

GULF WAR ILLNESS

[Targeting intracellular calcium stores alleviates neurological morbidities in a DFP-based rat model of Gulf War Illness.](#)

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Gulf War Illness (GWI) is a chronic multi-symptom disorder afflicting the veterans of the First Gulf War, and includes neurological symptoms characterized by depression and memory deficits. Chronic exposure to organophosphates (OP) is considered a leading cause for GWI, yet its pathobiology is not fully understood. We recently observed chronic elevations in neuronal Ca²⁺ levels ([Ca²⁺]_i) in an OP- diisopropyl fluorophosphate (DFP) based rat model for GWI. This study was aimed at identifying mechanisms underlying elevated [Ca²⁺]_i in this DFP model and investigating whether their therapeutic targeting could improve GWI-like neurological morbidities. Male Sprague-Dawley rats (9-wks) were exposed to DFP (0.5 mg/kg, s.c, 1x-daily for 5-d) and at 3-mos post DFP exposure, behavior was assessed and rats were euthanized for protein estimations and ratiometric Fura-2 [Ca²⁺]_i estimations in acutely dissociated hippocampal neurons. In DFP rats, a sustained elevation in intracellular Ca²⁺ levels occurred, and pharmacological blockade of Ca²⁺-induced Ca²⁺-release mechanisms significantly lowered elevated [Ca²⁺]_i in DFP neurons. Significant reductions in the protein levels of the ryanodine receptor (RyR) stabilizing protein Calstabin2 were also noted. Such a post-translational modification would render RyR "leaky" resulting in sustained DFP [Ca²⁺]_i elevations. Antagonism of RyR with levetiracetam significantly lower elevated [Ca²⁺]_i in DFP neurons and improved GWI-like behavioral symptoms. Since Ca²⁺ is a major second messenger molecule, such chronic increases in its levels could underlie pathological synaptic plasticity that expresses itself as GWI morbidities. Our studies show that treatment with drugs targeted at blocking intracellular Ca²⁺ release could be effective therapies for GWI neurological morbidities.

CHRONIC FATIGUE SYNDROME

[Diagnostic sensitivity of 2-day cardiopulmonary exercise testing in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.](#)

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J Transl Med. **2019 Mar 14**;17(1):80. doi: 10.1186/s12967-019-1836-0. PMID: 30871578.

BACKGROUND: There are no known objective biomarkers to assist with the diagnosis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). A small number of studies have shown that ME/CFS patients exhibit an earlier onset of ventilatory threshold (VT) on the second of two cardiopulmonary exercise tests (CPET) performed on consecutive days. However, cut-off values which could be used to differentiate between ME/CFS patients have not been established.

METHODS: 16 ME/CFS patients and 10 healthy controls underwent CPET on a cycle-ergometer on 2-consecutive days. Heart rate (HR), ventilation, ratings of perceived exertion (RPE) and work rate (WR) were assessed on both days.

RESULTS: WR at VT decreased from day 1 to day 2 and by a greater magnitude in ME/CFS patients ($p < 0.01$ group \times time interaction). No interaction effects were found for any other parameters. ROC curve analysis of the percentage change in WR at VT revealed decreases of -6.3% to -9.8% provided optimal sensitivity and specificity respectively for distinguishing between patients with ME/CFS and controls.

CONCLUSION: The decrease in WR at VT of 6.3-9.8% on the 2nd day of consecutive-day CPET may represent an objective biomarker that can be used to assist with the diagnosis of ME/CFS.

CHRONIC FATIGUE SYNDROME (Continued)

Implementation of stepped care for patients with chronic fatigue syndrome in community-based mental health care: outcomes at post-treatment and long-term follow-up.

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Behav Cogn Psychother. 2019 Mar 12:1-11. doi: 10.1017/S1352465819000110. PMID: 30859928. [Epub ahead of print]

BACKGROUND: Cognitive behavioural therapy (CBT) is an evidence-based treatment for chronic fatigue syndrome (CFS). Stepped care for CFS, consisting of a minimal intervention followed by face-to-face CBT, was found efficacious when tested in a CFS specialist centre. Stepped care implemented in a community-based mental health centre (MHC) has not yet been evaluated.

AIMS: (1) To test the effectiveness of stepped care for CFS implemented in a MHC at post-treatment and at long-term follow-up; and (2) compare post-treatment outcomes of implemented stepped care with treatment outcomes of a CFS specialist centre.

METHOD: An uncontrolled study was used to test effectiveness of stepped care implemented in a MHC (n = 123). The outcomes of implemented care were compared with the outcomes of specialist care reported in previous studies (n = 583). Data on outcomes from implemented stepped care were gathered at post-treatment and at long-term follow-up. Mixed models were used as method of analysis.

RESULTS: Fatigue decreased and physical functioning increased significantly following implemented stepped care (both p < .001). The follow-up was completed by 94 patients (78%) within 1-6 years after treatment. Treatment effects were sustained to follow-up. Patients in the MHC showed less improvement directly following stepped care compared with patients in a CFS specialist centre (p < .01).

CONCLUSION: Implemented stepped care for CFS is effective with sustained treatment gains at long-term follow-up. There is room for improvement when compared with outcomes of a CFS specialist centre. Some suggestions are made on how to improve stepped care.

Internet-Based Cognitive Behavioral Therapy in Stepped Care for Chronic Fatigue Syndrome: Randomized Noninferiority Trial.

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J Med Internet Res. 2019 Mar 14;21(3):e11276. doi: 10.2196/11276. PMID: 30869642.

BACKGROUND: Internet-based cognitive behavioral therapy (I-CBT) leads to a reduction of fatigue severity and disability in adults with chronic fatigue syndrome (CFS). However, not all patients profit and it remains unclear how I-CBT is best embedded in the care of CFS patients.

OBJECTIVE: This study aimed to compare the efficacy of stepped care, using therapist-assisted I-CBT, followed by face-to-face (f2f) cognitive behavioral therapy (CBT) when needed, with f2f CBT (treatment as usual [TAU]) on fatigue severity. The secondary aim was to investigate treatment efficiency.

