

GULF WAR ILLNESS

No Updates this Week for Gulf War Illness or Chronic Multisymptom Illness.

CHRONIC FATIGUE SYNDROME

[Treatment Avenues in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Split-gender Pharmacogenomic Study of Gene-expression Modules.](#)

[Jeffrey MG](#)¹, [Nathanson L](#)², [Aenlle K](#)³, [Barnes ZM](#)⁴, [Baig M](#)⁵, [Broderick G](#)⁶, [Klimas NG](#)⁷, [Fletcher MA](#)³, [Craddock TJA](#)⁸. Clin Ther. 2019 Mar 6. pii: S0149-2918(19)30047-5. doi: 10.1016/j.clinthera.2019.01.011. PMID: 30851951. [Epub ahead of print]

PURPOSE: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating multisymptom illness impacting up to 1 million people in the United States. As the pathogenesis and etiology of this complex condition are unclear, prospective treatments are limited. Identifying US Food and Drug Administration-approved drugs that may be repositioned as treatments for ME/CFS may offer a rapid and cost-effective solution.

METHODS: Here we used gene-expression data from 33 patients with Fukuda-defined ME/CFS (23 females, 10 males) and 21 healthy demographically comparable controls (15 females, 6 males) to identify differential expression of predefined gene-module sets based on nonparametric statistics. Differentially expressed gene modules were then annotated via over-representation analysis using the Consensus Pathway database. Differentially expressed modules were then regressed onto measures of fatigue and cross-referenced with drug atlas and pharmacogenomics databases to identify putative treatment agents.

FINDINGS: The top 1% of modules identified in males indicated small effect sizes in modules associated with immune regulation and mitochondrial dysfunction. In females, modules identified included those related to immune factors and cardiac/blood factors, returning effect sizes ranging from very small to intermediate ($0.147 < \text{Cohen } \delta < 0.532$). Regression analysis indicated that B-cell receptors, T-cell receptors, tumor necrosis factor α , transforming growth factor β , and metabolic and cardiac modules were strongly correlated with multiple composite measures of fatigue. Cross-referencing identified genes with pharmacogenomics data indicated immunosuppressants as potential treatments of ME/CFS symptoms.

IMPLICATIONS: The findings from our analysis suggest that ME/CFS symptoms are perpetuated by immune dysregulation that may be approached via immune modulation-based treatment strategies.

[Mitochondrial complex activity in permeabilised cells of chronic fatigue syndrome patients using two cell types.](#)

[Tomas C](#)¹, [Brown AE](#)¹, [Newton JL](#)^{1,2}, [Elson JL](#)^{3,4}.

PeerJ. 2019 Mar 1;7:e6500. doi: 10.7717/peerj.6500. eCollection 2019. PMCID: PMC6398432. PMID: 30847260.

Abnormalities in mitochondrial function have previously been shown in chronic fatigue syndrome (CFS) patients, implying that mitochondrial dysfunction may contribute to the pathogenesis of disease. This study builds on previous work showing that mitochondrial respiratory parameters are impaired in whole cells from CFS patients by investigating the activity of individual mitochondrial respiratory chain complexes. Two different cell types were used in these studies in order to assess individual complex activity locally in the skeletal muscle (myotubes) ($n = 6$) and systemically (peripheral blood mononuclear cells (PBMCs)) (control $n = 6$; CFS $n = 13$). Complex I, II and IV activity and respiratory activity supported by fatty acid oxidation and glutaminolysis were measured using extracellular flux analysis. Cells were permeabilised and combinations of substrates and inhibitors were added throughout the assays to allow states of mitochondrial respiration to be calculated and the activity of specific aspects of respiratory activity to be measured. Results showed there to be no significant differences in individual mitochondrial complex activity or respiratory activity supported by fatty acid oxidation or glutaminolysis between healthy control and CFS cohorts in either skeletal muscle ($p \geq 0.190$) or PBMCs ($p \geq 0.065$). This is the first study to use extracellular flux analysis to investigate individual mitochondrial complex activity in permeabilised cells in the context of CFS. The lack of difference in complex activity in CFS PBMCs suggests that the previously observed mitochondrial dysfunction in whole PBMCs is due to causes upstream of the mitochondrial respiratory chain.

CHRONIC FATIGUE SYNDROME (Continued)

[Assessment of Post-Exertional Malaise \(PEM\) in Patients with Myalgic Encephalomyelitis \(ME\) and Chronic Fatigue Syndrome \(CFS\): A Patient-Driven Survey.](#)

[Holtzman CS](#)¹, [Bhatia S](#)², [Cotler J](#)³, [Jason LA](#)⁴.

Diagnostics (Basel). 2019 Mar 2;9(1). pii: E26. doi: 10.3390/diagnostics9010026. PMID: 30832336.

Considerable controversy has existed with efforts to assess post-exertional malaise (PEM), which is one of the defining features of myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS). While a number of self-report questionnaires have been developed to assess this symptom, none have been comprehensive, and a recent federal government report has recommended the development of a new PEM measure. The current study involved a community-based participatory research process in an effort to develop a comprehensive PEM instrument, with critical patient input shaping the item selection and overall design of the tool. A survey was ultimately developed and was subsequently completed by 1534 members of the patient community. The findings of this survey suggest that there are key domains of this symptom, including triggers, symptom onset, and duration, which have often not been comprehensively assessed in a previous PEM instrument. This study indicates that there are unique benefits that can be derived from patients collaborating with researchers in the measurement of key symptoms defining ME and CFS.

