

GULF WAR ILLNESS

Dynamic cerebral autoregulation is impaired in Veterans with Gulf War Illness: A case-control study.

Falvo MJ^{1,2,3}, Lindheimer JB^{4,5}, Serrador JM^{1,2,6}.

PLoS One. 2018 Oct 15;13(10):e0205393. doi: 10.1371/journal.pone.0205393. PMID: 30321200. eCollection 2018.

Neurological dysfunction has been reported in Gulf War Illness (GWI), including abnormal cerebral blood flow (CBF) responses to physostigmine challenge. However, it is unclear whether the CBF response to normal physiological challenges and regulation is similarly dysfunctional. The goal of the present study was to evaluate the CBF velocity response to orthostatic stress (i.e., sit-to-stand maneuver) and increased fractional concentration of carbon dioxide. 23 cases of GWI (GWI+) and 9 controls (GWI) volunteered for this study. Primary variables of interest included an index of dynamic autoregulation and cerebrovascular reactivity. Dynamic autoregulation was significantly lower in GWI+ than GWI- both for autoregulatory index (2.99 ± 1.5 vs 4.50 ± 1.5 , $p = 0.017$). In addition, we observed greater decreases in CBF velocity both at the nadir after standing (-18.5 ± 6.0 vs $-9.8 \pm 4.9\%$, $p = 0.001$) and during steady state standing (-5.7 ± 7.1 vs $-1.8 \pm 3.2\%$, $p = 0.042$). In contrast, cerebrovascular reactivity was not different between groups. In our sample of Veterans with GWI, dynamic autoregulation was impaired and consistent with greater cerebral hypoperfusion when standing. This reduced CBF may contribute to cognitive difficulties in these Veterans when upright.

CHRONIC FATIGUE SYNDROME

Graded exercise therapy for myalgic encephalomyelitis/chronic fatigue syndrome is not effective and unsafe. Re-analysis of a Cochrane review.

Vink M¹, Vink-Niese A².

Health Psychol Open. 2018 Oct 8;5(2):2055102918805187. doi: 10.1177/2055102918805187. PMCID: PMC6176540. PMID: 30305916. eCollection 2018 Jul-Dec.

The analysis of the 2017 Cochrane review reveals flaws, which means that contrary to its findings, there is no evidence that graded exercise therapy is effective. Because of the failure to report harms adequately in the trials covered by the review, it cannot be said that graded exercise therapy is safe. The analysis of the objective outcomes in the trials provides sufficient evidence to conclude that graded exercise therapy is an ineffective treatment for myalgic encephalomyelitis/chronic fatigue syndrome.

Immunosignature Analysis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).

Günther OP¹, Gardy JL^{2,3}, Stafford P⁴, Fluge Ø⁵, Mella O⁵, Tang P⁶, Miller RR³, Parker SM⁷, Johnston SA⁴, Patrick DM^{8,9}.

Mol Neurobiol. 2018 Oct 8. doi: 10.1007/s12035-018-1354-8. PMID: 30298340. [Epub ahead of print]

A random-sequence peptide microarray can interrogate serum antibodies in a broad, unbiased fashion to generate disease-specific immunosignatures. This approach has been applied to cancer detection, diagnosis of infections, and interrogation of vaccine response. We hypothesized that there is an immunosignature specific to ME/CFS and that this could aid in the diagnosis. We studied two subject groups meeting the Canadian Consensus Definition of ME/CFS. ME/CFS ($n = 25$) and matched control ($n = 25$) sera were obtained from a Canadian study. ME/CFS ($n = 25$) sera were obtained from phase 1/2 Norwegian trials ([NCT01156909](#)). Sera from six healthy controls from the USA were included in the analysis. Canadian cases and controls were tested for a disease immunosignature. By combining results from unsupervised and supervised analyses, a candidate immunosignature with 654 peptides was able to differentiate ME/CFS from controls. The immunosignature was tested and further refined using the Norwegian and USA samples. This resulted in a 256-peptide immunosignature with the ability to separate ME/CFS cases from controls in the international data sets. We were able to identify a 256-peptide signature that separates ME/CFS samples from healthy controls, suggesting that the hit-and-run hypothesis of immune dysfunction merits further investigation. By extending testing of both our signature and one previously reported in the literature to larger cohorts, and further interrogating the specific peptides we and others have identified, we may deepen our understanding of the origins of ME/CFS and work towards a clinically meaningful diagnostic biomarker.

