toxicity. Here, we explored treatments for diseases in general that could be affected by FM and ME/CFS miRNomes, finding a long list of them, including treatments for lymphoma, a type of cancer affecting ME/CFS patients at a higher rate than healthy population. We conclude that FM and ME/CFS miRNomes could help refine pharmacogenomic/pharmacoepigenomic analysis to elevate future personalized medicine and precision medicine programs in the clinic.

HEADACHE and MIGRAINE

[Negative Short-Term Outcome of Detoxification Therapy in Chronic Migraine With Medication Overuse Headache: Role for Early Life Traumatic Experiences and Recent Stressful Events.](#)

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Front Neurol. **2019 Mar 7**;10:173. doi: 10.3389/fneur.2019.00173. PMCID: PMC6416203. PMID: 30899242. eCollection 2019.

Background: Early traumatic experiences and Stressful episodes appear to be associated to the development and perpetuation of chronic pain disorders and to dependence-related behaviors.

Objective: The present study evaluated whether these factors can be predictors, together with psychiatric conditions, of the outcome of a detoxification treatment in patients suffering from chronic migraine and medication-overuse headache in a 2-month follow-up.

Methods: Consecutive patients undergoing a detoxification program as therapy for treating chronic migraine and medication overuse headache at the Pavia Headache Center were analyzed. During this program, lasting about 1 week, all patients received the standard CARE in-patient withdrawal protocol, which consisted in discontinuing abruptly the overused drug(s) and receiving daily detoxification therapy. Data on childhood traumatic events and recent stressful ones were analyzed by means of the Childhood Trauma Questionnaire and Stressful life-events Questionnaire. Psychiatric conditions were evaluated using the Structured Clinical Interview for Diagnostic and Statistical Manual of mental disorders.

Results: A total of 166 (80% females; mean age 44.7) patients completed the follow-up at 2 months after the detoxification program: of these 118 (71%) (78% females; mean age 44.7) stopped overuse and reverted to an episodic pattern of headache (Group A); 19 (11%) (89% females; mean age 41.3) kept overusing and maintained a chronic pattern of headache (Group B); and 29 (18%) (79% females; mean age 46.9) stopped overuse without any benefit on headache frequency (Group C). At the multivariate analyses, a higher number of early life emotional distress (Odds Ratio 11.096; $p = 0.037$) arose as a prognostic factor for the outcome in Group B, while major depression during life-time (Odds Ratio 3.703; $p = 0.006$) and higher number of severe stressful episodes in the past 10 years (Odds Ratio 1.679; $p = 0.045$) were prognostic factors for the outcome of Group C.

Conclusions: Data suggest that early life traumas and stressful events have a negative impact on the outcome of the detoxification program in subjects overusing acute medication for headache. The history of emotional childhood traumas is associated to the failure to cease overuse, whereas recent very serious life events are associated to the persistence of headache chronicity.

HEADACHE and MIGRAINE (Continued)

[The Effectiveness of Acupuncture Combined with Tuina Therapy in Patients with Migraine.](#)

Nie L, Cheng J, Wen Y, Li J.

Complement Med Res. **2019 Mar 14**:1-13. doi: 10.1159/000496032. PMID: 30893677. [Epub ahead of print].

BACKGROUND: This study aimed to explore the effectiveness of acupuncture combined with tuina therapy in patients with migraine.

METHODS: A prospective, randomized controlled assessor-blind clinical trial was performed between January 2017 and May 2018, and 135 patients were assigned into acupuncture combined with tuina (A), acupuncture (B), and control (flunarizine hydrochloride) (C) groups, each with 45 patients. Treatments were performed for 12 weeks and a 4-week follow-up. Frequency of attacks, severity of pain, duration of migraine, associated symptoms, patient-reported outcome (PRO) scores, and frequency of analgesic consumption were assessed.

RESULTS: The total effective rate was 95.6, 88.9, and 75.6% for group A, B, and C, respectively, with a significant reduction in attack frequency, severity of pain, duration of migraine, and associated symptoms at post-treatment and follow-up compared to pre-treatment. The PRO scores and frequency of analgesic consumption were significantly improved (group A, $p < 0.01$; groups B and C, $p < 0.05$). The differences in pre-/post-treatment and in pre-treatment/follow-up in groups A and B were significantly improved compared to group C (A vs. C, $p < 0.01$; B vs. C, A vs. B, $p < 0.05$). No significant adverse events occurred.

CONCLUSION: Acupuncture combined with tuina could significantly increase the therapeutic effect of acupuncture in migraine treatment.

[Neurological manifestations and neuroimaging presentations in patients with severe preeclampsia: predisposing factors and clinical implications.](#)

Dong X¹, Nao J².

Neurol Sci. **2019 Mar 19**. doi: 10.1007/s10072-019-03833-3. [Epub ahead of print]

BACKGROUND AND PURPOSE: Neurological manifestations and neuroimaging abnormalities are common in patients with severe preeclampsia; however, the differences between these abnormal features occurring during early- and late-onset severe preeclampsia are unclear, and the factors associated with abnormal imaging changes in patients with neurological manifestations have not yet been fully elucidated.

MATERIALS AND METHODS: A retrospective study was conducted on 172 patients with severe preeclampsia from January 2017 to June 2018 in the Department of Neurology and Obstetrics, Shengjing Hospital of China Medical University. The neurological manifestations, clinical parameters, laboratory, and neuroimaging findings were analyzed.

RESULTS: Early- and late-onset preeclampsia were diagnosed in 83 and 89 patients, respectively. Headache and dizziness were more common in patients with early-onset preeclampsia than in patients with late-onset preeclampsia ($p = 0.013$, $p = 0.004$, respectively). Serum uric acid, creatinine, and urea nitrogen were significantly elevated in the patients with early-onset preeclampsia ($p < 0.001$, $p = 0.004$, and $p = 0.005$, respectively). Neuroimaging was performed in 81 patients, of which 57 were positive. Findings indicating cerebral edema were the most common neuroimaging abnormality. Gestational weeks ($p = 0.014$), headache ($p < 0.001$), and blood urea nitrogen level ($p = 0.027$) may be associated with positive imaging findings. By multiple logistic regression, headache (OR = 10.2, 95% CI, 2.4-42.7; $p = 0.002$) proved to be an independent factor associated with neuroimaging abnormality.

CONCLUSIONS: Neurological symptoms such as headache and dizziness were more common in patients with early-onset preeclampsia. Renal dysfunction may also associate with early-onset severe preeclampsia. Cerebral edema was the most common neuroimaging abnormality, and headache might be independently associated with abnormal imaging changes.

HEADACHE and MIGRAINE (Continued)

[Comparison of two ultrasound-guided techniques for greater occipital nerve injections in chronic migraine: a double-blind, randomized, controlled trial.](#)

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Reg Anesth Pain Med. **2019 Mar 18**. pii: rapm-2018-100306. doi: 10.1136/rapm-2018-100306. [Epub ahead of print]

BACKGROUND AND OBJECTIVES: Two ultrasound (US)-guided techniques for greater occipital nerve (GON) block have been described for the management of headache disorders: a "proximal or central" technique targeting the GON at the level of the second cervical vertebra and a "distal or peripheral" technique targeting the GON at the level of the superior nuchal line. In this multicenter, prospective, randomized control trial, we compared accuracy, effectiveness, and safety of these two techniques in patients with chronic migraines (CMs).

METHODS: Forty patients with refractory CMs were randomized to receive either a proximal or distal US-guided GON block with bupivacaine and methylprednisolone acetate. The primary outcome was the difference in Numerical Rating Score (NRS) for headache intensity at 1 month. Secondary outcomes were effectiveness, performance, and safety-related. Effectiveness-related outcomes included NRS for headache intensity, number of headache days per week, patient satisfaction, quality of life, assessment of sleep quality, and sleep interruption. Performance-related outcomes included procedure time, accuracy of block, and patient discomfort. Safety-related outcomes included an assessment for adverse effects.

RESULTS: NRS pain scores were significantly reduced at 24 hours and at 1 week postprocedure in both cohorts and at 1 and 3 months in the proximal group as compared with the baseline. There was no significant difference in NRS pain scores between the two cohorts at any of the follow-up time points. There was a significant reduction in number of headache days per week at 1 month in both groups, and a significant improvement in sleep interruption at 1 week in both groups. There were no significant adverse effects.

CONCLUSIONS: This study was designed to compare two different US-guided approaches for blocking the GON. Our results demonstrate that both distal and proximal techniques can provide a short-term improvement in headache intensity, reduction in number of headache days per week, and an improvement in sleep interruption. The proximal GON technique may confer more sustained analgesic benefit compared with the distal approach in patients with CM headaches.