METHODS: A total of 363 CFS patients were randomized to 1 of the 3 treatment arms (n=121). There were 2 stepped care conditions that differed in the therapists' feedback during I-CBT: prescheduled or on-demand. When still severely fatigued or disabled after I-CBT, the patients were offered f2f CBT. Noninferiority of both stepped care conditions to TAU was tested using analysis of covariance. The primary outcome was fatigue severity (Checklist Individual Strength). Disabilities (Sickness Impact Profile -8), physical functioning (Medical Outcomes Survey Short Form-36), psychological distress (Symptom Checklist-90), and proportion of patients with clinically significant improvement in fatigue were the secondary outcomes. The amount of invested therapist time was compared between stepped care and TAU. Exploratory comparisons were made between the stepped care conditions of invested therapist time and proportion of patients who continued with f2f CBT.

RESULTS: Noninferiority was indicated, as the upper boundary of the one-sided 98.75% CI of the difference in the change in fatigue severity between both forms of stepped care and TAU were below the noninferiority margin of 5.2 (4.25 and 3.81, respectively). The between-group differences on the secondary outcomes were also not significant (P=.11 to P=.79). Both stepped care formats required less therapist time than TAU (median 8 hours, 9 minutes and 7 hours, 25 minutes in stepped care vs 12 hours in TAU; P<.001). The difference in therapist time between both stepped care formats was not significant. Approximately half of the patients meeting step-up criteria for f2f CBT after I-CBT did not continue.

CONCLUSIONS: Stepped care, including I-CBT followed by f2f CBT when indicated, is noninferior to TAU of f2f CBT and requires less therapist time. I-CBT for CFS can be used as a first step in stepped care.

TRIAL REGISTRATION: Nederlands Trial Register NTR4809;

<http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4809> (Archived by WebCite at <http://www.webcitation.org/74SWkw1V5>).

CHRONIC FATIGUE SYNDROME (Continued)

[Artificial intelligence based discovery of the association between depression and chronic fatigue syndrome.](#)

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J Affect Disord. 2019 Mar 8;250:380-390. doi: 10.1016/j.jad.2019.03.011. 30877861. PMID: 30877861 [Epub ahead of print]

BACKGROUND: Both of the modern medicine and the traditional Chinese medicine classify depressive disorder (DD) and chronic fatigue syndrome (CFS) to one type of disease. Unveiling the association between depressive and the fatigue diseases provides a great opportunity to bridge the modern medicine with the traditional Chinese medicine.

METHODS: In this work, 295 general participants were recruited to complete Zung Self-Rating Depression Scales and Chalder Fatigue Scales, and meanwhile, to donate plasma and urine samples for ¹H NMR-metabolic profiling. Artificial intelligence methods was used to analysis the underlying association between DD and CFS. Principal components analysis (PCA) and partial least squares discriminant analysis (PLS-DA) were used to analyze the metabolic profiles with respect to gender and age. Variable importance in projection and t-test were employed in conjunction with the PLS-DA models to identify the metabolite biomarkers. Considering the asymmetry and complexity of the data, convolutional neural networks (CNN) model, an artificial intelligence method, was built to analyze the data characteristics between each groups.

RESULTS: The results showed the gender- and age-related differences for the candidate biomarkers of the DD and the CFS diseases, and indicated the same and different biomarkers of the two diseases. PCA analysis for the data characteristics reflected that DD and CFS was separated completely in plasma metabolite. However, DD and CFS was merged into one group.

LIMITATION: Lack of transcriptomic analysis limits the understanding of the association of the DD and the CFS diseases on gene level.

CONCLUSION: The unmasked candidate biomarkers provide reliable evidence to explore the commonality and differences of the depressive and the fatigue diseases, and thereby, bridge over the traditional Chinese medicine with the modern medicine.

HEADACHE and MIGRAINE

[What are the research priorities for idiopathic intracranial hypertension? A priority setting partnership between patients and healthcare professionals.](#)

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BMJ Open. 2019 Mar 15;9(3):e026573. doi: 10.1136/bmjopen-2018-026573. PMID: 30878991.

OBJECTIVE: Idiopathic intracranial hypertension (IIH) is under-researched and the aim was to determine the top 10 research priorities for this disease.

DESIGN: A modified nominal group technique was used to engage participants who had experience of IIH.

SETTING: This James Lind Alliance Priority Setting Partnership was commissioned by IIH UK, a charity.

PARTICIPANTS: People with IIH, carers, family and friends, and healthcare professionals participated in two rounds of surveys to identify unique research questions unanswered by current evidence. The most popular 26 uncertainties were presented to stakeholders who then agreed the top 10 topics.

RESULTS: The top 10 research priorities for IIH included aetiology of IIH, the pathological mechanisms of headache in IIH, new treatments in IIH, the difference between acute and gradual visual loss, the best ways to monitor visual function, biomarkers of the disease, hormonal causes of IIH, drug therapies for the treatment of headache, weight loss and its role in IIH and finally, the best intervention to treat IIH and when should surgery be performed.

CONCLUSIONS: This priority setting encouraged people with direct experience of IIH to collectively identify critical gaps in the existing evidence. The overarching research aspiration was to understand the aetiology and management of IIH.

HEADACHE and MIGRAINE (Continued)

[Psychometric Validation of the Role Function Restrictive Domain of the Migraine Specific Quality-of-Life Questionnaire Version 2.1 Electronic Patient-Reported Outcome in Patients With Episodic and Chronic Migraine.](#)

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Headache. **2019 Mar 12.** doi: 10.1111/head.13497. PMID: 30861580. [Epub ahead of print]

OBJECTIVES: To assess the measurement properties of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQv2.1) electronic patient-reported outcome (ePRO) Role Function-Restrictive (RFR) domain to evaluate the functional impact of migraine in patients with episodic (EM) or chronic migraine (CM) enrolled in clinical trials.

METHODS: The 7-item MSQv2.1 ePRO RFR measures the functional impact of migraine on relationships with family and friends, leisure time, work or daily activities, productivity, concentration, tiredness, and energy. Measurement properties of the RFR were assessed using data from 2 EM (CGAG [n = 851] and CGAH [n = 909]) and 1 CM (CGAI [n = 1090]) Phase 3 galcanezumab clinical trials. Anchor- and distribution-based analyses were utilized to derive a responder threshold for clinical interpretation of change over time. The Migraine Disability Assessment (MIDAS), Patient Global Impression of Severity (PGI-S), Patient Global Impression of Improvement (PGI-I), and migraine headache days (MHD) served as anchors. Responsiveness and responder threshold analyses were completed from baseline to the average of months 4-6 for EM studies, and from baseline to month 3 for the CM study; timeframes selected were based on the primary endpoints in these studies.