HEADACHE and MIGRAINE

[Cerebral cortical dimensions in headache sufferers aged 50-66 years: a population-based imaging study in the Nord-Trøndelag Health Study \(HUNT-MRI\).](#)

[Husøy AK](#)¹, [Håberg AK](#)^{1,2}, [Rimol LM](#)¹, [Hagen K](#)^{1,3}, [Vangberg TR](#)^{4,5}, [Stovner LJ](#)^{1,3}.

Pain. 2019 Mar 4. doi: 10.1097/j.pain.0000000000001550. PMID: 30839431. [Epub ahead of print]

Based on previous clinic-based MRI studies showing regional differences in the cerebral cortex between those with and without headache, we hypothesized that headache sufferers have a decrease in volume, thickness or surface area in anterior cingulate cortex (ACC), prefrontal cortex (PFC), and insula. In addition, exploratory analyses on volume, thickness and surface area across the cerebral cortical mantle were performed. 1006 participants (50-66 years) from the general population were selected to an imaging study of the head at 1.5 T (HUNT-MRI). 283 individuals suffered from headache, 80 with migraine and 87 with tension-type headache, whereas 309 individuals did not suffer from headache and were used as controls. T1 weighted 3D scans of the brain were analysed with voxel-based morphometry and FreeSurfer. The association between cortical volume, thickness and surface area and questionnaire-based headache diagnoses was evaluated, taking into consideration evolution of headache and frequency of attacks. There were no significant differences in cortical volume, thickness or surface area between headache sufferers and non-sufferers in ACC, PFC or insula. Similarly, the exploratory analyses across the cortical mantle demonstrated no significant differences in volume, thickness or surface area between any of the headache groups and the non-sufferers. Maps of effect sizes showed small differences in the cortical measures between headache sufferers and non-sufferers. Hence, there are probably no or only very small differences in volume, thickness or surface area of the cerebral cortex between those with and without headache in the general population.

HEADACHE and MIGRAINE (Continued)

[An open-label prospective study of the real-life use of onabotulinumtoxinA for the treatment of chronic migraine: the REPOSE study.](#)

[Ahmed F](#)¹, [Gaul C](#)², [García-Moncó JC](#)³, [Sommer K](#)⁴, [Martelletti P](#)^{5,6}; [REPOSE Principal Investigators](#).

J Headache Pain. 2019 Mar 7;20(1):26. doi: 10.1186/s10194-019-0976-1. PMID: 30845917.

BACKGROUND: The PREEMPT Studies established onabotulinumtoxinA as preventive treatment for adults with chronic migraine (CM). The purpose of the REal-life use of botulinum toxin for the symptomatic treatment of adults with chronic migraine, measuring healthcare resource utilisation, and Patient-reported OutcomeS observed in practice (REPOSE) Study was to observe real-life, long-term (24-month) use of onabotulinumtoxinA in adults with CM and report on the utilisation, effectiveness, safety, and tolerability.

METHODS: The REPOSE Study was a European, open-label, multicentre, prospective, noninterventional study. Patients received onabotulinumtoxinA approximately every 12 weeks according to their physician's usual practice, guided by the summary of product characteristics (SPC). Patients were observed for 24 months after initiating onabotulinumtoxinA treatment. Outcome measures were collected at baseline and all administration visits and included onabotulinumtoxinA injection practices, headache-day frequency, Migraine-Specific Quality-of-Life Questionnaire (MSQ), EuroQol 5-Dimension Questionnaire (EQ-5D), and adverse drug reactions (ADRs) to evaluate safety/tolerability.

RESULTS: Of 641 patients enrolled, 633 received ≥ 1 dose of onabotulinumtoxinA for a total of 3499 treatment sessions. At baseline, mean (SD) age was 45.4 (11.7) years; patients were predominantly women (85.3%). Injection practices closely followed the SPC in mean dosage (155.1 U) and injection sites per session (31.4), with the exception of a prolongation of the recommended 12-week dosing interval, with 79.1% of patients receiving ≥ 1 treatment session that was > 13 weeks after the previous treatment session. Headache-day frequency was reduced from a baseline mean (SD) of 20.6 (5.4) to 7.4 (6.6) days at administration visit 8 ($P < 0.001$). Each MSQ domain (restrictive, preventive, and emotional) was significantly reduced from baseline through each administration visit ($P < 0.001$). The median EQ-5D total and health state scores were significantly improved from baseline through each administration visit ($P < 0.001$). Overall, 18.3% of patients reported an ADR; most were mild to moderate intensity, with only 1.3% of patients reporting a serious ADR. Eyelid ptosis (5.4%), neck pain (2.8%), and musculoskeletal stiffness (2.7%) were the most frequently reported.

CONCLUSIONS: Long-term, real-world preventive treatment of CM with onabotulinumtoxinA showed effectiveness with a sustained reduction in headache-day frequency and significant improvement in quality-of-life measures. ADRs were mild to moderate, with no new safety concerns identified.

TRIAL REGISTRATION: Trial registration number: NCT01686581. Name of registry: ClinicalTrials.gov. URL of registry: <https://clinicaltrials.gov/ct2/show/NCT01686581>. Date of retrospective registration: September 18, 2012. Date of enrolment of first patient: July 23, 2012.

[Extracranial Trigger Site Surgery for Migraine: A Systematic Review With Meta-Analysis on Elimination of Headache Symptoms.](#)

[Vincent AJPE](#)¹, [van Hoogstraten WS](#)², [Maassen Van Den Brink A](#)³, [van Rosmalen J](#)⁴, [Bouwen BLJ](#)^{1,2}.