CHRONIC FATIGUE SYNDROME (Continued)

Reciprocal associations between daily need-based experiences, energy, and sleep in chronic fatigue syndrome.

Campbell R¹, Vansteenkiste M¹, Delesie L², Tobback E², Mariman A², Vogelaers D², Mouratidis A³.

Health Psychol. 2018 Oct 15. doi: 10.1037/heab0000621. PMID: 30321019. [Epub ahead of print]

OBJECTIVE: Previous findings indicate that patients with chronic fatigue syndrome (CFS) report significant day-to-day fluctuations in subjective energy and sleep. Herein, we examined whether daily variation in the satisfaction and frustration of the basic psychological needs for autonomy, competence, and relatedness would contribute to daily variation in subjective energy and quality and quantity of sleep. In addition, we examined whether daily variation in sleep would contribute to daily need-based experiences through (i.e., mediated by) daily fluctuations in subjective energy.

METHOD: CFS patients ($N = 120$; 92% female; $M_{age} = 42.10$ years, $SD = 10.46$) completed a diary for 14 days which assessed their need-based experiences and subjective energy every evening and sleep every morning.

RESULTS: Results indicated that subjective energy, sleep, and need experiences fluctuated significantly from day to day. Daily need satisfaction related to less daily fatigue and more daily vitality, while the opposite pattern was observed for daily need frustration. Daily need frustration was also uniquely related to poorer daily sleep quality. Lastly, better daily sleep quality was also uniquely related to more daily need satisfaction and less daily need frustration via (i.e., mediated by) daily variation in subjective energy. These reciprocal within-day associations remained significant after controlling for the previous day's level of each outcome, with the exception of the relation between need frustration and sleep quality.

CONCLUSION: The present findings underscore the reciprocal day-to-day association between need-based experiences and subjective energy in CFS. (PsycINFO Database Record (c) 2018 APA, all rights reserved).

Effects of unsupportive social interactions, stigma, and symptoms on patients with myalgic encephalomyelitis and chronic fatigue syndrome.

McManimen SL^{1,2}, McClellan D¹, Stoothoff J¹, Jason LA¹.

J Community Psychol. 2018 Nov;46(8):959-971. doi: 10.1002/jcop.21984. PMID: 30311972. Epub 2018 May 4.

Prior research has found a heightened risk of suicide in patients with myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS). It is possible that a number of factors including stigma, unsupportive social interactions, and severe symptoms could lead to the development of depression, suicidal ideation, and heightened risk of suicide in this patient population. Prior studies have indicated that patients often report the legitimacy of their illness being questioned by family, friends, and even their physicians. This study aimed to determine whether stigma experienced, social support, symptomology, and functioning may be associated with depression and endorsement of suicidal ideation (SI) in patients with a self-reported diagnosis of ME or CFS. Findings indicated that participants that endorsed both SI and depression, in contrast to those that did not, experienced more frequent unsupportive social interactions in the form of blame for their illness, minimization of its severity, and social distancing from others. In addition, 7.1% of patients with ME and CFS endorsed SI but do not meet the criteria for clinical depression. These findings highlight the importance of stigma and unsupportive social interactions as risk factors for suicidal thoughts or actions among patients with ME and CFS. Community psychologists have an important role to play in helping educate health care professionals and the public to these types of risk factors for patients marginalized by ME and CFS.

HEADACHE and MIGRAINE

Relationship between right-to-left shunt and migraine in patients with epilepsy: a single-centre, cross-sectional study in China.

Zhang L¹, Zhu X¹, Qiu X¹, Li Y², Chen Y², Wang H², He S¹, Lai W¹, Peng A¹, Ning M³, Chen L¹.

BMJ Open. 2018 Oct 8;8(10):e024144. doi: 10.1136/bmjopen-2018-024144. PMID: 30297353.