TRIAL REGISTRATION NUMBER: [NCT02031822](#).

[The association between migraine and restless legs syndrome: an updated systematic review and meta-analysis.](#)

[Wang J](#)¹, [Gao Y](#)², [Liu L](#)³, [Xu W](#)⁴, [Zhang P](#)⁵, [Liu Y](#)⁵, [Qian X](#)⁶, [Yu S](#)⁷.

Sleep Med. **2019 Feb 2**;57:21-29. doi: 10.1016/j.sleep.2019.01.027. PMID: 30897452. [Epub ahead of print]

OBJECTIVE: This study aims to gain further insight into the association between migraine and restless legs syndrome (RLS).

METHODS: A literature search of PubMed, Embase, and Web of Science was performed for studies investigating the association between any migraine and RLS; a meta-analysis of eligible studies was conducted to determine a pooled effect estimate for the association.

RESULTS: Fifteen studies were included in this meta-analysis. The studies differed in methodology, but all investigated the association between migraine and RLS. Pooled RLS prevalence was 17.0% [95% confidence interval (CI) 15.0%-20.0%] among migraineurs, and 7.0% (95% CI 5.0%-8.0%) among no migraine individuals. Pooled analyses showed that migraine was associated with RLS, but effect estimates were substantially higher in case-control studies [pooled odds ratio (OR) = 3.77, 95% CI 2.73-5.21; $I^2 = 50.1%$] than in cross-sectional studies (pooled OR = 1.25, 95% CI 1.11-1.41; $I^2 = 34.2%$). Subgroup analyses were not conducted to find potential factors that affect this association because of too few available studies.

CONCLUSIONS: This updated meta-analysis confirms the association between migraine and RLS. Future studies should specifically investigate the potential effects of gender, age, aura status, and type (episodic or chronic) of migraine on the association between the two disorders.

CHRONIC PAIN

[Changes in pain intensity after discontinuation of long-term opioid therapy for chronic noncancer pain.](#)

[McPherson S](#)^{1,2,3}, [Lederhos Smith C](#)^{1,2}, [Dobscha SK](#)^{4,5}, [Morasco BJ](#)^{4,5}, [Demidenko MI](#)⁴, [Meath THA](#)^{4,6}, [Lovejoy T](#)^{4,5,7}. *Pain*. 2018 Oct;159(10):2097-2104. doi: 10.1097/j.pain.0000000000001315. PMID: 29905648.

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

Little is known about changes in pain intensity that may occur after discontinuation of long-term opioid therapy (LTOT). The objective of this study was to characterize pain intensity after opioid discontinuation over 12 months. This retrospective U.S. Department of Veterans Affairs (VA) administrative data study identified N = 551 patients nationally who discontinued LTOT. Data over 24 months (12 months before and after discontinuation) were abstracted from VA administrative records. Random-effects regression analyses examined changes in 0 to 10 pain numeric rating scale scores over time, whereas growth mixture models delineated pain trajectory subgroups. Mean estimated pain at the time of opioid discontinuation was 4.9. Changes in pain after discontinuation were characterized by slight but statistically nonsignificant declines in pain intensity over 12 months after discontinuation (B = -0.20, P = 0.14). Follow-up growth mixture models identified 4 pain trajectory classes characterized by the following postdiscontinuation pain levels: no pain (average pain at discontinuation = 0.37), mild clinically significant pain (average pain = 3.90), moderate clinically significant pain (average pain = 6.33), and severe clinically significant pain (average pain = 8.23). Similar to the overall sample, pain trajectories in each of the 4 classes were characterized by slight reductions in pain over time, with patients in the mild and moderate pain trajectory categories experiencing the greatest pain reductions after discontinuation (B = -0.11, P = 0.05 and B = -0.11, P = 0.04, respectively). Pain intensity after discontinuation of LTOT does not, on average, worsen for patients and may slightly improve, particularly for patients with mild-to-moderate pain at the time of discontinuation. Clinicians should consider these findings when discussing risks of opioid therapy and potential benefits of opioid taper with patients.

[Evaluation of a multisite telehealth group model for persistent pain management for rural/remote participants.](#)

[Scriven H](#)¹, [Doherty DP](#)², [Ward EC](#)³.

Rural Remote Health. 2019 Mar;19(1):4710. doi: 10.22605/RRH4710. Epub 2019 Mar 19. PMID: 30884951.

INTRODUCTION: Individuals living in rural/remote areas have recognised barriers to specialist services for persistent pain management. Although there is current evidence to support the use of telehealth to deliver individual pain management support, there is minimal evidence to support the use of pain management programs delivered within a group model, using telehealth. The aim of the present research was to perform a formative evaluation of a persistent pain management program implemented using a multisite telehealth group model, and to examine consumer perceptions.

METHODS: The Manage Your Pain multisite telehealth group program was developed as a modified hub-and-spoke model. The model allowed participants from multiple rural/remote 'spoke' sites in Queensland, Australia to access four 2-hour specialist persistent pain management sessions from a metropolitan interdisciplinary persistent pain management centre ('hub' site, 491-1009 km from spoke sites), and simultaneously enable real-time access/interactions between participants at each of the spoke sites. Twenty-one individuals living with persistent pain participated in one of five multisite telehealth groups over the 10-month period. All participants completed standard pain scales before and after the pain management program, including Chronic Pain Acceptance Questionnaire 20 (CPAQ20), Brief Pain Inventory (BPI), Depression Anxiety Stress Scale (DASS 21), Pain Self Efficacy Questionnaire (PSEQ) and the Participant Reported Outcomes Measurement Information System PROMIS. The Patient Impression of Change Scale (PICS), a telehealth perceptions survey, and a semi-structured telephone interview were completed post-program.

RESULTS: Results revealed significant (p<0.05) improvements in the activity subscale and total score of the CPAQ, with 6 (30%) showing reliable improvement (90% confidence interval), indicating higher levels of activity engagement and pain acceptance after the program. Four (19%) participants made reliable improvement on the BPI interference. Post-program, the PICS revealed 65% of participants reported improvements in overall function, 61% indicated improved mood, 57% reported improved physical activity and 50% had some improvement in pain. Post-program, less than 10% of participants reported having technical (audio, visual) issues that had impacted on their sessions, and more than 90% found telehealth to be comfortable, convenient and would consider using it for their healthcare in the future. Post-program, most participants felt they had connected and were in a shared health experience with other group members through the multisite telehealth model. The interviews revealed three main themes: 'group experiences', which involved comments relating to the dynamics of the group and the shared experience; 'telehealth accessibility', which pertained to perceptions of the telehealth model for accessing specialist services; and 'limitations and concerns', where participants spoke of possible improvements to the program delivery model.

CONCLUSIONS: Results confirmed that participants received benefit from the pain management program and that they had positive perceptions of receiving the service using a telehealth model. The present findings provide positive data to support using telehealth to deliver specialist persistent pain management for individuals who face accessibility issues in rural and remote communities. The model also demonstrated that positive elements of group treatment can be achieved through telehealth group models.

CHRONIC PAIN (Continued)

[Association of Catechol-O-methyltransferase single nucleotide polymorphisms, ethnicity, and sex in a large cohort of fibromyalgia patients.](#)

[Lee C](#)¹, [Liptan G](#)², [Kantorovich S](#)¹, [Sharma M](#)³, [Brenton A](#)⁴.

BMC Rheumatol. 2018 Dec 12;2:38. doi: 10.1186/s41927-018-0045-4. PMCID: PMC6390547. PMID: 30886988. eCollection 2018.

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

Background: Fibromyalgia (FM) is a complex, centralized pain condition that is often difficult to diagnose and treat. FM is considered to have a genetic background due to its familial aggregation and due to findings from multiple candidate-gene studies implicating catecholaminergic and serotonergic neurotransmitter systems in chronic pain. However, a multi-factorial analysis of both genetic and environmental risk factors is lacking. A better characterization of the interplay of risk factors may assist in understanding the pathophysiology of FM, its clinical course, and assist in early diagnosis and treatment of the disorder.

Methods: This retrospective study included 60,367 total participants from 237 clinics across the USA. Of those, 2713 had been diagnosed with fibromyalgia, as indicated by ICD code. Logistic regression was used to test for associations of diagnosed FM in study subjects with *COMT* SNPs and *COMT* haplotypes, which were previously found to be linked with pain sensitivity, as well as demographics such as age, sex, and ethnicity. The minor allele frequencies of *COMT* SNPs in the FM population were compared with 1000 Genomes data using a χ^2 test to determine significant deviations from the estimated population allelic frequencies.