Front Neurol. 2019 Feb 14;10:89. doi: 10.3389/fneur.2019.00089. PMCID: PMC6383414. PMID: 30837930. eCollection 2019.

Introduction: The headache phase of migraine could in selected cases potentially be treated by surgical decompression of one or more "trigger sites," located at frontal, temporal, nasal, and occipital sites. This systematic review with subsequent meta-analysis aims at critically evaluating the currently available evidence for the surgical treatment of migraine headache and to determine the effect size of this treatment in a specific patient population.

Methods: This study was conducted following the PRISMA guidelines. An online database search was performed. Inclusion was based on studies published between 2000 and March 2018, containing a diagnosis of migraine in compliance with the classification of the International Headache Society. The treatment must consist of one or more surgical procedures involving the extracranial nerves and/or arteries with outcome data available at minimum 6 months.

Results: Eight hundred and forty-seven records were identified after duplicates were removed, 44 full text articles were assessed and 14 records were selected for inclusion. A total number of 627 patients were included in the analysis. A proportion of 0.38 of patients (random effects model, 95% CI [0.30-0.46]) experienced elimination of migraine headaches at 6-12 months follow-up. Using data from three randomized controlled trials, the calculated odds ratio for 90-100% elimination of migraine headaches is 21.46 (random effects model, 95% CI [5.64-81.58]) for patients receiving migraine surgery compared to sham or no surgery.

Conclusions: Migraine surgery leads to elimination of migraine headaches in 38% of the migraine patients included in this review. However, more elaborate randomized trials are needed with transparent reporting of patient selection, medication use, and surgical procedures and implementing detailed and longer follow-up times.

HEADACHE and MIGRAINE (Continued)

[Favourable prognosis of trigeminal neuralgia when enrolled in a multidisciplinary management program - a two-year prospective real-life study.](#)

[Heinskou TB](#)¹, [Maarbjerg S](#)², [Wolfram F](#)³, [Rochat P](#)⁴, [Brennum J](#)⁴, [Olesen J](#)², [Bendtsen L](#)².

J Headache Pain. **2019 Mar 4**;20(1):23. doi: 10.1186/s10194-019-0973-4. PMID: 30832577.

BACKGROUND: Prognosis of medically treated trigeminal neuralgia patients is assumed to be poor, but the evidence is lacking. Thus, prospective real-life studies of medical management of trigeminal neuralgia are warranted.

METHODS: This was an observational study. Patients were consecutively enrolled in a structured management program at a specialist centre for facial pain. Optimisation of medical treatment, physiotherapy, psychotherapy, and advice from trained nurses, were parts of the program. Medically intractable patients were referred for neurosurgery. Data-collection was prospective using standardised schemes and patient surveys. The aim was to describe the two-year outcome of medical treatment at the specialist centre. The primary outcome was a 50% reduction in the overall burden of pain according to a Numerical Rating Scale (NRS) after two years.

RESULTS: A total of 186 primary TN patients were enrolled in the program of which 103 patients remained medically managed and completed the two-year follow-up. Fifty patients were treated surgically within the first two years of follow-up. Half of the medically managed patients (53 (51%)), had more than a 50% reduction in the overall burden of pain over the two-year period. The overall burden of pain on NRS decreased from mean 5.34 to 3.00, $p < 0.01$. There was no significant association between primary outcome and sex, depression and/or anxiety, concomitant persistent pain, or neurovascular contact with morphological changes of the trigeminal nerve.

CONCLUSIONS: Patients with trigeminal neuralgia improve over a two-year period when enrolled in a structured medical management program. Optimisation of drug treatment, continuous advice and education and support by the multidisciplinary team, referral of the medically intractable patients for surgery or the natural history of the disease, can be some of the reasons for the improvement. The favourable prognosis provides hope and optimism for medically managed TN patients.

TRIAL REGISTRATION: Current study was observational, and patients were offered standard clinical care and laboratory workups according to current American Academy of Neurology and European Federation of Neurological Societies treatment guidelines. The study has been registered at ClinicalTrials.gov. ID: [NCT03838393](#).

[How much do periventricular lesions assist in distinguishing migraine with aura from CIS?](#)

[Lapucci C](#)¹, [Saitta L](#)², [Bommarito G](#)², [Sormani MP](#)², [Pardini M](#)², [Bonzano L](#)², [Mancardi GL](#)², [Gasperini C](#)², [Giorgio A](#)², [Inglese M](#)², [De Stefano N](#)², [Roccatagliata L](#)².

Neurology. **2019 Mar 8**. pii: 10.1212/WNL.0000000000007266. doi: 10.1212/WNL.0000000000007266. PMID: 30850445. [Epub ahead of print]

OBJECTIVE: To evaluate in clinically isolated syndrome (CIS) and migraine with aura (MA) how the number of periventricular lesions (PVLs) detected at MRI influences diagnostic performance when the Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) or the 2017 revised criteria are applied.

METHODS: In this retrospective study, white matter hyperintensities (WMH) of 84 patients with MA and 79 patients with CIS were assessed using manual segmentation technique. Lesion probability maps (LPMs) and voxel-wise analysis of lesion distribution by diagnosis were obtained. Furthermore, we performed a logistic regression analysis based on lesion locations and volumes.