OBJECTIVES: To investigate the relationship between right-to-left shunt and migraine to account for the unexplained high prevalence of migraine in patients with epilepsy.

DESIGN: This is a cross-sectional study. The diagnosis and interview process of patients with migraine was based on the International Classification of Headache Disorders-3 beta in patients with epilepsy. Participants underwent transthoracic echocardiography (TTE) with contrast medium to identify right-to-left shunt. The highest number of microbubbles were recorded in the left atrium before the complete microbubble outflow of the right atrium. A moderate-to-large shunt was defined as the presence of 10 or more microbubbles.

SETTING: A single-centre, cross-sectional study in China, 2015–2017.

PARTICIPANTS: Patients with epilepsy.

PRIMARY AND SECONDARY OUTCOME MEASURES: The primary outcome measures were the prevalence of migraine, the prevalence of right-to-left shunt in patients with migraine and those without migraine, and the prevalence of migraine in different degrees of shunting.

RESULTS: Three hundred thirty-nine participants with epilepsy who completed TTE were included in the analysis. The overall prevalence of migraine was 23.0%. One-third of the migraineurs had mild right-to-left shunt and one-fifth of the migraineurs had moderate-to-large right-to-left shunt. Patients with mild shunt did not have a higher prevalence of migraine than those without shunt (26.3% vs 18.1%, $p=0.102$); however, a higher prevalence of migraine was found in patients with moderate-to-large shunt (39.0% vs 18.1%, $OR=2.90$, 95% CI=1.41 to 5.98, $p=0.003$). Patients with migraine and patients without migraine had similar prevalence of mild shunt; however, patients with migraine had more moderate-to-large shunt (20.5% vs 9.6%, $p=0.002$). Right-to-left shunt and female were factors predicting migraine prevalence.

CONCLUSIONS: One-fifth of migraineurs were correlated with moderate-to-large right-to-left shunt which could be an underlying cause of migraine in epilepsy.

Headache disorder and the risk of dementia: a systematic review and meta-analysis of cohort studies.

Wang J^{1,2}, Xu W^{3,4}, Sun S^{3,4}, Yu S^{5,6}, Fan L⁷.

J Headache Pain. 2018 Oct 11;19(1):95. doi: 10.1186/s10194-018-0925-4. PMID: 30306350.

BACKGROUND: Until now, headache disorders have not been established as a risk factor for dementia. The aim of this study was to determine whether headache was associated with an increased risk of dementia.

METHODS: We systematically searched electronic databases, including PubMed, Embase, and Web of Science, for studies investigating the association between headache and dementia. We then conducted a meta-analysis to determine a pooled-effect estimate of the association.

RESULTS: We identified 6 studies (covering 291,549 individuals) to investigate the association between headache and the risk of all-cause dementia or Alzheimer's disease (AD). Pooled analyses showed that any headache was associated with a 24% greater risk of all-cause dementia (relative risk [RR] = 1.24; 95% confidential interval [CI]: 1.09-1.41; $P = 0.001$), and that any headache was not statistically significantly associated with an increased risk of AD (RR = 1.47; 95% CI: 0.82-2.63; $P = 0.192$).

CONCLUSIONS: Our results indicated that any headache was associated with an increased risk of all-cause dementia. However, additional studies are warranted to further

HEADACHE and MIGRAINE (Continued)

Oxygen treatment for cluster headache attacks at different flow rates: a double-blind, randomized, crossover study.

Dirkx THT¹, Haane DYP², Koehler PJ².

J Headache Pain. 2018 Oct 10;19(1):94. doi: 10.1186/s10194-018-0917-4. PMID: 30306284.

BACKGROUND: Cluster headache attacks can, in many patients, be successfully treated with oxygen via a non-rebreather mask. In previous studies oxygen at flow rates of both 7 L/min and 12 L/min was shown to be effective. The aim of this study was to compare the effect of 100% oxygen at different flow rates for the treatment of cluster headache attacks.