Results: FM diagnosis was strongly associated with sex, age, and ethnicity. Females, those between 49 and 63 years, and non-Caucasians were at higher risk of FM. Females had 1.72 increased odds of FM ($p = 1.17 \times 10^{-30}$). African-Americans were 1.52 times more likely to have a diagnosis of FM compared to Caucasians ($p = 3.11 \times 10^{-12}$). Hispanics were less likely to have a diagnosis of FM compared to Caucasians ($p = 3.95 \times 10^{-7}$). After adjusting for sex and ethnicity, those in the low age group and mid age group had 1.29 ($p = 1.02 \times 10^{-5}$) and 1.60 ($p = 1.93 \times 10^{-18}$) increased odds of FM, respectively, compared to the high age group, where age was categorized by tertile (low (<49), mid (49-63), and high (>63)). The *COMT* haplotypes associated with pain sensitivity were not associated with FM, but African-Americans were 11.3 times more likely to have a high pain sensitivity *COMT* diplotype, regardless of FM diagnosis. However, the minor alleles of *COMT* SNPs *rs4680*, *rs4818*, *rs4633* and *rs6269* were overrepresented in the FM population overall, and varied when compared with ethnically-similar populations from 1000 Genomes.

Conclusions: This is the largest study, to date, that examines demographic and genetic associations of FM in a diverse population. While pain sensitivity-associated *COMT* haplotypes were not found to be directly associated with FM diagnosis, the minor alleles that make up the *COMT* haplotypes were overrepresented in the FM population, suggesting a role of *COMT* in FM. Future studies are needed to elucidate the exact role of *COMT* variation in widespread pain conditions, such as FM. Clinically, this information can be used to provide insight into the pathways underlying FM and to identify those at greater risk of developing FM.

[Gender Differences in the Prevalence of Chronic Pain and Leisure Time Physical Activity Among US Adults: A NHANES Study.](#)

[Umeda M](#)¹, [Kim Y](#)².

Int J Environ Res Public Health. 2019 Mar 19;16(6). pii: E988. doi: 10.3390/ijerph16060988. PMID: 30893869.

Gender disparities in chronic pain are well documented in the literature. However, little is known regarding the relationship between physical activity (PA) and gender disparities in chronic pain. This study described gender differences in prevalence of chronic pain and PA, and identified a type of leisure time PA that individuals frequently chose in a nationally representative sample of US adults ($N = 14,449$). Data from the National Health Nutrition Examination Survey 1999-2004 were analyzed. Individuals were categorized into no chronic pain (NCP), localized chronic pain (LCP), and widespread chronic pain (WCP) groups based on responses to a pain questionnaire. A self-report PA questionnaire was used to estimate the time spent in different types of PA. Women showed higher prevalence of LCP and WCP compared to men. Men spent more hours per week for leisure time PA compared to women, but men and women showed similar prevalence of sufficient PA to meet a PA recommendation (≥ 150 min/week of moderate-to-vigorous intensity PA) across chronic pain categories. However, the prevalence of sufficient PA was substantially higher among men and women with NCP compared to men and women with LCP and WCP. Additionally, both men and women chose walking as the primary type of leisure time PA. Together, gender disparities exist in the prevalence of chronic pain and hours spent for leisure time PA. More research is needed to explore the role of increasing leisure time PA, such as walking, in reducing gender disparities in chronic pain.

CHRONIC PAIN (Continued)

[Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies.](#)

[Stockings E](#)¹, [Campbell G](#)¹, [Hall WD](#)^{2,3}, [Nielsen S](#)¹, [Zagic D](#)¹, [Rahman R](#)¹, [Murnion B](#)^{4,5}, [Farrell M](#)¹, [Weier M](#)¹, [Degenhardt L](#)¹.

Pain. **2018 Oct**;159(10):1932-1954. doi: 10.1097/j.pain.0000000000001293. PMID: 29847469.

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

This review examines evidence for the effectiveness of cannabinoids in chronic noncancer pain (CNCP) and addresses gaps in the literature by: considering differences in outcomes based on cannabinoid type and specific CNCP condition; including all study designs; and following IMMPACT guidelines. MEDLINE, Embase, PsycINFO, CENTRAL, and clinicaltrials.gov were searched in July 2017. Analyses were conducted using Revman 5.3 and Stata 15.0. A total of 91 publications containing 104 studies were eligible (n = 9958 participants), including 47 randomised controlled trials (RCTs) and 57 observational studies. Forty-eight studies examined neuropathic pain, 7 studies examined fibromyalgia, 1 rheumatoid arthritis, and 48 other CNCP (13 multiple sclerosis-related pain, 6 visceral pain, and 29 samples with mixed or undefined CNCP). Across RCTs, pooled event rates (PERs) for 30% reduction in pain were 29.0% (cannabinoids) vs 25.9% (placebo); significant effect for cannabinoids was found; number needed to treat to benefit was 24 (95% confidence interval [CI] 15-61); for 50% reduction in pain, PERs were 18.2% vs 14.4%; no significant difference was observed. Pooled change in pain intensity (standardised mean difference: -0.14, 95% CI -0.20 to -0.08) was equivalent to a 3 mm reduction on a 100 mm visual analogue scale greater than placebo groups. In RCTs, PERs for all-cause adverse events were 81.2% vs 66.2%; number needed to treat to harm: 6 (95% CI 5-8). There were no significant impacts on physical or emotional functioning, and low-quality evidence of improved sleep and patient global impression of change. Evidence for effectiveness of cannabinoids in CNCP is limited. Effects suggest that number needed to treat to benefit is high, and number needed to treat to harm is low, with limited impact on other domains. It seems unlikely that cannabinoids are highly effective medicines for CNCP.

[Pain-related functional interference in patients with chronic neuropathic postsurgical pain: an analysis of registry data.](#)

[Stamer UM](#)^{1,2}, [Ehrler M](#)¹, [Lehmann T](#)³, [Meissner W](#)⁴, [Fletcher D](#)⁵.

Pain. **2019 Mar 21**. doi: 10.1097/j.pain.0000000000001560. PMID: 30908358. [Epub ahead of print]

Although chronic postsurgical pain (CPSP) is a major health care problem, pain-related functional interference has rarely been investigated. Using the PAIN OUT registry we evaluated patients' pain-related outcomes on the first postoperative day, and their pain-related interference with daily living (Brief Pain Inventory) and neuropathic symptoms (DN4: douleur neuropathique en 4 questions) at six months after surgery. Endpoints were pain interference total scores (PITS) and their association with pain and DN4 scores. Furthermore, possible risk factors associated with impaired function at M6 were analyzed by ordinal regression analysis with PITS groups (no to mild, moderate and severe interference) as a dependent three-stage factor. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. Of 2,322 patients, 15.3% reported CPSP with an average pain score ≥ 3 (NRS 0-10). Risk for a higher PITS group increased by 190% (OR (95%-CI): 2.9 (2.7-3.2); $p < 0.001$) in patients with, compared to without CPSP. A positive DN4 independently increased risk by 29% (1.3 (1.12-1.45), $p < 0.001$). Pre-existing chronic pain (3.6 (2.6-5.1); $p < 0.001$), time spent in severe acute pain (2.9 (1.3-6.4); $p = 0.008$), neurosurgical back surgery in males (3.6 (1.7-7.6); $p < 0.001$) and orthopedic surgery in females (1.7 (1.0-3.0); $p = 0.036$) were the variables with strongest association with PITS. PITS might provide more precise information about patients' outcomes than pain scores only. As neuropathic symptoms increase PITS, a suitable instrument for their routine assessment should be defined.

CHRONIC PAIN (Continued)

[The Effect of Patient Characteristics on Acupuncture Treatment Outcomes: An Individual Patient Data Meta-Analysis of 20,827 Chronic Pain Patients in Randomized Controlled Trials.](#)

[Witt CM](#)^{1,2,3}, [Vertosick EA](#)⁴, [Foster NE](#)⁵, [Lewith G](#), [Linde K](#)⁶, [MacPherson H](#)⁷, [Sherman KJ](#)⁸, [Vickers AJ](#)⁴; [Acupuncture Trialists' Collaboration](#).

Clin J Pain. 2019 Mar 22. doi: 10.1097/AJP.0000000000000691. PMID: 30908336. [Epub ahead of print]

OBJECTIVES: To optimally select chronic pain patients for different treatments, as it is of interest to identify patient characteristics that might moderate treatment effect. Our aim was to evaluate the impact of possible moderators on the effect of acupuncture treatment using a large data set.

METHODS: We used data from an individual patient data meta-analysis of high-quality randomized trials of acupuncture for chronic headache and migraine, osteoarthritis, and back, neck, and shoulder pain. Using meta-analytic trial-level and patient-level regression analyses, we explored the impact of 5 documented patient characteristics (patients' age at baseline, sex, pain duration, baseline pain severity and baseline psychological distress) on the effect of acupuncture.