RESULTS: Compared to patients with MA, patients with CIS showed a significant overall higher T2 WMH mean number and volume (17.9 ± 16.9 vs 6.2 ± 11.9 and 3.1 ± 4.2 vs 0.3 ± 0.6 mL; $p < 0.0001$) and a significantly higher T2 WMH mean number in infratentorial, periventricular, and juxtacortical areas ($p < 0.0001$). LPMs identified the periventricular regions as the sites with the highest probability of detecting T2 WMH in patients with CIS. Voxel-wise analysis of lesion distribution by diagnosis revealed a statistically significant association exclusively between the diagnosis of CIS and the PVLs. MAGNIMS criteria demonstrated the highest specificity in differentiating patients with CIS from patients with MA (100% vs 87%) against a predictable lower sensitivity (63% vs 72%).

CONCLUSIONS: PVLs play a key role in the differential diagnosis between MA and CIS, particularly when there are more than 3. Future studies on multiple sclerosis criteria might reconsider the 3 PVLs to minimize the risk of misdiagnosis.

CLASSIFICATION OF EVIDENCE: This study provides Class IV evidence that the presence at least 3 PVLs increases the specificity in distinguishing MA from CIS.

CHRONIC PAIN

[Menopause symptoms and chronic pain in a national sample of midlife women veterans.](#)

[Gibson CJ](#)^{1,2}, [Li Y](#)¹, [Bertenthal D](#)¹, [Huang AJ](#)², [Seal KH](#)^{1,2}.

Menopause. **2019 Mar 4**. doi: 10.1097/GME.0000000000001312. PMID: 30839364. [Epub ahead of print]

OBJECTIVE: Women are more likely than men to suffer chronic pain, with the highest rates seen in midlife. The symptoms that characterize menopause broadly affect health and well-being, but their contribution to chronic pain risk during this period is poorly understood. To address this gap in knowledge, we examined relationships between indicators of menopause symptoms and chronic pain among midlife women veterans, a population with prevalent chronic pain diagnoses and elevated risk for bothersome menopause symptoms.

METHODS: This is a cross-sectional analysis of national Veterans Health Administration medical and pharmacy records. Using national medical and pharmacy records from women veterans aged 45 to 64 with at least one VA encounter during 2014 and/or 2015 (n=200,901), we developed multivariable logistic regression models to examine associations between menopause symptoms (defined by menopause symptom-related diagnoses on ≥ 2 encounters and/or menopause hormone therapy use) and chronic pain outcomes, adjusting for age, race, body mass index, mental health diagnoses, and substance use disorders.

RESULTS: In this national sample of midlife women veterans (mean age 54.3 ± 5.4), 26% had menopause symptoms, 52% had chronic pain, and 22% had ≥ 2 distinct chronic pain diagnoses. In multivariable analyses, women with menopause symptoms had nearly two-fold odds of chronic pain (odds ratio 1.89, 95% confidence interval 1.85-1.94, $P < 0.001$) and multiple chronic pain diagnoses (odds ratio 1.86, 95% confidence interval 1.83-1.90).

CONCLUSIONS: These findings raise the possibility within this vulnerable critical period, midlife women with a higher menopause symptom burden may be most vulnerable for chronic pain.

[Pain and sleep problems predict quality of life for veterans with serious mental illness.](#)

[Travaglini LE](#)¹, [Cosgrave J](#)², [Klingaman EA](#)¹.

Psychiatr Rehabil J. **2019 Mar 7**. doi: 10.1037/prj0000358. PMID: 30843720. [Epub ahead of print]

PURPOSE: Poor sleep and pain are common in veterans with serious mental illness (SMI), yet it is unclear how these may impact dimensions of quality of life. As such, this study examined independent and additive contributions of sleep and pain difficulties on quality of life (QoL) among a sample of veterans with SMI and insomnia.

METHOD: Participants were 57 veterans with SMI (schizophrenia spectrum, bipolar, or major depressive disorders with significant functional impairment) and at least subthreshold insomnia (Insomnia Severity Index ≥ 8). Measures assessed sleep quality (Pittsburgh Sleep Quality Index), pain intensity (Pain Numeric Rating Scale [PNRS]), pain interference (Short Form 12 Health Survey), and QoL (World Health Organization Quality of Life-BREF). Multivariate multiple regression analyses examined the effects of sleep quality and pain on QoL.

RESULTS: Forty-one veterans (71.9%) reported moderate-to-severe pain (PNRS ≥ 4). Poorer sleep quality was associated with greater pain interference and worse physical, emotional, and environmental QoL. Sleep quality, not pain, explained significant variance in environmental QoL ($b = -2.30$; 95% confidence interval [CI: -4.16, .43]). Pain interference, not sleep quality, explained significant variance in physical health-related QoL ($b = -.23$; 95% CI [-.38, -.08]).

CONCLUSIONS: Results reveal the importance of screening for insomnia and chronic pain among veterans with SMI. For these veterans who already struggle with daytime functioning, interventions such as integrated cognitive-behavioral therapy for pain-related insomnia are warranted. Such treatments must account for how sleep disturbance and chronic pain may differentially impact multiple facets of QoL

CHRONIC PAIN (Continued)

[NMDA receptor antagonists and pain relief: A meta-analysis of experimental trials.](#)

[Thompson T](#)¹, [Whiter F](#)², [Gallop K](#)², [Veronese N](#)², [Solmi M](#)², [Newton P](#)², [Stubbs B](#)².

Neurology. **2019 Mar 6**. pii: 10.1212/WNL.0000000000007238. doi: 10.1212/WNL.0000000000007238. PMID: 30842296. [Epub ahead of print]

OBJECTIVE: We conducted a meta-analysis of controlled trials that used experimental models of acute pain and hyperalgesia to examine the analgesic effects of NMDA receptor (NMDAR) antagonists.