METHODS: In a double-blind, randomized, crossover study, oxygen naïve cluster headache patients, treated attacks with oxygen at 7 and 12 L/min. The primary outcome measure was the percentage of attacks after which patients (treating at least 2 attacks/day) were painfree after 15 min, in the first two days of the study. Secondary outcome measures were percentage of successfully treated attacks, percentage of attacks after which patients were painfree, drop in VAS score and patient preference in all treatment periods (14 days).

RESULTS: Ninety-eight patients were enrolled, 70 provided valid data, 56 used both flow rates. These 56 patients recorded 604 attacks, eligible for the primary analysis. An exploratory analysis was conducted using all eligible attacks of 70 patients who provided valid data. We could only include 5 patients, treating 27 attacks on the first two days of the study, for our primary outcome, which did not show a significant difference ($p = 0.180$). Patients tended to prefer 12 L/min ($p = 0.005$). Contradicting this result, more patients were painfree using 7 L/min ($p = 0.039$). There were no differences in side effects or in our other secondary outcome measures. The exploratory analysis showed an odds ratio of being painfree using 12 L/min of 0.73 (95% CI 0.52-1.02) compared to 7 L/min ($p = 0.061$) as scored on a 5-point scale. The average drop in score on this 5-point scale, however, was equal between groups. Also slightly more patients noticed, no or not much, relief on 7 L/min, and found 12 L/min to be effective in all their attacks.

CONCLUSION: There is lack of evidence to support differences in the effect of oxygen at a flow rate of 12 L/min compared to 7 L/min. More patients were painfree using 7 L/min, but our other outcome measures did not confirm a difference in effect between flow rates. As most patients prefer 12 L/min and treatments were equally safe, this could be used in all patients. It might be more cost-effective, however, to start with 7 L/min and, if ineffective, to switch to 12 L/min.

TRIAL REGISTRATION: European Union Clinical Trials Register (2012-003648-59), registered 1 October 2012. Dutch Trial Register (NTR3801), registered 14 January 2013.

Characteristics and clinical correlates of white matter changes in brain magnetic resonance of migraine females.

Roćiszewska-Żukowska I¹, Zajac-Mnich M², Janik P³.

Neurol Neurochir Pol. 2018 Sep 27. pii: S0028-3843(18)30005-7. doi: 10.1016/j.pjnns.2018.09.007. PMID: 30297100. [Epub ahead of print]

OBJECTIVE: White matter hyperintensities (WMHs) were often found in migraine patients. The aim of study was to characterize WMHs, assess their prevalence, determine relationship to clinical symptoms and homocysteine levels in migraine females.

METHODS: 69 women 38 with migraine without aura (MO), 31 with migraine with aura (MA) who underwent brain MRI with 1.5T scanner were enrolled. The WMHs number, location and size in FLAIR sequence were evaluated. Migraine severity was measured by pain intensity, number of attacks per month and MIDAS scale.

RESULTS: WMHs were found in 39.1% females. There was no WMHs and migraine type correlation. The total WMHs number was higher in MO ($p=0.027$). Patients with WMHs were older ($p=0.025$), have higher BMI ($p=0.042$), suffered longer ($p=0.001$), more often had positive pregnancy history ($p=0.010$) and less frequent prodromal symptoms. The age of onset, migraine's severity and homocysteine did not correlate with WMHs. No effect of antimigraine medication and oral contraceptive pills (OCP) was found. Both in MO and MA groups WMHs were located only supratentorially. In MO females WMHs were mainly located in one cerebral hemisphere ($p=0.024$) whereas in MA were found bilaterally. WMHs were most commonly located in the frontal lobes. In MO lesions were small ≤ 3 mm and present in almost all MO patients ($p=0.027$).

CONCLUSION: WMHs are present in more than one third of migraine females, regardless of aura. WHMs are located supratentorially, subcortically and in the frontal lobes. Older age, longer disease's duration, obesity and positive history of pregnancy are main risk factors for WMHs. Symptomatology and migraine severity, hyperhomocysteinemia, OCP and anti-migraine medications do not increase WMHs.

CHRONIC PAIN

The mechanosensitive ion channel Piezo2 mediates sensitivity to mechanical pain in mice.