RESULTS: A total of 39 trials met the inclusion criteria: 25 use sham-acupuncture controls (n=7097) and 25 non-acupuncture controls (n=16,041). Of the 5 patient characteristics analyzed, only baseline pain severity was found to potentially moderate the treatment effect of acupuncture, with patients reporting more severe pain at baseline experiencing more benefit from acupuncture compared to either sham-control or non-acupuncture control. Baseline psychological distress showed small treatment moderating effects, and results for sex were inconsistent. There was no strong evidence that age or duration of pain influenced the response to acupuncture.

DISCUSSION: Of 5 patient characteristics tested, we found only baseline severity of pain to potentially moderate the effect of acupuncture treatment. For clinical practice, the evidence from this analysis does not justify stratifying chronic pain patients into subgroups that should or should not receive acupuncture on the basis of these 5 characteristics. Future acupuncture trials should assess other potentially important effect moderators.

[A Long Noncoding RNA \(lncRNA\)-Associated Competing Endogenous RNA \(ceRNA\) Network Identifies Eight lncRNA Biomarkers in Patients with Osteoarthritis of the Knee.](#)

[Chen Y](#)¹, [Lin Y](#)², [Bai Y](#)^{1,3}, [Cheng D](#)¹, [Bi Z](#)¹.

Med Sci Monit. 2019 Mar 20;25:2058-2065. doi: 10.12659/MSM.915555.

BACKGROUND Osteoarthritis (OA) of the knee is a common disease that is associated with chronic pain. This study aimed to identify and investigate the functional role of biomarkers associated with long noncoding RNA (lncRNA) in the progression of OA of the knee by lncRNA-associated competing endogenous RNA (ceRNA) integrated network analysis.

MATERIAL AND METHODS High-quality microRNA (miRNA)-lncRNA and miRNA-mRNA interactions and lncRNA and mRNA expression profiles for patients with OA of the knee with mild and severe pain were obtained from the Gene Expression Omnibus (GEO) database (GSE99662). A three-step computational method was used to construct the lncRNA-associated ceRNA interaction network in OA by integrating miRNA-lncRNA/mRNA interactions and lncRNA/mRNA expression profiles in patients with OA with mild and severe pain.

RESULTS A total of 1,870 dysregulated lncRNA-mRNA interactions were obtained in the lncRNA-associated ceRNA network in OA, including 476 gain and 1,394 loss interactions, covering 131 lncRNAs and 1,251 mRNAs. Characterization of the lncRNA-associated ceRNA network in OA indicated that lncRNAs had roles in the network. Further differential expression analysis identified eight lncRNA biomarkers, which could distinguish between patients with OA with mild pain and severe pain. These lncRNA-associated interactions showed significantly different co-expression patterns in samples from patients with OA of the knee associated with mild pain.

CONCLUSIONS Integrated network analysis of lncRNA-associated ceRNA identified eight lncRNA molecular biomarkers associated with the progression of OA of the knee.

CHRONIC PAIN (Continued)

[The behavioural inhibition system, behavioural activation system and experiential avoidance as explanatory variables of comorbid chronic pain and posttraumatic stress symptoms.](#)

[Serrano-Ibáñez ER](#)¹, [Ramírez-Maestre C](#)¹, [Esteve R](#)¹, [López-Martínez AE](#)¹.

Eur J Psychotraumatol. 2019 Mar 11;10(1):1581013. doi: 10.1080/20008198.2019.1581013. PMID: PMC6419650. PMID: 30891160. eCollection 2019.

Background: The variables that underlie comorbid chronic pain and posttraumatic stress symptoms (PTSS) are not yet clearly established.

Objective: The aim of the present study was to analyse the role of the behavioural inhibition system (BIS), behavioural approach system (BAS) and experiential avoidance (EA) in pain adjustment (i.e. pain intensity, daily functioning and pain-related impairment) in patients with chronic pain and PTSS.

Methods: A battery of instruments was administered to 388 chronic pain patients. The sample was divided into those with PTSS ($n = 194$) and those without PTSS ($n = 194$).

Results: Significant differences were found between groups in the BIS, EA, impairment and daily functioning. No differences were found between groups in the BAS. Structural equation modelling showed that the BIS and EA were associated with worse adjustment in the 194 patients with both chronic pain and PTSS. The BAS was associated with a lower level of pain and greater daily functioning.

Conclusion: The findings provide evidence that BIS and BAS activation and EA play a role in adjustment to chronic pain in patients with concurrent PTSS. These results may help guide the development of psychological treatments for patients with both conditions.

[Expansion and activation of distinct central memory T lymphocyte subsets in complex regional pain syndrome.](#)

[Russo MA](#)^{1,2}, [Fiore NT](#)³, [van Vreden C](#)^{4,5}, [Bailey D](#)², [Santarelli DM](#)², [McGuire HM](#)^{4,6}, [Fazekas de St Groth B](#)^{4,6}, [Austin PJ](#)⁷.

J Neuroinflammation. 2019 Mar 18;16(1):63. doi: 10.1186/s12974-019-1449-9. PMID: 30885223.

BACKGROUND: Complex regional pain syndrome (CRPS) is a debilitating condition where trauma to a limb results in devastating persistent pain that is disproportionate to the initial injury. The pathophysiology of CRPS remains unknown; however, accumulating evidence suggests it is an immunoneurological disorder, especially in light of evidence of auto-antibodies in ~ 30% of patients. Despite this, a systematic assessment of all circulating leukocyte populations in CRPS has never been performed.

METHODS: We characterised 14 participants as meeting the Budapest clinical criteria for CRPS and assessed their pain ratings and psychological state using a series of questionnaires. Next, we performed immunophenotyping on blood samples from the 14 CRPS participants as well as 14 healthy pain-free controls using mass cytometry. Using a panel of 38 phenotypic and activation markers, we characterised the numbers and intracellular activation status of all major leukocyte populations using manual gating strategies and unsupervised cluster analysis.

RESULTS: We have shown expansion and activation of several distinct populations of central memory T lymphocytes in CRPS. The number of central memory CD8⁺ T cells was increased 2.15-fold; furthermore, this cell group had increased phosphorylation of NFκB and STAT1 compared to controls. Regarding central memory CD4⁺ T lymphocytes, the number of Th1 and Treg cells was increased 4.98-fold and 2.18-fold respectively, with increased phosphorylation of NFκB in both populations. We also found decreased numbers of CD1c⁺ myeloid dendritic cells, although with increased p38 phosphorylation. These changes could indicate dendritic cell tissue trafficking, as well as their involvement in lymphocyte activation.

CONCLUSIONS: These findings represent the first mass cytometry immunophenotyping study in any chronic pain state and provide preliminary evidence of an antigen-mediated T lymphocyte response in CRPS. In particular, the presence of increased numbers of long-lived central memory CD4⁺ and CD8⁺ T lymphocytes with increased activation of pro-inflammatory signalling pathways may indicate ongoing inflammation and cellular damage in CRPS.

CHRONIC PAIN (Continued)

[Visualizing neuroinflammation with fluorescence and luminescent lanthanide-based in situ hybridization.](#)

[Parker LM](#)¹, [Sayyadi N](#)², [Staikopoulos V](#)^{3,4}, [Shrestha A](#)², [Hutchinson MR](#)^{3,4}, [Packer NH](#)^{2,5}.

J Neuroinflammation. **2019 Mar 21**;16(1):65. doi: 10.1186/s12974-019-1451-2. PMID: 30898121.

BACKGROUND: Neurokinin signaling via the release of neurally active cytokines arises from glial reactivity and is mechanistically implicated in central nervous system (CNS) pathologies such as chronic pain, trauma, neurodegenerative diseases, and complex psychiatric illnesses. Despite significant advancements in the methodologies used to conjugate, incorporate, and visualize fluorescent molecules, imaging of rare yet high potency events within the CNS is restricted by the low signal to noise ratio experienced within the CNS. The brain and spinal cord have high cellular autofluorescence, making the imaging of critical neurokinin signaling and permissive transcriptional cellular events unreliable and difficult in many cases.

METHODS: In this manuscript, we developed a method for background-free imaging of the transcriptional events that precede neurokinin signaling using targeted mRNA transcripts labeled with luminescent lanthanide chelates and imaged via time-gated microscopy. To provide examples of the usefulness this method can offer to the field, the mRNA expression of toll-like receptor 4 (TLR4) was visualized with traditional fluorescent in situ hybridization (FISH) or luminescent lanthanide chelate-based in situ hybridization (LISH) in mouse BV2 microglia or J774 macrophage phenotype cells following lipopolysaccharide stimulation. TLR4 mRNA staining using LISH- and FISH-based methods was also visualized in fixed spinal cord tissues from BALB/c mice with a chronic constriction model of neuropathic pain or a surgical sham model in order to demonstrate the application of this new methodology in CNS tissue samples.