RESULTS: Cronbach's alpha values for internal consistency reliability were 0.93, 0.92, and 0.92, for CGAG, CGAH, and CGAI, respectively. Test-retest reliability intra-class correlation coefficients were 0.82 and 0.84 for CGAG and CGAH, and 0.85 for CGAI in stable patients. Convergent validity was supported by moderate to strong correlations (≥ 0.30) between the RFR and both MIDAS and PGI-S. Known-groups validity was established between subgroups stratified by baseline PGI-S and MHD ($P < .05$; $\delta = 0.35$ -1.96). For the EM studies, anchor variables suggested a change of ≥ 25 points (equivalent to 9 points/state changes on raw scale) in the RFR was an appropriate threshold to interpret a treatment benefit. For the CM study a change of ≥ 17.14 points (6 points/state changes on raw scale) was an appropriate threshold. In all 3 studies, significantly ($P < .01$) more galcanezumab patients achieved the responder definition thresholds, as compared to placebo (odds ratios of 1.98, 2.45, 2.27, 2.44, 1.64, and 1.66 for the 120 and 240 mg arms in the CGAG, CGAH, and CGAI trials, respectively).

CONCLUSION: The MSQv2.1 ePRO RFR has sufficient reliability, validity, responsiveness, and appropriate interpretation standards for use in EM and CM clinical trials to assess the functional impact of migraine.

[Does insomnia modify the association between C-reactive protein and migraine? The Tromsø Study 2015-2016.](#)

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Cephalalgia. **2019 Mar 12:**333102418825370. doi: 10.1177/0333102418825370. PMID: 30862180. [Epub ahead of print]

BACKGROUND: The relationship between high sensitivity C-reactive protein and migraine is unclear. The aim of this cross-sectional population-based study was to investigate the association between high sensitivity C-reactive protein and types of headache, and to evaluate the impact of insomnia on this association.

METHODS: A total of 20,486 (63%) out of 32,591 invited, aged ≥ 40 years or older, participated in the seventh wave of the Tromsø study conducted in 2015-2016 and had valid information on headache, insomnia and high sensitivity C-reactive protein. The influence of insomnia on the association between questionnaire-based diagnoses of headache and elevated high sensitivity C-reactive protein defined as >3.0 mg/L was assessed using multiple logistic regression, estimating prevalence odds ratio with 95% confidence intervals.

RESULTS: A total of 6290 participants (30.7%) suffered from headache during the last year. Among these, 1736 (8.5%) fulfilled the criteria of migraine, 991 (4.8%) had migraine with aura, 746 (3.6%) migraine without aura (3.8%), and 4554 (22.2%) had non-migrainous headache. In the final multi-adjusted analysis, elevated high sensitivity C-reactive protein was associated with headache (odds ratio 1.10, 95% confidence interval 1.01-1.20), migraine (odds ratio 1.17, 95% confidence interval 1.01-1.35), and migraine with aura (odds ratio 1.23, 95% confidence interval 1.01-1.53). No association was found between elevated high sensitivity C-reactive protein and migraine without aura or non-migrainous headache. The association between high sensitivity C-reactive protein and migraine was strongly dependent on insomnia status. Among individuals with insomnia, elevated high sensitivity C-reactive protein was associated with migraine (odds ratio 1.49, 95% confidence interval 1.02-2.17), and migraine with aura (odds ratio 1.59, 95% confidence interval 1.03-2.45), whereas no such relationship was found among those without insomnia.

CONCLUSIONS: In this cross-sectional study, participants with migraine, in particular migraine with aura, were more likely to have elevated high sensitivity C-reactive protein, evident only among those with insomnia.

HEADACHE and MIGRAINE (Continued)

[Patient Preferences for Preventive Migraine Treatments: A Discrete-Choice Experiment.](#)

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Headache. **2019 Mar 12.** doi: 10.1111/head.13498. PMID: 30861110. [Epub ahead of print]

OBJECTIVE: To understand treatment preferences of people with migraine and the relative importance of improvements in efficacy and avoiding adverse events (AEs), such as cognition problems or weight gain.

BACKGROUND: Current preventive migraine medicines are associated with poor adherence and tolerability. There is an unmet need for effective migraine-specific preventive treatments with fewer AEs.

METHODS: In a web-based discrete-choice experiment survey, respondents who self-reported having ≥ 6 migraine days/month were offered choices between pairs of hypothetical preventive migraine medicines. Six attributes, each with 3 levels, defined the medicines: reduction in headache days per month (10%, 25%, or 50%), frequency of limitations with physical activities (none, 1-category improvement, or 2-category improvement), cognition problems (no problems, thinking problems, or memory problems), weight gain (none, 5% body weight gain, or 10% body weight gain), how the medicine is taken (daily oral pill, once-monthly injection, or twice-monthly injection), and monthly out-of-pocket cost (\$5, \$60, or \$175). The attributes and levels were informed by clinician input, the clinical literature, and 2 focus groups. An experimental design was used to create the pairs of hypothetical medicines for the discrete-choice experiment questions. Random-parameters logit was used to estimate the relative importance of the medicine attributes, and the results were used to predict the percentage of respondents who would select one medicine profile over another and to calculate willingness to pay for changes in attribute levels.

RESULTS: The sample included 300 respondents; 72% indicated that migraines make physical activities difficult all or most of the time, and 81% had taken a prescription medicine to prevent migraine in the last 6 months. Respondents reported having, on average, approximately 16 headache days per month. Among noncost attributes, respondents valued a change from a 10% reduction in migraine days to a 50% reduction more highly than avoiding the worst levels of AEs, but were willing to trade off efficacy for less-severe AEs. Avoiding memory problems was more important than avoiding thinking problems. Avoiding a 10% weight gain was more important than avoiding thinking and memory problems. Respondents preferred a once-monthly injection or daily pill to twice-monthly injection. Respondents, on average, were willing to pay \$84 (95% confidence interval [CI], \$64-\$103) per month to avoid a 10% weight gain, \$59 (95% CI, \$42-\$76) per month to avoid memory problems, \$35 (95% CI, \$20-\$51) per month to avoid a 5% weight gain, and \$32 (95% CI, \$18-\$46) per month to avoid thinking problems.