[Murthy SE¹](#), [Loud MC¹](#), [Daou I¹](#), [Marshall KL¹](#), [Schwaller F²](#), [Kühnemund J²](#), [Francisco AG¹](#), [Keenan WT¹](#), [Dubin AE¹](#), [Lewin GR^{2,3}](#), [Patapoutian A⁴](#).

Sci Transl Med. 2018 Oct 10;10(462). pii: eaat9897. doi: 10.1126/scitranslmed.aat9897. PMID: 30305457.

The brush of a feather and a pinprick are perceived as distinct sensations because they are detected by discrete cutaneous sensory neurons. Inflammation or nerve injury can disrupt this sensory coding and result in maladaptive pain states, including mechanical allodynia, the development of pain in response to innocuous touch. However, the molecular mechanisms underlying the alteration of mechanical sensitization are poorly understood. In mice and humans, loss of mechanically activated PIEZO2 channels results in the inability to sense discriminative touch. However, the role of Piezo2 in acute and sensitized mechanical pain is not well defined. Here, we showed that optogenetic activation of *Piezo2*-expressing sensory neurons induced nociception in mice. Mice lacking *Piezo2* in caudal sensory neurons had impaired nociceptive responses to mechanical stimuli. Consistently, ex vivo recordings in skin-nerve preparations from these mice showed diminished A δ -nociceptor and C-fiber firing in response to mechanical stimulation. Punctate and dynamic allodynia in response to capsaicin-induced inflammation and spared nerve injury was absent in *Piezo2*-deficient mice. These results indicate that *Piezo2* mediates inflammation- and nerve injury-induced sensitized mechanical pain, and suggest that targeting PIEZO2 might be an effective strategy for treating mechanical allodynia.

Use of Complementary and Integrated Health: A Retrospective Analysis of U.S. Veterans with Chronic Musculoskeletal Pain Nationally.

[Taylor SL^{1,2}](#), [Herman PM³](#), [Marshall NJ⁴](#), [Zeng Q^{5,6}](#), [Yuan A¹](#), [Chu K¹](#), [Shao Y⁵](#), [Morioka C⁷](#), [Lorenz KA⁴](#).

J Altern Complement Med. 2018 Oct 12. doi: 10.1089/acm.2018.0276. PMID: 30312109. [Epub ahead of print]

OBJECTIVE: To partially address the opioid crisis, some complementary and integrative health (CIH) therapies are now recommended for chronic musculoskeletal pain, a common condition presented in primary care. As such, healthcare systems are increasingly offering CIH therapies, and the Veterans Health Administration (VHA), the nation's largest integrated healthcare system, has been at the forefront of this movement. However, little is known about the uptake of CIH among patients with chronic musculoskeletal pain. As such, we conducted the first study of the use of a variety of nonherbal CIH therapies among a large patient population having chronic musculoskeletal pain.

MATERIALS AND METHODS: We examined the frequency and predictors of CIH therapy use using administrative data for a large retrospective cohort of younger veterans with chronic musculoskeletal pain using the VHA between 2010 and 2013 ($n = 530,216$). We conducted a 2-year effort to determine use of nine types of CIH by using both natural language processing data mining methods and administrative and CPT4 codes. We defined chronic musculoskeletal pain as: (1) having 2+ visits with musculoskeletal diagnosis codes likely to represent chronic pain separated by 30–365 days or (2) 2+ visits with musculoskeletal diagnosis codes within 90 days and with 2+ numeric rating scale pain scores ≥ 4 at 2+ visits within 90 days.

RESULTS: More than a quarter (27%) of younger veterans with chronic musculoskeletal pain used any CIH therapy, 15% used meditation, 7% yoga, 6% acupuncture, 5% chiropractic, 4% guided imagery, 3% biofeedback, 2% t'ai chi, 2% massage, and 0.2% hypnosis. Use of any CIH therapy was more likely among women, single patients, patients with three of the six pain conditions, or patients with any of the six pain comorbid conditions.

CONCLUSIONS: Patients appear willing to use CIH approaches, given that 27% used some type. However, low rates of some specific CIH suggest the potential to augment CIH use.