METHODS: Six major databases were systematically searched (to March 2018) for studies using human evoked pain models to compare NMDAR antagonists with no-intervention controls. Pain outcome data were analyzed with random-effects meta-analysis.

RESULTS: Searches identified 70 eligible trials (n = 1,069). Meta-analysis found that low-dose ketamine (<1 mg/kg) produced a decrease in hyperalgesic area (standardized mean difference 0.54, 95% confidence interval [CI] 0.34, 0.74, *p* < 0.001) and a 1.2-point decrease (95% CI 0.88, 1.44, *p* < 0.001) in pain ratings from 4.6 to 3.4 on a 0-10 scale (a 26% reduction). Similar analgesia was observed for acute and hyperalgesic models and was constant across the dosing range (0.03-1.00 mg/kg). Moderate to high variability in effect size was observed and mild side effects (e.g., sedation, sensory disturbance) were common. No effects of dextromethorphan were found.

CONCLUSIONS: Findings provide robust evidence for analgesic and antihyperalgesic effects of ketamine, supporting its utility for acute and chronic pain management. However, pain relief was modest, suggesting ketamine may potentially be most useful when opioids are contraindicated, rapid analgesia is required, or for pain resistant to conventional medication.

[Evaluation of the Preliminary Validity of Misuse of Prescription Pain Medication Items from the Patient-Reported Outcomes Measurement Information System \(PROMIS\)®.](#)

[You DS](#)¹, [Hah JM](#)¹, [Collins S](#)¹, [Ziadni MS](#)¹, [Domingue BW](#)², [Cook KF](#)³, [Mackey SC](#)¹.

Pain Med. **2019 Mar 11**. pii: pnz001. doi: 10.1093/pm/pnz001. PMID: 30856659. [Epub ahead of print]

OBJECTIVE: The National Institutes of Health's Patient-Reported Outcomes Measurement Information System (PROMIS)® includes an item bank for measuring misuse of prescription pain medication (PROMIS-Rx Misuse). The bank was developed and its validity evaluated in samples of community-dwelling adults and patients in addiction treatment programs. The goal of the current study was to investigate the validity of the item bank among patients with mixed-etiology chronic pain conditions.

METHOD: A consecutive sample of 288 patients who presented for initial medical evaluations at a tertiary pain clinic completed questionnaires using the open-source Collaborative Health Outcomes Information Registry. Participants were predominantly middle-aged (M [SD] = 51.6 [15.5] years), female (62.2%), and white/non-Hispanic (51.7%). Validity was evaluated by estimating the association between PROMIS-Rx Misuse scores and scores on other measures and testing the ability of scores to distinguish among risk factor subgroups expected to have different levels of prescription pain medicine misuse (known groups analyses).

RESULTS: Overall, score associations with other measures were as expected and scores effectively distinguished among patients with and without relevant risk factors.

CONCLUSION: The study results supported the preliminary validity of PROMIS-Rx Misuse item bank scores for the assessment of prescription opioid misuse in patients visiting an outpatient pain clinic.

[Interprofessional care improves health-related well-being and reduces medical costs for chronic pain patients.](#)

[Seitz T](#)^{1,2}, [Stastka K](#)³, [Schiffinger M](#)⁴, [Turk BR](#)⁵, [Löffler-Stastka H](#)¹.

Bull Menninger Clin. **2019 Mar 6**:1-23. doi: 10.1521/bumc_2019_83_01. PMID: 30840490. [Epub ahead of print]

This study evaluated whether patients with somatic symptom disorder, expressing chronic pain that could not be attributed to a medical condition, would benefit from an 8-week inpatient residence at a psychiatric ward. In the 1-year follow-up after termination the authors examined the extent to which the integrated treatment decreased patient costs. A total of 106 patients participated in the follow-up and reported a significant improvement in their general health (Cohen's *d* = 1.5-2.21), a decrease in impairment due to pain (*d* = 2.24), and a decrease in symptom severity (*d* = 1.29). They took fewer medications and sick days, reported fewer hospital stays and medical examinations, and consulted and changed physicians and outpatient clinics less often (*d* = 0.55-1.1). The average cost per patient was cut in half, down to €80,000/\$96,000 per year. From a clinical standpoint, group analysis that focused on aggression was the most effective intervention.

IRRITABLE BOWEL SYNDROME

[Rifaximin for Irritable Bowel Syndrome \(IBS\) in Gulf War Veterans: Losing the Battle but Winning the War?](#)

Harris LA¹.

Dig Dis Sci. 2019 Mar;64(3):609-610. doi: 10.1007/s10620-019-05505-w. PMID: 30725300.

Conquering the treatment of irritable bowel syndrome (IBS) is somewhat like trying to win a war. Many enemies have been implicated in its causation, among them visceral hypersensitivity, alterations in intestinal permeability and motility, brain–gut dysregulation, defects in the autonomic nervous system, alterations in GI immune function, hormones, psychosocial factors, and most recently alterations in the gut microbiome. Many have realized that the symptoms of small intestinal bacterial overgrowth (SIBO) such as changes in bowel habit, cramping, and bloating to mention just a few are remarkably similar to IBS. Therefore, testing for SIBO and treating it with antibiotics, particularly the poorly absorbable broad-spectrum antibiotic rifaximin, have conceptually evolved in the area of IBS therapies. Further support for the post-infectious nature of IBS is also found in the identification of biomarkers that are antibodies to bacterial toxins in patients who have IBS with diarrhea (IBS-D) or mixed bowel habits (IBS-M) combined with the observation that chronic diseases such as IBS can often follow infectious gastroenteritis. With over 50% of military personnel having gastroenteritis while being deployed in the Gulf, this would seem to be an ideal population in which to study post-infectious IBS. In this issue of *Digestive Diseases and Sciences*, Tuteja et al. reported that up to a third of Gulf War (GW) Veterans have IBS, and despite the pressures of war and posttraumatic stress disorder, the biggest risk factor for getting IBS may indeed be prior infection. Given the high number of subjects identified, the authors tested the hypothesis that rifaximin would “normalize SIBO” and thus reduce IBS symptoms.