CONCLUSIONS: A preventive migraine medicine with improved efficacy and AE profile and a favorable mode of administration would be valuable to migraine sufferers. Patients may be willing to trade off efficacy for better AE profiles. Clinicians should work with patients to select treatments that meet each patient's needs.

[DFN-02, Sumatriptan 10 mg Nasal Spray with Permeation Enhancer, for the Acute Treatment of Migraine: A Randomized, Double-Blind, Placebo-Controlled Study Assessing Functional Disability and Subject Satisfaction with Treatment.](#)

[Lipton RB](#)¹, [Munjal S](#)², [Brand-Schieber E](#)², [Rapoport AM](#)³.

CNS Drugs. **2019 Mar 15.** doi: 10.1007/s40263-019-00614-6. PMID: 30877622. [Epub ahead of print]

BACKGROUND: The commercial formulation of sumatriptan nasal spray is an effective option for migraine patients requiring or preferring a non-oral route of drug administration, but its utility is limited by poor absorption and tolerability issues. DFN-02, a new formulation of sumatriptan 10 mg nasal spray, is co-formulated with a permeation enhancer that gives it pharmacokinetics comparable to subcutaneous sumatriptan. As reported previously, DFN-02 was significantly better than placebo on multiple efficacy endpoints at 2 h postdose, including pain freedom, absence of the most bothersome symptom, and pain relief, and its safety and tolerability profiles were excellent.

OBJECTIVE: The objective of this study was to assess the efficacy of acute treatment of migraine with DFN-02, including its effect on migraine-related functional disability and patient satisfaction with treatment.

METHODS: This was a multicenter, randomized, double-blind, placebo-controlled efficacy and safety study of DFN-02 in adults with episodic migraine. Functional disability and subject satisfaction with treatment were prespecified endpoints, assessed in real-time by subjects, using an electronic diary.

RESULTS: In total, 107 subjects were randomized. DFN-02 was significantly superior to placebo for the reduction in functional disability score from pre-dose level at 2 h after treatment (-1.2 vs. -0.6, $p < 0.001$). Subjects treated with DFN-02 were also more likely to be satisfied or very satisfied than subjects treated with placebo at 2 h postdose (70.0% vs. 44.2%, $p = 0.027$). Using the Patient Perception of Migraine Questionnaire-Revised at 24 h postdose, DFN-02 mean scores were significantly superior to placebo for the subscales of efficacy (65.2 vs. 42.5, $p = 0.016$) and function (68.9 vs. 42.1, $p = 0.001$), and for total score (71.0 vs. 56.6, $p = 0.016$); global medication effectiveness ($p = 0.027$); and overall satisfaction ($p = 0.019$). Placebo was significantly better than DFN-02 on the tolerability subscale (94.8 vs. 88.5, $p = 0.026$). At 24 h postdose, subjects reported significantly higher satisfaction with DFN-02 compared with satisfaction reported pre-randomization regarding their usual migraine medication ($p = 0.012$).

CONCLUSION: DFN-02 was superior to placebo for the relief of migraine-related functional disability, and provided greater satisfaction than placebo or subjects' usual acute treatment.

TRIAL REGISTRATION: ClinicalTrials.gov identifier: [NCT02856802](#).

HEADACHE and MIGRAINE (Continued)

[Phase clustering in transcranial magnetic stimulation-evoked EEG responses in genetic generalized epilepsy and migraine.](#)

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Epilepsy Behav. **2019 Mar 12**;93:102-112. doi: 10.1016/j.yebeh.2019.01.029. PMID: 30875639. [Epub ahead of print]

BACKGROUND: Epilepsy and migraine are paroxysmal neurological conditions associated with disturbances of cortical excitability. No useful biomarkers to monitor disease activity in these conditions are available. Phase clustering was previously described in electroencephalographic (EEG) responses to photic stimulation and may be a potential epilepsy biomarker.

OBJECTIVE: The objective of this study was to investigate EEG phase clustering in response to transcranial magnetic stimulation (TMS), compare it with photic stimulation in controls, and explore its potential as a biomarker of genetic generalized epilepsy or migraine with aura.

METHODS: People with (possible) juvenile myoclonic epilepsy (JME), migraine with aura, and healthy controls underwent single-pulse TMS with concomitant EEG recording during the interictal period. We compared phase clustering after TMS with photic stimulation across the groups using permutation-based testing.

RESULTS: We included eight people with (possible) JME (five off medication, three on), 10 with migraine with aura, and 37 controls. The TMS and photic phase clustering spectra showed significant differences between those with epilepsy without medication and controls. Two phase clustering-based indices successfully captured these differences between groups. One participant was tested multiple times. In this case, the phase clustering-based indices were inversely correlated with the dose of antiepileptic medication. Phase clustering did not differ between people with migraine and controls.

CONCLUSION: We present methods to quantify phase clustering using TMS-EEG and show its potential value as a measure of brain network activity in genetic generalized epilepsy. Our results suggest that the higher propensity to phase clustering is not shared between genetic generalized epilepsy and migraine.

CHRONIC PAIN

[Qualitative evaluation of an interdisciplinary chronic pain intervention: outcomes and barriers and facilitators to ongoing pain management.](#)

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J Pain Res. **2019 Mar 1**;12:865-878. doi: 10.2147/JPR.S185652. eCollection 2019. PMID: 30881097.

Background: Many leaders in the field of chronic pain treatment consider interdisciplinary pain management programs to be the most effective treatments available for chronic pain. As programs are instituted and expanded to address demands for nonpharmacological chronic pain interventions, we need to better understand how patients experience program impacts, as well as the challenges and supports patients encounter in trying to maintain and build on intervention gains.

Methods: We conducted a qualitative evaluation of an interdisciplinary chronic pain coaching program at the Atlanta Veterans Affairs. A purposive sample of Veterans were engaged in interviews (n=41) and focus groups (n=20) to elicit patient outcomes and barriers and facilitators to sustainment of improvements. Transcripts were analyzed using matrix and thematic analyses.

Results: Veterans reported various outcomes. Most frequently they described adopting new self-care or lifestyle practices for pain management and health. They also often described accepting pain, being better able to adjust and set boundaries, feeling more in control, participating in life, and changing their medication use. A small portion of the sample reported no improvement in their conditions. When outcomes were examined as a whole, individuals described impacts that could be placed along a spectrum from whole life change to no change. Facilitators to maintenance of improvements included having building blocks (eg, carrying forward practices learned), support (eg, access to resources), and energy (eg, motivation), and improving incrementally. Challenges were not having building blocks (eg, life disruptions), support (eg, unknown follow-up options), and energy (eg, competing demands) and having an unbalanced rate of improvement.