RESULTS: Significant increases in TLR4 mRNA expression and autofluorescence were visualized over time in mouse BV2 microglia or mouse J774 macrophage phenotype cells following lipopolysaccharide (LPS) stimulation. When imaged in a background-free environment with LISH-based detection and time-gated microscopy, increased TLR4 mRNA was observed in BV2 microglia cells 4 h following LPS stimulation, which returned to near baseline levels by 24 h. Background-free imaging of mouse spinal cord tissues with LISH-based detection and time-gated microscopy demonstrated a high degree of regional TLR4 mRNA expression in BALB/c mice with a chronic constriction model of neuropathic pain compared to the surgical sham model.

CONCLUSIONS: Advantages offered by adopting this novel methodology for visualizing neurokinin signaling with time-gated microscopy compared to traditional fluorescent microscopy are provided.

[Trends in Yoga, Tai Chi, and Qigong Use Among US Adults, 2002-2017.](#)

[Wang CC](#)¹, [Li K](#)¹, [Choudhury A](#)¹, [Gaylord S](#)¹.

Am J Public Health. **2019 Mar 21**;e1-e7. doi: 10.2105/AJPH.2019.304998. PMID: 30896991. [Epub ahead of print]

OBJECTIVES: To examine the characteristics and temporal trends of yoga, tai chi, and qigong (YTQ) use among US adults.

METHODS: Using the 2002, 2007, 2012, and 2017 National Health Interview Surveys, we examined the prevalence, patterns, and predicting factors of YTQ use by Taylor series linear regression, the Wald F χ^2 test, and multivariable logistic regression models ($n = 116\,404$).

RESULTS: YTQ use increased from 5.8% in 2002 to 14.5% in 2017 ($P \leq .001$). Only 6.6% of YTQ users were referred by their medical doctors, and approximately one third disclosed their use of YTQ to medical professionals. Reasons for using YTQ included (1) YTQ was beneficial, (2) YTQ focused on the whole person, and (3) YTQ was natural. Acute and chronic pain, arthritis, and depression were the top 3 medical conditions for which people used YTQ the most.

CONCLUSIONS: YTQ use is increasing substantially, mainly because of its natural and holistic healing approach toward health and chronic diseases. Future studies aiming to explore how to best integrate YTQ into the current health care system are warranted.

IRRITABLE BOWEL SYNDROME

[Gut Microbiota in Patients With Irritable Bowel Syndrome-a Systematic Review.](#)

[Pittayanon R](#)¹, [Lau JT](#)², [Yuan Y](#)², [Leontiadis GI](#)², [Tse F](#)², [Surette M](#)², [Moayyedi P](#)³.

Gastroenterology. **2019 Mar 30**. pii: S0016-5085(19)34649-9. doi: 10.1053/j.gastro.2019.03.049. PMID: 30940523. [Epub ahead of print]

BACKGROUND & AIMS: Irritable bowel syndrome (IBS) is common but difficult to treat. Altering the gut microbiota has been proposed as a strategy for treatment of IBS, but the association between the gut microbiome and IBS symptoms has not been well established. We performed a systematic review to explore evidence for this association.

METHODS: We searched databases, including MEDLINE, EMBASE, Cochrane CDSR, and CENTRAL, through April 2, 2018 for case-control studies comparing the fecal or colon microbiomes of adult or pediatric patients with IBS with microbiomes of healthy individuals (controls). The primary outcome was differences in specific gut microbes between patients with IBS and controls.

RESULTS: The search identified 2631 citations; 24 studies from 22 articles were included. Most studies evaluated adults presenting with various IBS subtypes. Family Enterobacteriaceae (phylum Proteobacteria), family Lactobacillaceae, and genus Bacteroides were increased in patients with IBS compared with controls, whereas uncultured Clostridiales I, genus Faecalibacterium (including Faecalibacterium prausnitzii), and genus Bifidobacterium were decreased in patients with IBS. The diversity of the microbiota was either decreased or not different in IBS patients compared with controls. More than 40% of included studies did not state whether cases and controls were comparable (did not describe sex and/or age characteristics).

CONCLUSIONS: In a systematic review, we identified specific bacteria associated with microbiomes of patients with IBS vs controls. Studies are needed to determine whether these microbes are a product or cause of IBS.

[Similarities and differences between IBS-C and FC with regards to symptomatology, sleep quality and psychological attributes.](#)

[Chen HD](#)¹, [Bair MJ](#)², [Chang WC](#)³, [Hsu CS](#)¹, [Wong MW](#)⁴, [Hung JS](#)⁵, [Liu TT](#)⁵, [Yi CH](#)⁵, [Lei WY](#)⁵, [Chen CL](#)⁶.

J Formos Med Assoc. **2019 Mar 25**. pii: S0929-6646(18)30667-3. doi: 10.1016/j.jfma.2019.02.017. PMID: 30922615. [Epub ahead of print]

BACKGROUND: Irritable bowel syndrome (IBS) and functional constipation (FC) are highly prevalent in the general population and have significant symptom overlap, while the clinical associations and psychological links between IBS and FC remains poorly understood. We aimed to compare the clinical, metabolic and psychological factors between patients with FC patients and constipation predominated IBS.

METHODS: We consecutively enrolled 360 patients from the outpatient clinics of Hualien Tzu Chi medical center. Constipation-predominant IBS (IBS-C) and FC were diagnosed based on Rome III criteria. All participants completed the Pittsburg Sleep Quality Index (PSQI) score, the State Trait Anxiety Inventory (STAI) score and the Taiwanese Depression Questionnaire (TDQ) score.

RESULTS: Fifty-four patients had FC and twenty-three patients had IBS-C. Compared to asymptomatic controls, FC/IBS-C groups had female predominance ($p < 0.001$), FC as well as more GI discomforts and inferior psychosocial characteristics ($p < 0.05$). Compared to FC, IBS-C had higher severity scores of abdominal distention (4.52 ± 1.90 vs. 3.07 ± 1.88) and heartburn (2.17 ± 1.50 vs. 1.46 ± 1.14). However, FC was independently associated with poor sleep quality [adjusted OR: 1.19 (1.08-1.31), $p < 0.001$] and IBS-C with depression [adjusted OR: 1.07 (1.02-1.12), $p = 0.005$].

CONCLUSION: Patients with FC and IBS-C shared many similar GI complaints and psychosocial characteristics, however IBS-C had more severe bloating, heartburn and depression and FC had worse sleeping quality.

IRRITABLE BOWEL SYNDROME (Continued)

[Transcranial direct current stimulation in inflammatory bowel disease patients modifies resting-state functional connectivity: A RCT.](#)

[Neeb L](#)¹, [Bayer A](#)², [Bayer KE](#)³, [Farmer A](#)⁴, [Fiebach JB](#)⁵, [Siegmond B](#)⁶, [Volz MS](#)⁷.

Brain Stimul. **2019 Mar 5**. pii: S1935-861X(19)30080-4. doi: 10.1016/j.brs.2019.03.001. PMID: 30905546. [Epub ahead of print]

BACKGROUND: Chronic pain is known to be associated with functional and structural changes in the brain. Inflammatory bowel disease (IBD) presents with chronic abdominal pain in almost 35% of all patients. This study investigates structural and functional changes in magnetic resonance imaging (MRI) after transcranial direct current stimulation (tDCS) applied to ameliorate pain in IBD.

METHODS: This phase-III, placebo-controlled, randomized study included 36 patients with IBD and chronic pain. MRI scans were performed before and following tDCS, which was applied for 5 days.

RESULTS/CONCLUSION: For the first time, this study revealed an association of changes in resting-state functional MRI and pain reduction in IBD. There was a significant increase in functional connectivity after active tDCS within the visual medial and the right frontoparietal network being connected with the amygdala, the insula, and the primary somatosensory cortex indicating central pain mechanisms in IBD. Moreover, tDCS offers a novel therapeutic strategy for abdominal pain.

[Agonist-dependent development of delta opioid receptor tolerance in the colon.](#)

[DiCello JJ](#)^{1,2}, [Saito A](#)^{3,4}, [Rajasekhar P](#)^{3,4}, [Sebastian BW](#)³, [McQuade RM](#)^{3,5}, [Gondin AB](#)³, [Veldhuis NA](#)^{3,4}, [Canals M](#)^{3,4}, [Carbone SE](#)^{3,4}, [Poole DP](#)^{6,7,8}.