In this double-blind, placebo-controlled trial, [link to abstract of [Tuteja et al. article](#), previously cited in Research Alerts] the authors identified 120 GW Veterans meeting Rome III criteria for IBS. Fifty of those with non-constipated IBS were randomized after lactulose hydrogen breath testing (LHBT) to receive either rifaximin 550 mg or placebo b.i.d. after a 2-week “run-in” period. Patients were advised to not change medications or diet during the study period. Evaluated outcome measures included stool frequency, stool consistency (via the Bristol stool scale), urgency, severity of abdominal pain, severity of bloating, and global improvement. Quality of life (QoL) was assessed with the IBS-QoL scale. Lactulose breath testing was performed at baseline and again after 2 weeks of treatment. Only 44 patients completed the study (38 men, 6 women, median age = 52). Rifaximin was not associated with significant improvement in global symptoms, abdominal pain, stool frequency, urgency, bloating, or stool consistency (all $P \geq 0.25$) or QoL (all $P \geq 0.26$). Lactulose breath testing showed no difference between rifaximin and placebo (7% vs. 22%, $P = 0.54$). ...

Link to full text of this excerpt of Editorial in [Digestive Diseases and Sciences](#)

[Fasting-Mimicking Diet Modulates Microbiota and Promotes Intestinal Regeneration to Reduce Inflammatory Bowel Disease Pathology.](#)

Rangan P¹, Choi I¹, Wei M¹, Navarrete G¹, Guen E¹, Brandhorst S¹, Enyati N², Pasia G¹, Maesincee D¹, Ocon V¹, Abdulridha M¹, Longo VD³.

Cell Rep. 2019 Mar 5;26(10):2704-2719.e6. doi: 10.1016/j.celrep.2019.02.019. PMID: 30840892.

Dietary interventions are potentially effective therapies for inflammatory bowel diseases (IBDs). We tested the effect of 4-day fasting-mimicking diet (FMD) cycles on a chronic dextran sodium sulfate (DSS)-induced murine model resulting in symptoms and pathology associated with IBD. These FMD cycles reduced intestinal inflammation, increased stem cell number, stimulated protective gut microbiota, and reversed intestinal pathology caused by DSS, whereas water-only fasting increased regenerative and reduced inflammatory markers without reversing pathology. Transplants of *Lactobacillus* or fecal microbiota from DSS- and FMD-treated mice reversed DSS-induced colon shortening, reduced inflammation, and increased colonic stem cells. In a clinical trial, three FMD cycles reduced markers associated with systemic inflammation. The effect of FMD cycles on microbiota composition, immune cell profile, intestinal stem cell levels and the reversal of pathology associated with IBD in mice, and the anti-inflammatory effects demonstrated in a clinical trial show promise for FMD cycles to ameliorate IBD-associated inflammation in humans.

IRRITABLE BOWEL SYNDROME (Continued)

[Opioid-induced constipation in chronic pain: Experience with 180 patients.](#)

[Rivera IV](#)¹, [Clavarana LV](#)², [Velasco PG](#)³, [Ramos CM](#)³.

J Opioid Manag. **2019 Jan/Feb**;15(1):69-76. doi: 10.5055/jom.2019.0487. PMID: 30855724.

BACKGROUND: Opioid-induced constipation (OIC) is a common adverse effect of opioid analgesic therapy that significantly affects the patient's quality of life and may lead to poor adherence and treatment failure. Tapentadol, oxycodone/naloxone, and some transcutaneous opioids were associated with less frequent OIC than morphine or oxycodone in controlled clinical trials. However, few studies compare these newer opioids with each other in terms of OIC.

METHODS AND PATIENTS: We performed a cross-sectional observational study that evaluated the degree of OIC and risk factors in patients receiving long-term treatment (>1 year) at a tertiary care pain unit with tapentadol, oxycodone/naloxone, hydromorphone, fentanyl, or buprenorphine. The degree of constipation was evaluated using the Bowel Function Index (BFI).

RESULTS: Out of 180 enrolled patients (median age: 61.5 years, 66.7 percent women, mean treatment duration: 3 years), 57.2 percent suffered from nociceptive pain, 33.9 percent from mixed pain, and 8.9 percent from neuropathic pain. The most commonly prescribed opioids were oxycodone/naloxone (44.4 percent) and tapentadol (37.8 percent). At the time of the study, 73.9 percent of patients had constipation (BFI > 29), and 21.7 percent had severe constipation (BFI > 69). In a multiple linear regression analysis, previous constipation, morphine equivalent dose, treatment with fentanyl and interaction between morphine equivalent dose and hydromorphone were associated with more severe constipation.

CONCLUSIONS: Most patients receiving long-term treatment with opioids present symptoms of constipation. The bowel function profile was more favorable for tapentadol and oxycodone, with no differences between them, even though morphine equivalent doses were on average higher in the tapentadol group.