Conclusion: Most Veterans identified experiencing multiple areas of improvement, especially learning about and taking up new pain and general health management skills. Ensuring participants can build on and find support for these outcomes when applying what they have learned in their dynamic social and physical worlds remains a challenge for this program and other relatively short-term interdisciplinary chronic pain interventions.

CHRONIC PAIN (Continued)

[A Replicable and Sustainable Whole Person Care Model for Chronic Pain.](#)

[Hansen KA](#)^{1,2,3}, [McKernan LC](#)^{1,2,4}, [Carter SD](#)^{1,2}, [Allen C](#)^{1,2}, [Wolever RQ](#)^{1,2,3,4}.

J Altern Complement Med. **2019 Mar**;25(S1):S86-S94. doi: 10.1089/acm.2018.0420. PMID: 30870025.

BACKGROUND: Integrative health is an expanding field that is increasingly called upon by conventional medicine to provide care for patients with chronic pain and disease. Although evidence has mounted for delivering integrative therapies individually, there is little consensus on how best to deliver these therapies in tandem as part of whole person care. While many models exist, few are financially sustainable.

METHODS AND RESULTS: This article describes a conceptual and logistical model for providing integrative outpatient health care within an academic medical center or hospital system to patients with chronic pain and disease. In hopes that the model will be replicated, administrative details are provided to explain how the model operates and has been maintained over nine years. The details include the intentional building of a particular work culture.

CONCLUSION: This whole person care model that addresses chronic pain and disease in an outpatient integrative clinic has been successful, sustainable and can be replicated in other academic medical centers or hospital clinics.

[Perspective of Pain Clinicians in Three Global Cities on Local Barriers to Providing Care for Chronic Noncancer Pain Patients.](#)

[Lakha SF](#)¹, [Ballantyne P](#)², [Badr H](#)³, [Agboatwala M](#)⁴, [Mailis A](#)^{1,5}, [Pennefather P](#)^{1,6}.

Pain Res Manag. **2019 Feb 3**;2019:3091309. doi: 10.1155/2019/3091309. PMCID: PMC6377973. PMID: 30863473. eCollection 2019.

An increasing proportion of the global chronic pain population is managed through services delivered by specialized pain clinics in global cities. This paper describes the results of a survey of pain clinic leaders in three global cities on barriers influencing chronic noncancer pain (CNCP) management provided by those clinics. It demonstrates a pragmatic qualitative approach for characterizing how the global city location of the clinic influences those results. A cross-sectional prospective survey design was used, and data were analyzed using quantitative and qualitative content analysis. Key informants were pain clinicians ($n = 4$ women and 8 men) responsible for outputs of specialized pain clinics in academic hospital settings in three global cities: Toronto, Kuwait, and Karachi. Krippendorff's thematic clustering technique was used to identify the repetitive themes in the data. All but one of the key informants had their primary pain training from Europe or North America. In Kuwait and Karachi, pain specialists were anesthesiologists and provided CNCP management services independently. In Toronto, pain clinic leaders were part of some form of the multidisciplinary team. Using the results of a question that asked informants to list their top three barriers, ten themes were identified. These themes were artificially organized in three thematic domains: infrastructure, clinical services, and education. In parallel, 31 predefined barriers identified from the literature were scored. The results showed variation in perception of barriers that not only depended on the clinic location but also demonstrated shared experiences across thematic domains. This study demonstrates a simple methodology for informing global and local efforts to improve access to and implementation of CNCP services globally.

[Whole Systems Within Whole Systems: The Oregon Health Plan's Expansion of Services for Back and Neck Pain.](#)

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J Altern Complement Med. **2019 Mar**;25(S1):S61-S68. doi: 10.1089/acm.2018.0431. PMID: 30870022.

OBJECTIVES: The authors employ a Whole Systems framework to explore implementation of new guidelines for back and neck pain in Oregon's Medicaid system. Whole Systems research is useful for understanding the relationship between complementary and integrative health care (CIH) and conventional health care systems in real-world clinical and practice settings.

DESIGN: Preliminary results are from an observational study designed to evaluate state-wide implementation of CIH and other non-pharmacological treatments for neck and back pain among Oregon Medicaid patients. This natural experiment, even in early stages, provides insight into the challenges of integrating Whole Systems oriented therapies into Medicaid billing and treatment.

METHODS: Qualitative data are drawn from: (1) semi-structured interviews with representatives of each of the 16 coordinated care organizations (CCOs) responsible for administering the Oregon's Medicaid insurance through the Oregon Health Plan (OHP); and (2) open-ended survey responses from acupuncturists in all 16 CCO areas.

RESULTS: Implementation of the new policy guidelines poses logistical and epistemological challenges. Differences in worldview, inadequate reimbursement, and simple lack of awareness of CIH among medical providers are some of the factors that pose barriers to merging CIH therapies into conventional frameworks.

CONCLUSIONS: In this article, we explore the potential for a Whole Systems perspective to better explain the complexity of integrating CIH and other non-pharmacological services into a state financed health care system. Oregon's expansion of services for back and neck pain presents an opportunity to explore challenges and successes in melding multiple approaches to health and pain management into a managed system such as the OHP.

CHRONIC PAIN (Continued)

[Who benefits from multimodal rehabilitation - an exploration of pain, psychological distress, and life impacts in over 35,000 chronic pain patients identified in the Swedish Quality Registry for Pain Rehabilitation.](#)

[Gerdle B](#)¹, [Åkerblom S](#)^{2,3}, [Brodda Jansen G](#)⁴, [Enthoven P](#)¹, [Ernberg M](#)^{5,6}, [Dong HJ](#)¹, [Stålnacke BM](#)⁷, [Äng BO](#)^{8,9,10}, [Boersma K](#)¹¹.

J Pain Res. 2019 Mar 7;12:891-908. doi: 10.2147/JPR.S190003. PMID: PMC6411315. PMID: 30881099. eCollection 2019.

Background: Chronic pain patients frequently suffer from psychological symptoms. There is no consensus concerning the prevalence of severe anxiety and depressive symptoms and the strength of the associations between pain intensity and psychological distress. Although an important aspect of the clinical picture is understanding how the pain condition impacts life, little is known about the relative importance of pain and psychological symptoms for individual's life impact. The aims of this study were to identify subgroups of pain patients; to analyze if pain, psychological distress, and life impact variables influence subgrouping; and to investigate how patients in the subgroups benefit from treatments.