CHRONIC PAIN (Continued)

Interstate data sharing of prescription drug monitoring programs and associated opioid prescriptions among patients with non-cancer chronic pain.

Lin HC¹, Wang Z², Simoni-Wastila L³, Boyd C⁴, Buu A⁵.

Prev Med. 2018 Oct 11. pii: S0091-7435(18)30330-X. doi: 10.1016/j.ypmed.2018.10.011. PMID: 30316875. [Epub ahead of print]

All fifty states have implemented prescription drug monitoring programs (PDMPs) to reduce misuse and diversion of controlled drugs. Interstate PDMP data sharing has been called for by clinical practitioners, but evidence to support the effectiveness of PDMP data sharing is lacking. This study examined whether PDMP interstate data sharing with bordering states was associated with prescriptions of opioids. This was a cross-sectional study that included patients with non-cancer chronic pain from the 2014 National Ambulatory Medical Care Survey (weighted N = 66,198,751; unweighted N = 2846). Multinomial logistic regression was performed to examine the association between PDMP interstate data sharing status and patients' being prescribed opioids for pain treatment, controlling for covariates guided by the Eisenberg's model of physician decision-making. Findings indicated that patients residing in states with interstate PDMP data sharing with all or partial bordering states were not less likely to be prescribed opioids compared to those living in states without interstate data sharing. Other factors such as patient age, health insurance type, new patient status, and physician adoption of electronic medical records were associated with the likelihood of patients' being prescribed opioids. This study concluded that current practice of interstate PDMP data sharing with bordering states was not associated with patients' being prescribed opioids for non-cancer chronic pain treatment. Future studies and policy efforts that unravel technological, legal, and political barriers to reciprocal and equal interstate data sharing with bordering states should be warranted to inform PDMP redesign and in turn, augment overall PDMP effectiveness in reducing misuse of prescription opioids.

Sleep disturbances and sleep disorders in adults living with chronic pain: a meta-analysis.

Mathias JL¹, Cant ML², Burke ALJ³.

Sleep Med. 2018 Jun 11. pii: S1389-9457(18)30216-8. doi: 10.1016/j.sleep.2018.05.023. PMID: 30314881. [Epub ahead of print]

OBJECTIVES: Chronic pain, with or without an identified diagnosis or cause, is widespread and commonly associated with sleep disturbances. However, research has often used poor quality measures of sleep and focused on specific pain conditions, thereby limiting its reliability and applicability to the wider CP population. This study meta-analysed the findings from studies that used objective polysomnographic measures of sleep or examined diagnosed sleep disorders in people with CP.

METHODS: Three databases were searched (PubMed, PsychINFO, Embase; inception to June 2017) for case-controlled polysomnography studies and studies that reported the prevalence of diagnosed sleep disorders in adults with CP. Hedge's g effect sizes and prevalence rates were calculated using the data from 37 studies.

RESULTS: Polysomnographic measures of sleep onset latency and efficiency, time awake after sleep onset and awakenings were all significantly worse in those with CP when compared to healthy controls (large effects). Total sleep time, light sleep duration (NREM 1), number of stage-shifts, respiratory-related events and periodic limb-movements were also worse for those with CP, albeit to a lesser extent (small to medium effects). The pooled prevalence of sleep disorders in CP was 44%, with insomnia (72%), restless legs syndrome (32%) and obstructive sleep apnea (32%) being the most common diagnoses.

CONCLUSIONS: Objective polysomnographic measures indicate that individuals with CP experience significant sleep disturbances, particularly with respect to sleep initiation and maintenance. Clinically diagnosed sleep disorders are also very prevalent. It is imperative that sleep disturbances and disorders be assessed and treated in conjunction with the CP.

OTHER RESEARCH OF INTEREST

Effect of Genetic Diagnosis on Patients with Previously Undiagnosed Disease.