OTHER RESEARCH OF INTEREST

[Comparing post-Gulf War and post-9/11 era of service among veterans: Intimate partner violence and substance use by race and ethnicity.](#)

[Cancio R](#)¹, [Altal D](#)¹.

J Ethn Subst Abuse. **2019 Feb 26**:1-27. doi: 10.1080/15332640.2019.1571978. PMID: 30806199. [Epub ahead of print]

Using structural equation modeling to examine intimate partner violence (IPV) among post-Gulf War and post-9/11 military families, this study considers variations of IPV from the point of the perpetrator to test the impact of demographic factors on the type of IPV most prevalent among military perpetrators. The study sample contains information about 449 male veterans from the National Longitudinal Study of Adolescent to Adult Health (1994-2008): Waves I and IV in-home interviews. Study findings indicate that the perpetration of physical and sexual IPV depends on the context of veteran cohort and race/ethnicity.

[Ad libitum Weekend Recovery Sleep Fails to Prevent Metabolic Dysregulation during a Repeating Pattern of Insufficient Sleep and Weekend Recovery Sleep.](#)

[Depner CM](#)¹, [Melanson EL](#)², [Eckel RH](#)³, [Snell-Bergeon JK](#)⁴, [Perreault L](#)³, [Bergman BC](#)³, [Higgins JA](#)⁴, [Guerin MK](#)¹, [Stothard ER](#)¹, [Morton SJ](#)¹, [Wright KP Jr](#)⁵.

Curr Biol. **2019 Feb 11**. pii: S0960-9822(19)30098-3. doi: 10.1016/j.cub.2019.01.069. PMID: 30827911. [Epub ahead of print]

People commonly increase sleep duration on the weekend to recover from sleep loss incurred during the workweek. Whether ad libitum weekend recovery sleep prevents metabolic dysregulation caused by recurrent insufficient sleep is unknown. Here, we assessed sleep, circadian timing, energy intake, weight gain, and insulin sensitivity during sustained insufficient sleep (9 nights) and during recurrent insufficient sleep following ad libitum weekend recovery sleep. Healthy, young adults were randomly assigned to one of three groups: (1) control (CON; 9-h sleep opportunities, n = 8), (2) sleep restriction without weekend recovery sleep (SR; 5-h sleep opportunities, n = 14), and (3) sleep restriction with weekend recovery sleep (WR; insufficient sleep for 5-day workweek, then 2 days of weekend recovery, then 2 nights of insufficient sleep, n = 14). For SR and WR groups, insufficient sleep increased after-dinner energy intake and body weight versus baseline. During ad libitum weekend recovery sleep, participants cumulatively slept ~1.1 h more than baseline, and after-dinner energy intake decreased versus insufficient sleep. However, during recurrent insufficient sleep following the weekend, the circadian phase was delayed, and after-dinner energy intake and body weight increased versus baseline. In SR, whole-body insulin sensitivity decreased ~13% during insufficient sleep versus baseline, and in WR, whole-body, hepatic, and muscle insulin sensitivity decreased ~9%-27% during recurrent insufficient sleep versus baseline. Furthermore, during the weekend, total sleep duration was lower in women versus men, and energy intake decreased to baseline levels in women but not in men. Our findings suggest that weekend recovery sleep is not an effective strategy to prevent metabolic dysregulation associated with recurrent insufficient sleep.

OTHER RESEARCH OF INTEREST (Continued)

[Ozone therapy in 65 patients with fibromyalgia: an effective therapy.](#)

[Tirelli U](#)¹, [Cirrito C](#), [Pavanello M](#), [Piasentin C](#), [Lleshi A](#), [Taibi R](#).

Eur Rev Med Pharmacol Sci. **2019 Feb**;23(4):1786-1788. doi: 10.26355/eurrev_201902_17141. PMID: 30840304.

OBJECTIVE: Fibromyalgia is a chronic disorder with a very complex symptomatology. Although generalized severe pain is considered to be the cardinal symptom of the disease, many other associated symptoms, especially non-restorative sleep, chronic fatigue, anxiety, and depressive symptoms also play a relevant role in the degree of disability characteristic of the disease. Ozone therapy, which is used to treat a wide range of diseases and seems to be particularly useful in the treatment of many chronic diseases, is thought to act by exerting a mild, transient, and controlled oxidative stress that promotes an up-regulation of the antioxidant system and a modulation of the immune system. According to these mechanisms of action, it was hypothesized that ozone therapy could be useful in fibromyalgia management, where the employed therapies are very often ineffective.

PATIENTS AND METHODS: Sixty-five patients with fibromyalgia, according to the definition of the American College of Rheumatology (Arthritis Rheum 1990; 33: 160-172), were treated at the MEDE Clinic (Sacile, Pordenone, Italy) from February 2016 to October 2018. Females were 55 and males were 10; age ranged from 30 to 72 years, and the time from fibromyalgia diagnosis ranged from 0.5 to 33 years. Treatment was made by autohemotransfusion in 55 patients and by ozone rectal insufflations in 10 patients, according to SIOOT (Scientific Society of Oxygen Ozone Therapy) protocols, twice a week for one month and then twice a month as maintenance therapy.

RESULTS: We found a significant improvement (>50% of symptoms) in 45 patients (70%). No patient reported important side effects. In conclusion, at our knowledge, this is the largest study of patients with fibromyalgia treated with ozone therapy reported in the literature and it demonstrates that the ozone therapy is an effective treatment for fibromyalgia patients without significant side effects.

CONCLUSIONS: At the moment, ozone therapy seems a treatment that, also because without any side effect, is possible to be proposed to patients with fibromyalgia that are not obtaining adequate results from other available treatments and it can be considered as complementary/integrative medicine.