Methods: Background variables, pain aspects (intensity/severity and spreading), psychological distress (depressive and anxiety symptoms), and two life impact variables (pain interference and perceived life control) were obtained from the Swedish Quality Registry for Pain Rehabilitation for chronic pain patients and analyzed mainly using advanced multivariate methods.

Results: Based on >35,000 patients, 35%-40% had severe anxiety or depressive symptoms. Severe psychological distress was associated with being born outside Europe (21%-24% vs 6%-8% in the category without psychological distress) and low education level (20.7%-20.8% vs 26%-27% in the category without psychological distress). Dose relationships existed between the two psychological distress variables and pain aspects, but the explained variances were generally low. Pain intensity/severity and the two psychological distress variables were significantly associated ($R^2=0.40-0.48$; $P>0.001$) with the two life impact variables (pain interference and life control). Two subgroups of patients were identified at baseline (subgroup 1: $n=15,901-16,119$; subgroup 2: $n=20,690-20,981$) and the subgroup with the worst situation regarding all variables participated less in an MMRP (51% vs 58%, $P<0.001$) but showed the largest improvements in outcomes.

Conclusion: The results emphasize the need to assess both pain and psychological distress and not take for granted that pain involves high psychological stress in the individual case. Not all patients benefit from MMRP. A better matching between common clinical pictures and the content of MMRPs may help improve results. We only partly found support for treatment resistance in patients with psychological distress burden.

[Impact of transcutaneous electrical nerve stimulation on sleep in chronic low back pain: a real-world retrospective cohort study.](#)

[Gozani SN](#)¹, [Ferree TC](#)¹, [Moynihán M](#)¹, [Kong X](#)¹.

J Pain Res. 2019 Feb 25;12:743-752. doi: 10.2147/JPR.S196129. PMID: PMC6394244. PMID: 30881088. eCollection 2019.

Objective: The purpose of this study was to determine if transcutaneous electrical nerve stimulation (TENS) improves sleep in chronic low back pain (CLBP).

Background: There is uncertainty over the effectiveness of TENS in CLBP. In most studies, pain intensity has been the primary outcome measure. Although sleep abnormalities are common in CLBP, sleep outcomes have not been evaluated in most studies of TENS effectiveness. Subjective and objective sleep measures are often inconsistent in CLBP, suggesting that perception of sleep and actual sleep may differ.

Methods: This retrospective cohort study evaluated TENS for CLBP over 10 weeks. The source database included demographics, pain characteristics, pain intensity and interference on an 11-point numerical rating scale, adherence and actigraphic sleep data from real-world TENS users. Key inclusion criteria were CLBP with self-reported history of back injury and baseline pain interference with sleep ≥ 4 . Study participants were stratified into improved and unimproved groups based on changes in pain interference with sleep (improved ≥ 1 -point decrease). Actigraphic sleep metrics were compared between the two groups for weeks 1-2 and weeks 9-10.

Results: The inclusion criteria were met by 554 TENS users. There were 282 (50.9%) participants in the improved group and 272 (49.1%) in the unimproved group. The two groups had similar baseline characteristics and high TENS adherence. At the weeks 1-2 assessment, there were no differences among actigraphic sleep. At the weeks 9-10 assessment, there was a difference in total sleep time, with the improved group sleeping 29 minutes longer. In addition, the periodic leg movement (PLM) index was lower in the improved group.

Conclusion: Regular TENS improved self-reported and objective sleep measures in individuals with CLBP. When compared to the unimproved group, the improved group had longer total sleep time and fewer PLMs. Sleep may be an important outcome for TENS effectiveness in CLBP.

CHRONIC PAIN (Continued)

[Psychological and work-related outcomes after inpatient multidisciplinary rehabilitation of chronic low back pain: a prospective randomized controlled trial.](#)

[Hampel P](#)¹, [Köpnick A](#)², [Roch S](#)².

BMC Psychol. **2019 Feb 15**;7(1):6. doi: 10.1186/s40359-019-0282-3. PMCID: PMC6377771. PMID: 30770763.

BACKGROUND: This study investigated the long-term effects (12 months post-rehabilitation) of a standard inpatient multidisciplinary rehabilitation program for patients with chronic low back pain (CLBP), in which a control group (CG) received pain competence training and an intervention group (IG) received combined pain competence and depression prevention training.

METHODS: In this prospective control group study with cluster-block randomization, a total of n = 583 patients were included into per protocol analyses. To examine the effects of rehabilitation on depressive symptoms, pain self-efficacy, and work ability, patients were stratified in repeated-measures analyses of variance by treatment condition (IG vs. CG), level of depressive symptoms (low vs. high), and time of assessment (pre, post, 6, and 12 months after rehabilitation). The impact of each treatment on pain-related days of sick leave (DSL; dichotomized into ≤ vs. > 2 weeks) was determined separately by conducting non-parametric analyses. Multiple imputations (n = 1225) confirmed the results. Effects were interpreted if clinical significance was given.

RESULTS: Only patients with high levels of depressive symptoms showed long-term improvements in depressive symptoms and self-efficacy. Long-term improvements in work ability index and mental work ability item were restricted to the IG. Furthermore, long-term effects on pain-related DSL were ascertained by per protocol and multiple imputation analyses only for the IG.

CONCLUSIONS: Patients with high levels of depressive symptoms showed improvements in depressive symptoms and self-efficacy, supporting the psychological effectiveness of both interventions. However, the beneficial long-term effects of rehabilitation on work ability and pain-related DSL among the IG support implementation of combined pain competence and depression prevention training.

TRIAL REGISTRATION: DRKS00015465 (German Clinical Trial Register DRKS); date of registration: 03.09.2018.

IRRITABLE BOWEL SYNDROME

[Is there an appropriate strategy for treating co-morbid irritable bowel syndrome and bladder pain syndrome?](#)

[Dellis AE](#)^{1,2}, [Mozaffari S](#)^{3,4}, [Nikfar S](#)^{4,5}, [Papatsoris AG](#)⁶, [Abdollahi M](#)^{7,8}.

Expert Opin Pharmacother. **2019 Mar**;20(4):411-414. doi: 10.1080/14656566.2018.1559821. PMID: 30589379. Epub 2018 Dec 27.