Splinter K¹, Adams DR¹, Bacino CA¹, Bellen HJ¹, Bernstein JA¹, Cheatile-Jarvela AM¹, Eng CM¹, Esteves C¹, Gahl WA¹, Hamid R¹, Jacob HJ¹, Kikani B¹, Koeller DM¹, Kohane IS¹, Lee BH¹, Loscalzo J¹, Luo X¹, McCray AT¹, Metz TO¹, Mulvihill JJ¹, Nelson SF¹, Palmer CGS¹, Phillips JA 3rd¹, Pick L¹, Postlethwait JH¹, Reuter C¹, Shashi V¹, Sweetser DA¹, Tifft CJ¹, Walley NM¹, Wangler MF¹, Westerfield M¹, Wheeler MT¹, Wise AL¹, Worthey EA¹, Yamamoto S¹, Ashley EA¹; Undiagnosed Diseases Network.

N Engl J Med. 2018 Oct 10. doi: 10.1056/NEJMoa1714458. PMID: 30304647. [Epub ahead of print]

BACKGROUND: Many patients remain without a diagnosis despite extensive medical evaluation. The Undiagnosed Diseases Network (UDN) was established to apply a multidisciplinary model in the evaluation of the most challenging cases and to identify the biologic characteristics of newly discovered diseases. The UDN, which is funded by the National Institutes of Health, was formed in 2014 as a network of seven clinical sites, two sequencing cores, and a coordinating center. Later, a central biorepository, a metabolomics core, and a model organisms screening center were added.

METHODS: We evaluated patients who were referred to the UDN over a period of 20 months. The patients were required to have an undiagnosed condition despite thorough evaluation by a health care provider. We determined the rate of diagnosis among patients who subsequently had a complete evaluation, and we observed the effect of diagnosis on medical care.

RESULTS: A total of 1519 patients (53% female) were referred to the UDN, of whom 601 (40%) were accepted for evaluation. Of the accepted patients, 192 (32%) had previously undergone exome sequencing. Symptoms were neurologic in 40% of the applicants, musculoskeletal in 10%, immunologic in 7%, gastrointestinal in 7%, and rheumatologic in 6%. Of the 382 patients who had a complete evaluation, 132 received a diagnosis, yielding a rate of diagnosis of 35%. A total of 15 diagnoses (11%) were made by clinical review alone, and 98 (74%) were made by exome or genome sequencing. Of the diagnoses, 21% led to recommendations regarding changes in therapy, 37% led to changes in diagnostic testing, and 36% led to variant-specific genetic counseling. We defined 31 new syndromes.

CONCLUSIONS: The UDN established a diagnosis in 132 of the 382 patients who had a complete evaluation, yielding a rate of diagnosis of 35%. (Funded by the National Institutes of Health Common Fund.).

Characteristics and determinants of dietary intake and physical activity in a group of patients with multiple chemical sensitivity.

Aguilar-Aguilar E¹, Marcos-Pasero H¹, de la Iglesia R¹, Espinosa-Salinas I¹, Ramírez de Molina A¹, Reglero G², Loria-Kohen V³.

Endocrinol Diabetes Nutr. 2018 Oct 8. pii: S2530-0164(18)30193-9. doi: 10.1016/j.endinu.2018.07.009. PMID: 30309810. [Epub ahead of print]

BACKGROUND AND OBJECTIVE: Multiple chemical sensitivity (MCS) is a complex, acquired, chronic syndrome of multifactorial etiology with multiple symptoms. The aim of the study was to assess the nutritional habits, dietary characteristics and physical activity, as well as their determinants, of a population diagnosed with MCS, which may allow for a more precise approach to nutritional improvement.

PATIENTS AND METHOD: A descriptive, cross-sectional study in patients diagnosed with MCS. Information was collected using adapted questionnaires. Data included presence of comorbidities, nutritional (use of supplements, types of diet) and food purchasing habits. Dietary intake, food intolerances, and physical activity were also recorded.

RESULTS: The study included of 52 patients (48 female) aged 50.9 ± 10.3 years. Diagnosis of MCS was commonly associated to chronic fatigue syndrome (70.1%), fibromyalgia (65.4%), or electrosensitivity (51.9%). The most common comorbidities were irritable bowel, gastroesophageal reflux, and depression/anxiety-depressive disorder. Exclusion diets were followed by 57.7%, 52.1% commonly used supplements (6.4 ± 5.2 per person), and 16.0% took more than 10 daily. A high proportion of volunteers did not take the recommended amounts of dairy products (84.3%), fruit (82.3%), and cereals (64.7%), the foods to which intolerance was greatest. As regards physical activity, active subjects only represented 12.5%.