[Accuracy, completeness and accessibility of online information on fibromyalgia.](#)

[Basavakumar D](#)¹, [Flegg M](#)², [Eccles J](#)¹, [Ghezzi P](#)³.

Rheumatol Int. **2019 Mar 6**. doi: 10.1007/s00296-019-04265-0. PMID: 30840100. [Epub ahead of print]

Fibromyalgia is a multi-factorial illness primarily characterised by widespread chronic pain and fatigue, with several symptoms and associated conditions. Due to a lack of clinical awareness and an absence of objective diagnostic measures, fibromyalgia patients often engage with online health information. The aim is to investigate the completeness and trustworthiness of the information available online on fibromyalgia. Google.co.uk was searched for 'fibromyalgia', the first 200 webpages were imported and 148 were analysed for standard health information quality criteria (JAMA score, HONcode) as well as completeness of information in terms of symptoms, causes and treatments mentioned. The most frequent typology of webpages was from health professionals (38%), with commercial websites being less frequent (7%). Overall, the quality, completeness and accessibility of online health information was poor. Completeness of coverage for symptoms, causes and associated conditions was especially lacking, with pages from not-for-profit organisations discussing the highest number of symptoms (median 8, min 0, max 11, interquartile range, IQR 4.5; n = 14) compared to the rest of the websites in the search engine results (median 4, min 0, max 11, IQR 4; n = 134). Mean readability was grade 9 (median 9, min 1, max 18, IQR 3), with only 8% websites meeting the recommended readability of grade 6. The Internet provides incomplete information on fibromyalgia, which does not fulfil the most queried aspect(s) by patients, symptoms, and may be difficult to understand by lay persons. Not-for-profit organisations provide the most complete information compared to other types of websites.

OTHER RESEARCH OF INTEREST (Continued)**[Variability in daily self-reported emotional symptoms and fatigue measured over eight weeks in community dwelling individuals with traumatic brain injury.](#)**

[Juengst SB](#)^{1,2}, [Terhorst L](#)^{3,4}, [Kew CL](#)^{1,2}, [Wagner AK](#)^{5,6,7}.

Brain Inj. **2019 Mar 5**:1-7. doi: 10.1080/02699052.2019.1584333. PMID: 30836017. [Epub ahead of print]

OBJECTIVE: To investigate within-person variability in daily self-reported emotional and fatigue symptoms and factors associated with high within-person variability among individuals with chronic traumatic brain injury (TBI).

DESIGN: This was a prospective descriptive pilot study of n = 18 adults with chronic TBI (2-27 years post-injury) who owned and could independently use an Apple or Android device.

METHODS: Participants completed daily assessments for 8 weeks via smartphone. Outcome measures included the Positive and Negative Affect Schedule, Patient Health Questionnaire-2, Generalized Anxiety Disorder-2, and a 7-point fatigue rating. We examined within-person variability over time using individual Multilevel Linear Models. We categorized within-person variability as High or Low based on individual standard deviations in relationship to sample standard deviation.

RESULTS: Significant temporal within-person variability occurred for all measures. High variability was associated with more symptom reporting versus Low variability, and variability was associated with sex (High variability: 88% women; Low variability 90% men).

CONCLUSIONS: Symptom measurement at a single time point among adults with chronic TBI may not capture day-to-day symptom fluctuation and may misidentify individuals in need of intervention. Assessing symptom profiles over time to capture temporal and individual variability may provide a more ecologically valid measure for managing long-term symptoms after TBI.

[Effects of a Novel Barley-based Formulation on Allergic Rhinitis: A Randomized Controlled Trial.](#)

[Derakhshan A](#)¹, [Khodadoost M](#)², [Ghanei M](#)³, [Gachkar L](#)⁴, [Hajimahdipour H](#)⁵, [Taghipour A](#)⁶, [Yousefi J](#)⁷, [Khoshkhui M](#)⁸, [Azad FJ](#)⁸.

Endocr Metab Immune Disord Drug Targets. **2019 Mar 5**. doi: 10.2174/1871530319666190306100611. PMID: 30843497. [Epub ahead of print]

INTRODUCTION: Current treatment options for Allergic Rhinitis (AR) may have their own limitations and side effects. This study aimed to investigate the effects of Ma-al-Shaeer (MS), a novel natural formulation based on *Hordeum vulgare*, in treatment of AR compared with Fexofenadine (FX).

METHOD: A total of 77 patients with AR were divided into two groups: MS group (n=38) and FX group (n=39). The first group received 15 mg of dried MS powder, and the second group received 60 mg of FX twice daily for 14 days. At baseline (week zero) and after the 14-day treatment period (week two), both groups were evaluated for sneezing, rhinorrhea, nasal congestion, nasal itching, post nasal drip, eye, throat, or ear symptoms, headache, cough, mental function, quality of life scores, blood eosinophil count and total IgE levels. Rhinitis control assessment tests were conducted at week zero and again at one week after cessation of treatment (week three) in both groups.

RESULTS: All symptoms of AR except cough were significantly reduced in both groups; for nasal congestion, post nasal drip, and headache, the MS treatment was found to be superior. Rhinitis control was significantly increased after treatment in both groups (p value < 0.001). Both drugs significantly reduced total IgE levels. There was no significant change in eosinophil count in either group.

CONCLUSION: MS formulation based on *H. vulgare* may be an effective treatment for AR. Further studies are needed to confirm the effect of MS as an alternative treatment in AR.

###