Two of the most frequent components of chronic pelvic pain syndrome (CPPS) are irritable bowel syndrome (IBS) and bladder pain syndrome (BPS), characterized by considerable overlapping symptoms and pathophysiology. Currently, its management is challenging meaning there is high the demand for novel efficient therapeutics to aid patient care and to tackle the socioeconomic burden of IBS and BPS. As there are presently no sufficient treatment strategies, identifying the mechanisms that result in their main symptoms is the opportunity for developing appropriate therapies. Areas covered: Herein, the authors explore the potential common treatment strategies for co-morbid IBS and BPS and highlight the absolute need for further research of these deliberating clinical entities. Expert opinion: In the future, the authors summarise that the discovery of predictive molecular biomarkers combined with clinical phenotypic categorization will likely allow for more definitive differentiation of patients and thus for better treatment options. Furthermore, it has been suggested that effective IBS treatment strategies would be of great value to co-morbid IBS and BPS therapy.

IRRITABLE BOWEL SYNDROME (Continued)

[Coexistence of Alterations of Gastrointestinal Function and Mechanical Allodynia in the Reserpine-Induced Animal Model of Fibromyalgia.](#)

[Uchida M](#)¹, [Kobayashi O](#)¹, [Yoshida M](#)², [Miwa M](#)², [Miura R](#)², [Saito H](#)², [Nagakura Y](#)^{3,4,5}.

Dig Dis Sci. **2019 Mar 14**. doi: 10.1007/s10620-019-05577-8. PMID: 30874990. [Epub ahead of print]

BACKGROUND: Fibromyalgia (FM) is a disorder characterized by widespread chronic pain as core symptom and a broad range of comorbidities. Despite the prevalence of gastrointestinal (GI) comorbidities in patients with FM, GI functions have rarely been investigated in animal models of FM.

AIMS: The purpose of the present study is to investigate the coexistence of alterations of GI function in the reserpine-induced myalgia (RIM) rat, a validated FM model associated with disruption of monoamine system.

METHODS: Paw withdrawal threshold (von Frey hair test) was assessed as pain-associated indicator. Gastric emptying (¹³C breath test), small intestinal transit (charcoal meal test), and fecal water content were investigated as GI functions.

RESULTS: The specific regimen of reserpine for the RIM rat, i.e., 1 mg/kg s.c., once daily for three consecutive days, caused a reduction of paw withdrawal threshold (i.e., mechanical allodynia) on days 3, 5, and 7 after the first injection. The ¹³CO₂ excreted from the RIM rat was significantly increased on day 7. The RIM rat exhibited an acceleration of small intestinal transit on day 5. Fecal water content collected from the RIM rat was significantly increased on days 3 and 5. The amount of noradrenaline was significantly decreased in GI tissues on days 3, 5, and 7 in the RIM rat. **Conclusions** This study revealed that accelerated gastric emptying, accelerated small intestinal transit, and increase in fecal water content coexist with mechanical allodynia in the RIM rat, simulating the coexistence of chronic pain and alterations of GI function in patients with FM.

OTHER RESEARCH OF INTEREST

[Mexican Americans' diabetes symptom prevalence, burden, and clusters.](#)

[García AA](#)¹, [Bose E](#)², [Zuñiga JA](#)², [Zhang W](#)².

Appl Nurs Res. **2019 Apr**;46:37-42. doi: 10.1016/j.apnr.2019.02.002. PMID: 30853074. Epub 2019 Feb 13.

AIMS: Type 2 diabetes mellitus (T2DM), serious and increasingly prevalent among Mexican Americans, produces symptoms related to high and low glucose levels, medication side effects, and long-term complications. This secondary analysis explored symptom prevalence, differences among symptom burden levels, and how symptoms clustered.

METHODS: Clinical measurements and survey data (demographic, quality of life, and the symptom subscale of the Diabetes Symptom Self-Management Inventory) collected from Mexican American adults with T2DM (n = 71) were analyzed for symptom prevalence, differences across levels of symptom burden, and symptom clusters. Agglomerative hierarchical and k-means clustering analyses were performed on a Gower matrix. Internal validation methods and rank aggregation were used to identify the best clustering method of the two techniques and to identify symptoms that clustered together.

RESULTS: Participants reported mean = 14 symptoms; tiredness and trouble sleeping were most prevalent. People with high symptom burden had significantly lower quality of life and perceptions of worse diabetes severity. Hierarchical clustering produced three symptom clusters: cluster 1 = 9 symptoms (e.g. intense thirstiness, dry mouth); cluster 2 = 9 symptoms (e.g., itching skin, weight gain, noise or light sensitivity); cluster 3 = 13 symptoms (e.g., nervous, headache, trouble concentrating, and memory loss).

CONCLUSION: Mexican Americans with T2DM report several co-occurring symptoms. Quality of life is significantly worse for people with high symptom burden. Three distinct symptom clusters were identified. Studies with larger samples are needed to further diabetes symptom science. Clinicians should assess and address patients' co-occurring symptoms as a potential means of decreasing symptom burden and improving quality of life.

OTHER RESEARCH OF INTEREST (Continued)**[Do sociodemographic characteristics associated with the use of CAM differ by chronic disease?](#)**

[Drieskens S](#)¹, [Tafforeau J](#)¹, [Demarest S](#)¹.

Eur J Public Health. **2019 Mar 8**. pii: ckz030. doi: 10.1093/eurpub/ckz030. PMID: 30851104. [Epub ahead of print]

BACKGROUND: Complementary and alternative medicine (CAM) is often used to alleviate the discomfort, disability and pain involved in many chronic diseases. Besides this, females, middle-aged and higher educated people are also known to use CAM the most. This study explores whether the sociodemographic characteristics associated with CAM use differ by type of disease.

METHODS: The following data were taken from the Belgian Health Interview Survey 2013 for the individuals aged 15+ years (n = 8942): sociodemographic characteristics, past 12-month diseases (using a list) and contact with a homeopath, chiropractor, acupuncturist and/or osteopath (CAM-therapists) in the past year. The association between CAM use and disease, controlled for gender, age, education and conventional medicine use, was assessed through logistic regressions. When interactions with the sociodemographic characteristics were found, stratified regressions were conducted.