CONCLUSIONS: The data collected support the need to improve food pattern and to perform physical activity according to individual characteristics. Nutritional education and diet personalization could prevent incomplete, monotonous, and unbalanced diets which impair quality of life and physiological status.

OTHER RESEARCH OF INTEREST (Continued)**Association of Fatigue With TPH2 Genetic Polymorphisms in Women With Irritable Bowel Syndrome.**

Han CJ¹, Jarrett ME², Cain KC³, Jun S⁴, Heitkemper MM².

Biol Res Nurs. 2018 Oct 11:1099800418806055. doi: 10.1177/1099800418806055. PMID: 30309244. [Epub ahead of print]

Fatigue is the most common extraintestinal symptom in women with irritable bowel syndrome (IBS). Genetic polymorphisms of monoamines are associated with fatigue in many chronic diseases. In this pilot exploratory study, the primary aim was to determine whether genetic polymorphisms of tryptophan hydroxylase (TPH1/TPH2), serotonin reuptake transporter (SERT), or catechol-O-methyltransferase (COMT) are associated with fatigue in women with IBS. Additionally, analysis explored whether these genetic associations with fatigue would be present when controlling for abdominal pain, psychological distress, feeling stressed, and sleepiness during the day. Secondary analysis of two randomized controlled trial baseline data sets in Caucasian women with IBS (N = 185) was conducted. Participants kept a daily diary with one dimension (i.e., severity) for each of the 26 symptoms, including fatigue, for 28 days prior to randomization. DNA samples were tested for single-nucleotide polymorphisms (SNPs) of TPH1 (four SNPs) /TPH2 (one SNP), SERT (one SNP), and COMT (one SNP). Analysis of covariance was used to examine associations of percentage of diary days with moderate to very severe symptoms with genetic polymorphisms. Only one SNP, TPH2 rs4570625, was significantly associated with fatigue ($p = .005$). T-allele (low functional) carriers of TPH2 (i.e., G/T or T/T genotypes) reported a greater percentage of days with moderate to very severe fatigue than G/G homozygotes ($p = .001$). Reduced synthesis of tryptophan in the central nervous system may contribute to reports of fatigue in women with IBS. Understanding genetic risk factors for fatigue may elucidate preemptive strategies to reduce fatigue in individuals with IBS.

The Most Commonly Treated Acupuncture Indications in the United States: A Cross-Sectional Study.

Wang H^{1,2}, Yang G³, Wang S^{4,2}, Zheng X^{5,2}, Zhang W⁶, Li Y².

Am J Chin Med. 2018 Oct 9:1-33. doi: 10.1142/S0192415X18500738. PMID: 30298749. [Epub ahead of print]

Acupuncture has been a popular alternative medicine in the United States for several decades. Its therapeutic effects on pain have been validated by both basic and clinical researches, and it is currently emerging as a unique non-pharmaceutical choice for pain against opioid crisis. However, the full spectrum of acupuncture indications remains unexplored. In this study, we conducted a cross-sectional survey among 419 acupuncturists nation-wide to investigate the top 10 and top 99 acupuncture indications in private clinics in the United States. We found the top 10 indications to be: lower back pain, depression, anxiety, headache, arthritis, allergies, general pain, female infertility, insomnia, neck pain and frozen shoulder. Among the top 99 indications, pain represents the largest category; and mental health management, especially for mood disorders, is in greatest demand. The following popular groups are: immune system dysfunctions, gastrointestinal diseases, gynecology and neurology. In addition, specialty index, commonality index, and the potential to become medical specialties were estimated for each indication. Demographic analysis suggests that China trained acupuncturists tend to have broader indication spectrums, but the top conditions treated are primarily decided by local needs. Also, gender, resident states, age and clinical experience all affect indication distributions. Our data for the first time outlines the profile of acupuncture treatable conditions in the US and is valuable for strategic planning in acupuncture training, healthcare administration and public education.