Cell Mol Life Sci. **2019 Mar 23**. doi: 10.1007/s00018-019-03077-6. PMID: 30904952. [Epub ahead of print]

The use of opioid analgesics is severely limited due to the development of intractable constipation, mediated through activation of mu opioid receptors (MOR) expressed by enteric neurons. The related delta opioid receptor (DOR) is an emerging therapeutic target for chronic pain, depression and anxiety. Whether DOR agonists also promote sustained inhibition of colonic transit is unknown. This study examined acute and chronic tolerance to SNC80 and ARM390, which were full and partial DOR agonists in neural pathways controlling colonic motility, respectively. Excitatory pathways developed acute and chronic tolerance to SNC80, whereas only chronic tolerance developed in inhibitory pathways. Both pathways remained functional after acute or chronic ARM390 exposure. Propagating colonic motor patterns were significantly reduced after acute or chronic SNC80 treatment, but not by ARM390 pre-treatment. These findings demonstrate that SNC80 has a prolonged inhibitory effect on propagating colonic motility. ARM390 had no effect on motor patterns and thus may have fewer gastrointestinal side-effects.

OTHER RESEARCH OF INTEREST

[Characteristics of younger women Veterans with service connected disabilities.](#)

[Maynard C](#)^{1,2}, [Nelson K](#)^{1,2,3}, [Fihn SD](#)^{2,3}.

Heliyon. **2019 Mar 1**;5(3):e01284. doi: 10.1016/j.heliyon.2019.e01284. PMCID: PMC6401532. PMID: 30886930. eCollection 2019 Mar.

Objectives: There has been an increase in the number of women Veterans with service connected disabilities, which are illnesses or injuries incurred or aggravated during military service. We compared military service and disability characteristics in women and men ≤50 years of age.

Methods: This study included 4,029,672 living Veterans who had at least 1 service connected condition and an active award status as of October 1, 2016. The date of last award as well as demographic, military service, and disability characteristics were obtained from the Veterans Benefits Administration (VBA) VETSNET file.

Results: Among 388,947 women Veterans with service connected conditions, almost 60% (n = 231,364) were ≤50 years of age. Roughly 55% of both women and men ≤50 years had a ≥50% combined rating, although there were differences with respect to individual service connected conditions. Women less often had service connected post traumatic stress disorder (23% vs 32%), but more often had major depression (15% vs 7%). While traumatic brain disease was more common in men, migraine headache was much more common in women (32% vs 18%). Less than half had a VA outpatient visit in the previous year.

Conclusions: The findings of significant numbers of younger women with service connected PTSD, depression, or migraine headache should be considered within the context of post deployment health. These findings raise questions regarding outreach to women Veterans who have these conditions, but do not use VA health care.

OTHER RESEARCH OF INTEREST (Continued)**[Increased risk of reproductive dysfunction in women prescribed long-term opioids for musculoskeletal pain: A matched cohort study in the Clinical Practice Research Datalink.](#)**

[Richardson E](#)¹, [Bedson J](#)¹, [Chen Y](#)¹, [Lacey R](#)¹, [Dunn KM](#)¹.

Eur J Pain. 2018 Oct;22(9):1701-1708. doi: 10.1002/ejp.1256. PMID: 29873872. Epub 2018 Jun 27.

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

BACKGROUND: One-fifth of primary care attendees suffer chronic noncancer pain, with musculoskeletal conditions the leading cause. Twelve percent of patients with chronic noncancer pain are prescribed strong opioids. Evidence suggests long-term opioid use is related to hypogonadism in men, but the relationship in women is unclear. Our aim was to investigate reproductive dysfunction in women prescribed long-term opioids for musculoskeletal pain.

METHODS: We undertook a matched (matched 1:1; for year of birth, year of start of follow-up and practice) cohort study of women aged 18-55 years old, with musculoskeletal pain and an opioid prescription in the Clinical Practice Research Datalink (a primary care database) between 2002 and 2013. Long-term opioid users (≥ 90 days) were compared with short-term opioid users (< 90 days) for four reproductive conditions (abnormal menstruation, low libido, infertility and menopause) using Cox proportional hazards models.

RESULTS: A total of 44,260 women were included; the median cohort age at baseline was 43 years (Interquartile Range 36-49). Long-term opioid use was associated with an increased risk of altered menstruation (hazard ratio 1.13 95% CI 1.05-1.21) and with an increased risk of menopause (hazard ratio 1.16 95% CI 1.10-1.23).

No significant association was found for libido (hazard ratio 1.19 95% CI 0.96-1.48) or infertility (hazard ratio 0.82 95% CI 0.64-1.06).

CONCLUSIONS: The risk of menopause and abnormal menstruation was increased in long-term opioid users. This has implications for clinicians as reproductive dysfunction will need to be considered when prescribing long-term opioids to women with musculoskeletal conditions.

SIGNIFICANCE: This is a large-scale cohort examining the relationship between long-term opioid use and reproductive dysfunction using a UK national primary care database. There is an increased risk of reproductive dysfunction associated with long-term opioid use.

[Physical Inactivity in Pulmonary Sarcoidosis.](#)

[Cho PSP](#)¹, [Vasudevan S](#)², [Maddocks M](#)³, [Spinou A](#)⁴, [Chamberlain Mitchell S](#)⁵, [Wood C](#)⁶, [Jolley CJ](#)¹, [Birring SS](#)^{7,8}.

Lung. 2019 Mar 19. doi: 10.1007/s00408-019-00215-6. PMID: 30888492. [Epub ahead of print]

PURPOSE: Reduced physical activity in many chronic diseases is consistently associated with increased morbidity. Little is known about physical activity in sarcoidosis. The aim of this study was to objectively assess physical activity in patients with pulmonary sarcoidosis and investigate its relationship with lung function, exercise capacity, symptom burden, and health status.

METHODS: Physical activity was assessed over one week in 15 patients with pulmonary sarcoidosis and 14 age-matched healthy controls with a tri-axial accelerometer (ActivPal™) and the International Physical Activity Questionnaire (IPAQ). All participants underwent pulmonary function tests, 6-min walk test (6MWT) and completed the Fatigue Assessment Scale (FAS), Medical Research Council (MRC) Dyspnoea Scale and the King's Sarcoidosis Questionnaire (KSQ).

RESULTS: Patients with sarcoidosis had significantly lower daily step counts than healthy controls; mean (SD) 5624 (1875) versus 10,429 (2942) steps ($p < 0.01$) and a trend towards fewer sit-to-stand transitions each day ($p = 0.095$). Only two patients (13%) self-reported undertaking vigorous physical activity (IPAQ) compared to half of healthy individuals ($p < 0.01$). Daily step count was significantly associated with 6MWT distance in sarcoidosis ($r = 0.634$, $p = 0.01$), but not with forced vital capacity ($r = 0.290$), fatigue ($r = 0.041$), dyspnoea ($r = -0.466$) or KSQ health status ($r = 0.099-0.484$). Time spent upright was associated with fatigue ($r = -0.630$, $p = 0.012$) and health status (KSQ Lung scores $r = 0.524$, $p = 0.045$), and there was a significant correlation between the number of sit-to-stand transitions and MRC dyspnoea score ($r = -0.527$, $p = 0.044$).

CONCLUSION: Physical activity is significantly reduced in sarcoidosis and is associated with reduced functional exercise capacity (6MWD). Fatigue, exertional symptoms and health status were more closely associated with time spent upright and the number of bouts of physical activity, as compared to step counts. Further studies are warranted to identify the factors that determine different physical activity profiles in sarcoidosis.

OTHER RESEARCH OF INTEREST (Continued)

[Memantine for dementia.](#)

[McShane R¹](#), [Westby MJ](#), [Roberts E](#), [Minakaran N](#), [Schneider L](#), [Farrimond LE](#), [Maayan N](#), [Ware J](#), [Debarros J](#).

Cochrane Database Syst Rev. 2019 Mar 20;3:CD003154. doi: 10.1002/14651858.CD003154.pub6. PMID: 30891742. [Epub ahead of print]

BACKGROUND: Memantine is a moderate affinity uncompetitive antagonist of glutamate NMDA receptors. It is licensed for use in moderate and severe Alzheimer's disease (AD); in the USA, it is also widely used off-label for mild AD.

OBJECTIVES: To determine efficacy and safety of memantine for people with dementia. To assess whether memantine adds benefit for people already taking cholinesterase inhibitors (ChEIs).

SEARCH METHODS: We searched ALOIS, the Cochrane Dementia and Cognitive Improvement Group's register of trials (<http://www.medicine.ox.ac.uk/alois/>) up to 25 March 2018. We examined clinical trials registries, press releases and posters of memantine manufacturers; and the web sites of the FDA, EMEA and NICE. We contacted authors and companies for missing information.