RESULTS: People with musculoskeletal diseases [odds ratio (OR) = 2.6], allergy (OR = 1.4) and severe headache (OR = 1.5) had higher odds of using CAM in the past year with statistical significance. For musculoskeletal diseases, the odds of using CAM was higher, with statistical significance, for every sociodemographic subclass. For allergy, CAM use was higher among men, people aged 45+ years and lower educated people, while for severe headache CAM use was higher among women, people aged 45+ years and higher educated people, all with statistical significance.

CONCLUSIONS: Sociodemographic characteristics associated with CAM use differ by diseases. The role of CAM in disease management cannot be ignored. Making physicians aware for which disease CAM is used and by whom, may facilitate disease management.

["N-of-1" -Study: A concept of acute and chronic stress research using the example of ballroom dancing.](#)

[Strahler J](#)^{1,2}, [Luft C](#)¹.

Scand J Med Sci Sports. **2019 Mar 18**. doi: 10.1111/sms.13417. [Epub ahead of print]

Athletes often report on heightened stress, higher disease susceptibility, and a deterioration in mood and performance throughout periods of high training load and competitions. This paper presents a single-case study combining different research approaches to monitor the dynamic, idiosyncratic responses to competitive stress in elite sports using the example of professional ballroom dancing. Throughout an 8-months period (313 data points), one international-level female dancer provided data on mood, stress, and fatigue. In parallel, she collected saliva samples for the assessment of cortisol (sCort) and alpha-amylase (sAA). A hair strand was collected every 3-months to examine cumulative cortisol secretion. As expected, perceived stress was related to a reduction in well-being. On a daily basis, sCort predicted lower fatigue. In addition, tournaments resulted in a 3-fold and a 2-fold increase in sCort and sAA, respectively, and there was a pronounced drop in hair cortisol in the aftermath of a surgery-related break from dancing. We confirm competitive ballroom dancing to constitute a major stressor with immediate and prolonged consequences for self-reported well-being and biological stress markers. Single-case studies offer much potential for the observation of complex dynamic associations. In a next step, this approach will also become relevant when evaluating the efficacy of preventive and therapeutic interventions on an individual level.

OTHER RESEARCH OF INTEREST (Continued)

Caregiver strain among life partners of persons with mild disability due to relapsing-remitting multiple sclerosis.

[van der Hiele K](#)¹, [van Gorp DAM](#)², [Heerings MAP](#)³, [Jongen PJ](#)⁴, [van der Klink JJJ](#)⁵, [Beenakker EAC](#)⁶, [van Eijk JJJ](#)⁷, [Frequin STFM](#)⁸, [van Geel BM](#)⁹, [Hengstman GJD](#)¹⁰, [Hoitsma E](#)¹¹, [Mostert JP](#)¹², [Verhagen WIM](#)¹³, [de Gans K](#)¹⁴, [Zemel D](#)¹⁵, [Middelkoop HAM](#)¹⁶, [Visser LH](#)¹⁷.

Mult Scler Relat Disord. **2019 Mar 6**;31:5-11. doi: 10.1016/j.msard.2019.03.005. PMID: 30877926. [Epub ahead of print]

BACKGROUND: Multiple sclerosis (MS) is a chronic disorder of the central nervous system with an unpredictable disease course. Life partners often become caregivers, which can be both rewarding and challenging, as the caregiver's physical and mental health is often negatively affected. Previous studies on caregiver strain focused on caregivers of persons with MS with relatively high disability levels, while caregiver strain may already be experienced by life partners living with mildly disabled persons with MS.

OBJECTIVE: The current study examines factors associated with caregiver strain in life partners of persons with mild disability due to relapsing-remitting MS.

METHODS: We included 173 persons with relapsing-remitting MS (79% female; mean age 42.8 years; 90% employed; median EDSS 2.0) and their life partners. The life partners completed questionnaires on caregiver strain and neuropsychiatric and cognitive functioning of the person with MS. The persons with MS completed questionnaires about demographics, fatigue, personality, physical, cognitive and neuropsychiatric functioning, and underwent neuropsychological and neurological examinations. A linear regression analysis was conducted to examine predictors of caregiver strain.

RESULTS: 24% of the life partners experienced above average levels of caregiver strain. A multivariate linear regression analysis revealed that a higher age of the person with MS ($\beta = 0.16$, $p = 0.04$), more physical disability ($\beta = 0.17$, $p = 0.04$), more cognitive and neuropsychiatric problems of the person with MS as reported by the life partner ($\beta = 0.33$, $p = 0.001$) and higher severity of neuropsychiatric symptoms as reported by the life partner ($\beta = 0.32$, $p = 0.001$) were associated with higher caregiver strain ($R^2 = 0.49$).

CONCLUSION: Higher caregiver strain in life partners of persons with mild disability due to relapsing-remitting MS was primarily associated with cognitive and neuropsychiatric problems of the person with MS.

Sleep disturbances and daytime fatigue: data from the Brazilian National Health Survey, 2013.

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Cad Saude Publica. **2019 Mar 11**;35(3):e00086918. PMID: 30864612. doi: 10.1590/0102-311X00086918.

This study aims to describe the prevalence of sleep disturbances and daytime fatigue and their association with socio-demographic and behavioral factors. Data from the Brazilian National Health Survey conducted in 2013 with 60,202 adults (≥ 18 years old) were used. The outcomes evaluated were self-reported sleep disturbances and daytime fatigue in the last two weeks. Sleep disturbance was defined as the presence of difficulty to fall asleep, frequently waking up during the night or sleeping more than usual; daytime fatigue was defined as the presence of not feeling rested and motivated during the day, feeling tired and lacking energy. Sociodemographic, lifestyle and chronic health aspects were explored as exposures for both outcomes. Prevalence of sleep disturbances and daytime fatigue were 14.9% (14.4-15.4) and 11.9% (11.4-12.3), respectively. Both outcomes were more common in women, older people, people with no formal education, smokers and among physically inactive individuals. The association with education was inverse (the highest the level of education the lower the prevalence ratio - PR - of sleep disturbances and daytime fatigue; adjusted p-value for trend < 0.001). Prevalence of sleep disturbances combined with daytime fatigue was 6.7% (6.4-7.1) and was about 6 times higher among those with three or more chronic health disturbances (PR = 6.2; 95%CI: 5.3-7.2). Strategies to decrease the prevalence of sleep disturbances and daytime fatigue should be encouraged and focused on chronically ill individuals that share other modifiable risk factors.