SELECTION CRITERIA: Double-blind, parallel group, placebo-controlled, randomised trials of memantine in people with dementia.

DATA COLLECTION AND ANALYSIS: We pooled and analysed data from four clinical domains across different aetiologies and severities of dementia and for AD with agitation. We assessed the impact of study duration, severity and concomitant use of ChEIs. Consequently, we restricted analyses to the licensed dose (20 mg/day or 28 mg extended release) and data at six to seven months duration of follow-up, and analysed separately results for mild and moderate-to-severe AD. We transformed results for efficacy outcomes into the difference in points on particular outcome scales.

MAIN RESULTS: Across all types of dementia, data were available from almost 10,000 participants in 44 included trials, most of which were at low or unclear risk of bias. For nearly half the studies, relevant data were obtained from unpublished sources. The majority of trials (29 in 7885 participants) were conducted in people with AD.1. Moderate-to-severe AD (with or without concomitant ChEIs). High-certainty evidence from up to 14 studies in around 3700 participants consistently shows a small clinical benefit for memantine versus placebo: clinical global rating (CGR): 0.21 CIBIC+ points (95% confidence interval (CI) 0.14 to 0.30); cognitive function (CF): 3.11 Severe Impairment Battery (SIB) points (95% CI 2.42 to 3.92); performance on activities of daily living (ADL): 1.09 ADL19 points (95% CI 0.62 to 1.64); and behaviour and mood (BM): 1.84 Neuropsychiatric Inventory (NPI) points (95% CI 1.05 to 2.76). There may be no difference in the number of people discontinuing memantine compared to placebo: risk ratio (RR) 0.93 (95% CI 0.83 to 1.04) corresponding to 13 fewer people per 1000 (95% CI 31 fewer to 7 more). Although there is moderate-certainty evidence that fewer people taking memantine experience agitation as an adverse event: RR 0.81 (95% CI 0.66 to 0.99) (25 fewer people per 1000, 95% CI 1 to 44 fewer), there is also moderate-certainty evidence, from three additional studies, suggesting that memantine is not beneficial as a treatment for agitation (e.g. Cohen Mansfield Agitation Inventory: clinical benefit of 0.50 CMAI points, 95% CI -3.71 to 4.71). The presence of concomitant ChEI does not impact on the difference between memantine and placebo, with the possible exceptions of the BM outcome (larger effect in people taking ChEIs) and the CF outcome (smaller effect).2. Mild AD (Mini Mental State Examination (MMSE) 20 to 23): mainly moderate-certainty evidence based on post-hoc subgroups from up to four studies in around 600 participants suggests there is probably no difference between memantine and placebo for CF: 0.21 ADAS-Cog points (95% CI -0.95 to 1.38); performance on ADL: -0.07 ADL 23 points (95% CI -1.80 to 1.66); and BM: -0.29 NPI points (95% CI -2.16 to 1.58). There is less certainty in the CGR evidence, which also suggests there may be no difference: 0.09 CIBIC+ points (95% CI 0.12 to 0.30). Memantine (compared with placebo) may increase the numbers of people discontinuing treatment because of adverse events (RR 2.12, 95% CI 1.03 to 4.39).3. Mild-to-moderate vascular dementia. Moderate- and low-certainty evidence from two studies in around 750 participants indicates there is probably a small clinical benefit for CF: 2.15 ADAS-Cog points (95% CI 1.05 to 3.25); there may be a small clinical benefit for BM: 0.47 NOSGER disturbing behaviour points (95% CI 0.07 to 0.87); there is probably no difference in CGR: 0.03 CIBIC+ points (95% CI -0.28 to 0.34); and there may be no difference in ADL: 0.11 NOSGER II self-care subscale points (95% CI -0.35 to 0.54) or in the numbers of people discontinuing treatment: RR 1.05 (95% CI 0.83 to 1.34). There is limited, mainly low- or very low-certainty efficacy evidence for other types of dementia (Parkinson's disease and dementia Lewy bodies (for which CGR may show a small clinical benefit; four studies in 319 people); frontotemporal dementia (two studies in 133 people); and AIDS-related Dementia Complex (one study in 140 people)). There is high-certainty evidence showing no difference between memantine and placebo in the proportion experiencing at least one adverse event: RR 1.03 (95% CI 1.00 to 1.06); the RR does not differ between aetiologies or severities of dementia. Combining available data from all trials, there is moderate-certainty evidence that memantine is 1.6 times more likely than placebo to result in dizziness (6.1% versus 3.9%), low-certainty evidence of a 1.3-fold increased risk of headache (5.5% versus 4.3%), but high-certainty evidence of no difference in falls.

AUTHORS' CONCLUSIONS: We found important differences in the efficacy of memantine in mild AD compared to that in moderate-to-severe AD. There is a small clinical benefit of memantine in people with moderate-to-severe AD, which occurs irrespective of whether they are also taking a ChEI, but no benefit in people with mild AD. Clinical heterogeneity in AD makes it unlikely that any single drug will have a large effect size, and means that the optimal drug treatment may involve multiple drugs, each having an effect size that may be less than the minimum clinically important difference. A definitive long-duration trial in mild AD is needed to establish whether starting memantine earlier would be beneficial over the long term and safe: at present the evidence is against this, despite it being common practice. A long-duration trial in moderate-to-severe AD is needed to establish whether the benefit persists beyond six months.

OTHER RESEARCH OF INTEREST (Continued)**[The preferences of potential stakeholders in psychiatric genomic research regarding consent procedures and information delivery.](#)**

[Sundby A](#)¹, [Boolsen MW](#)², [Burgdorf KS](#)³, [Ullum H](#)³, [Hansen TF](#)⁴, [Middleton A](#)⁵, [Mors O](#)⁶.

Eur Psychiatry. 2019 Jan;55:29-35. doi: 10.1016/j.eurpsy.2018.09.005. PMID: 30384109. Epub 2018 Oct 29.

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

BACKGROUND: Genomic sequencing plays an increasing role in genetic research, also in psychiatry. This raises challenges concerning the validity and type of the informed consent and the return of incidental findings. However, no solution currently exists on the best way to obtain the informed consent and deliver findings to research subjects.

AIMS: This study aims to explore the attitudes among potential stakeholders in psychiatric genomic research toward the consenting procedure and the delivery of incidental findings.

METHODS: We developed a cross-sectional web-based survey among five groups of stakeholders. A total of 2637 stakeholders responded: 241 persons with a mental disorder, 671 relatives, 1623 blood donors, 74 psychiatrists, and 28 clinical geneticists.

RESULTS: The stakeholders wanted active involvement as 92.7% preferred a specific consent and 85.1% wanted to receive information through a dynamic consent procedure. The majority of stakeholders preferred to receive genomic information related to serious or life-threatening health conditions through direct contact (69.5%) with a health professional, i.e. face-to-face consultation or telephone consultation (82.4%). Persons with mental disorders and relatives did not differ in their attitudes from the other stakeholder groups.

CONCLUSION: The findings illustrate that the stakeholders want to be more actively involved and consider consent as a reciprocal transaction between the involved subjects and the researchers in the project. The results highlight the importance of collaboration between researchers and clinical geneticists as the latter are trained, through their education and clinical experience, to return and explain genomic data to patients, relatives, and research subjects.

[Genome-wide association analysis reveals KCTD12 and miR-383-binding genes in the background of rumination.](#)

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Transl Psychiatry. 2019 Mar 18;9(1):119. doi: 10.1038/s41398-019-0454-1. PMID: 30886212.

Ruminative response style is a passive and repetitive way of responding to stress, associated with several disorders. Although twin and candidate gene studies have proven the genetic underpinnings of rumination, no genome-wide association study (GWAS) has been conducted yet. We performed a GWAS on ruminative response style and its two subtypes, brooding and reflection, among 1758 European adults recruited in the general population of Budapest, Hungary, and Manchester, United Kingdom. We evaluated single-nucleotide polymorphism (SNP)-based, gene-based and gene set-based tests, together with inferences on genes regulated by our most significant SNPs. While no genome-wide significant hit emerged at the SNP level, the association of rumination survived correction for multiple testing with KCTD12 at the gene level, and with the set of genes binding miR-383 at the gene set level. SNP-level results were concordant between the Budapest and Manchester subsamples for all three rumination phenotypes. SNP-level results and their links to brain expression levels based on external databases supported the role of KCTD12, SRGAP3, and SETD5 in rumination, CDH12 in brooding, and DPYSL5, MAPRE3, KCNK3, ATXN7L3B, and TPH2 in reflection, among others. The relatively low sample size is a limitation of our study. Results of the first GWAS on rumination identified genes previously implicated in psychiatric disorders underscoring the transdiagnostic nature of rumination, and pointed to the possible role of the dorsolateral prefrontal cortex, hippocampus, and cerebellum in this cognitive process.

OTHER RESEARCH OF INTEREST (Continued)**Betahistine for tinnitus.**

[Wegner I](#)¹, [Hall DA](#), [Smit AL](#), [McFerran D](#), [Stegeman I](#).

Cochrane Database Syst Rev. **2018 Dec 28**;12:CD013093. doi: 10.1002/14651858.CD013093.pub2. PMID: 30908589. [Epub ahead of print]

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

BACKGROUND: Tinnitus is a symptom defined as the perception of sound in the absence of an external source. In England alone there are an estimated ¾ million general practice consultations every year where the primary complaint is tinnitus, equating to a major burden on healthcare services. Clinical management strategies include education and advice, relaxation therapy, tinnitus retraining therapy, cognitive behavioural therapy, sound enrichment using ear-level sound generators or hearing aids, and drug therapies to manage co-morbid symptoms such as sleep difficulties, anxiety or depression. As yet, no drug has been approved for tinnitus by a regulatory body. Nonetheless, over 100,000 prescriptions for betahistine are being filled every month in England, and nearly 10% of general practitioners prescribe betahistine for tinnitus.

OBJECTIVES: To assess the effects of betahistine in patients with subjective idiopathic tinnitus.

SEARCH METHODS: The Cochrane ENT Information Specialist searched the Cochrane ENT Register; Central Register of Controlled Trials (CENTRAL, via the Cochrane Register of Studies); Ovid MEDLINE; Ovid Embase; Web of Science; ClinicalTrials.gov; ICTRP and additional sources for published and unpublished trials. The date of the search was 23 July 2018.

SELECTION CRITERIA: Randomised controlled trials (RCTs) recruiting patients of any age with acute or chronic subjective idiopathic tinnitus were included. We included studies where the intervention involved betahistine and this was compared to placebo, no intervention or education and information. We included all courses of betahistine, regardless of dose regimens or formulations and for any duration of treatment.

DATA COLLECTION AND ANALYSIS: We used the standard methodological procedures expected by Cochrane. Our primary outcomes included tinnitus loudness and significant adverse effects (upper gastrointestinal discomfort). Our secondary outcomes included tinnitus symptom severity as measured by the global score on a multi-item tinnitus questionnaire, depressive symptoms, symptoms of generalised anxiety, health-related quality of life, other adverse effects (e.g. headache, drowsiness, allergic skin reactions (pruritis, rashes) and exacerbation of tinnitus) and tinnitus intrusiveness. We used GRADE to assess the quality of evidence for each outcome; this is indicated in italics.

MAIN RESULTS: This review included five studies (with a total of 303 to 305 participants) comparing the effects of betahistine with placebo in adults with subjective idiopathic tinnitus. Four studies were parallel-group RCTs and one had a cross-over design. The risk of bias was unclear in all of the included studies. Due to heterogeneity in the outcomes measured and measurement methods used, very limited data pooling was possible. When we pooled the data from two studies for the primary outcome tinnitus loudness, the mean difference on a 0- to 10-point visual analogue scale at one-month follow-up was not significant between betahistine and placebo (-0.16, 95% confidence interval (CI) -1.01 to 0.70; 81 participants) (very low-quality evidence). There were no reports of upper gastrointestinal discomfort (significant adverse effect) in any study. As a secondary outcome, one study found no difference in the change in the Tinnitus Severity Index between betahistine and placebo (mean difference at 12 weeks 0.02, 95% CI -1.05 to 1.09; 50 participants) (moderate-quality evidence). None of the studies reported the other secondary outcomes of changes in depressive symptoms or depression, anxiety symptoms or generalised anxiety, or health-related quality of life as measured by a validated instrument, nor tinnitus intrusiveness. Other adverse effects that were reported were not treatment-related.

AUTHORS' CONCLUSIONS: There is an absence of evidence to suggest that betahistine has an effect on subjective idiopathic tinnitus when compared to placebo. The evidence suggests that betahistine is generally well tolerated with a similar risk of adverse effects to placebo treatments. The quality of evidence for the reported outcomes, using GRADE, ranged from moderate to very low. If future research into the effectiveness of betahistine in patients with tinnitus is felt to be warranted, it should use rigorous methodology. Randomisation and blinding should be of the highest quality, given the subjective nature of tinnitus and the strong likelihood of a placebo response. The CONSORT statement should be used in the design and reporting of future studies. We also recommend the development of validated, patient-centred outcome measures for research in the field of tinnitus.

OTHER RESEARCH OF INTEREST (Continued)

[Association of dietary patterns with systemic inflammation, quality of life, disease severity, relapse rate, severity of fatigue and anthropometric measurements in MS patients.](#)

[Moravejolahkami AR](#)¹, [Paknahad Z](#)², [Chitsaz A](#)³.

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BACKGROUND: Multiple sclerosis (MS) is associated with changes in quality of life, disability, fatigue and anthropometric measurements. The important relationship of dietary patterns with such clinical manifestations was not completely investigated.

AIMS: The goal of this study was to define the dietary patterns and their association with systemic inflammation, Health-Related Quality Of Life, disease severity, Relapse Rate, severity of fatigue and anthropometric measurements in MS subjects.

METHODS: This cross-sectional study was conducted in 261 MS patients (mean age 38.9 ± 8.3). Dietary patterns were explored by a Food Frequency Questionnaire. Serum hs-CRP, Multiple Sclerosis Quality Of Life-54 item questionnaire, Extended Disability Status Scale, Fatigue Severity Scale and Visual Analog Fatigue Scale, Relapse Rate, Height, Weight and Deurenberg Equation were also used as tools. Data were analyzed by SPSS₂₄, and using ANOVA, Tukey, Chi-square and ANCOVA tests.

RESULTS: Fruits, Vegetables, Low fat dairy-based pattern and Mediterranean-Like pattern were associated with lower serum hs-CRP (F = 6.037, $P_{\text{adjusted}} < 0.01$), higher Physical and Mental Health Composite Scores ($P_{\text{adjusted}} < 0.001$), lower attacks (F = 4.475, $P_{\text{adjusted}} < 0.05$), lower acute and chronic fatigue (F = 5.353 and F = 7.011, respectively, $P_{\text{adjusted}} < 0.01$), lower BMI (F = 7.528, $P_{\text{adjusted}} < 0.01$) and Percent Body Fat (F = 6.135, $P_{\text{adjusted}} < 0.01$); but no difference was observed about EDSS across the patterns.

CONCLUSIONS: Adherence to healthy dietary patterns may reduce systemic inflammation, severity of fatigue, MS attacks, improved quality of life and balance weight especially body fat in MS patients.

[Safety, Tolerability, and Nocebo Phenomena During Transcranial Magnetic Stimulation: A Systematic Review and Meta-Analysis of Placebo-Controlled Clinical Trials.](#)

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Neuromodulation. **2019 Mar 21**. doi: 10.1111/ner.12946. PMID: 30896060. [Epub ahead of print]

BACKGROUND: The methodology used for the application of repetitive transcranial magnetic stimulation (TMS) is such that it may induce a placebo effect. Respectively, adverse events (AEs) can occur when using a placebo, a phenomenon called nocebo. The primary aim of our meta-analysis is to establish the nocebo phenomena during TMS. Safety and tolerability of TMS were also studied.

METHODS: After a systematic Medline search for TMS randomized controlled trials (RCTs), we assessed the number of patients reporting at least one AE and the number of discontinuations because of AE in active and sham TMS groups.

RESULTS: Data were extracted from 93 RCTs. The overall pooled estimate of active TMS and placebo treated patients who discontinued treatment because of AEs was 2.5% (95% CI 1.9%-3.2%) and 2.7% (95% CI 2.0%-3.5%), respectively. The pooled estimate of active TMS and placebo treated patients experiencing at least one AE was 29.3% (95% CI 19.0%-22.6%) and 13.6% (95% CI 11.6%-15.8%), respectively, suggesting that the odds of experiencing an AE is 2.60 times higher (95% CI 1.75-3.86) in the active treatment group compared to placebo ($p < 0.00001$). The most common AE was headache, followed by dizziness. Secondary meta-analyses in depression and psychotic disorders showed that the odds of experiencing an AE is 3.98 times higher (95% CI 2.14-7.40) and 2.93 times higher (95% CI 1.41-6.07), respectively, in the active treatment groups compared to placebo.

CONCLUSIONS: TMS is a safe and well-tolerated intervention. Nocebo phenomena do occur during TMS treatment and should be acknowledged during clinical trial design and daily clinical practice.