



CUTTING EDGE

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Welcome to the first issue of *Cutting Edge - COPCs Research Advances*, an electronic newsletter published by the Chronic Pain Research Alliance. Developed to keep the medical-scientific community abreast of recent research advances, this publication contains abstracts of recently published studies on the epidemiology, pathophysiology and clinical management of Chronic Overlapping Pain Conditions (i.e., overlap of chronic low back pain, chronic migraine and tension-type headache, endometriosis, fibromyalgia, vulvodynia, myalgic encephalomyelitis/chronic fatigue syndrome, temporomandibular disorders, irritable bowel syndrome and interstitial cystitis/painful bladder syndrome.)

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FEATURE EDITORIAL

Challenges in drug discovery for overcoming 'dysfunctional pain': an emerging category of chronic pain.

Nagakura Y.

Expert Opin Drug Discov. 2015 Oct;10(10):1043-5. doi: 10.1517/17460441.2015.1066776.

<http://www.tandfonline.com/doi/full/10.1517/17460441.2015.1066776>

'Dysfunctional pain', a type of chronic pain, is associated with a broad range of clinical disorders, including fibromyalgia, irritable bowel syndrome and interstitial cystitis. It is emerging as a serious issue due to the negative impact of inexplicable pain on quality of life, lack of effective therapies and health care cost. Although drug discovery efforts in pain research have so far focused primarily on inflammatory and neuropathic pain, this editorial attracts attention to dysfunctional pain research and discusses a possible fundamental framework for tackling this difficult issue. While dysfunctional pain is characterized by chronic widespread or regional pain symptoms and occurrence of pain amplification, underlying pathophysiologies remain to be identified. Thus, a pivotal step in future research would be the exploration of pathophysiological pathways, such as relevant molecular networks, which are responsible for dysfunctional pain. Utilization of developing technologies paves the way for the identification of underlying pathophysiologies and the development of effective drugs which would eventually solve the clinical issues associated with dysfunctional pain.

NATIONAL STUDIES

Pain and Interoception Imaging Network (PAIN): A multimodal, multisite, brain-imaging repository for chronic somatic and visceral pain disorders.

Labus JS, Naliboff B, Kilpatrick L, Liu C, Ashe-McNalley C, Dos Santos IR, Alaverdyan M, Woodworth D, Gupta A, Ellingson BM, Tillisch K, Mayer EA.

Neuroimage. 2015 Apr 19. pii: S1053-8119(15)00308-0. doi:10.1016/j.neuroimage.2015.04.018.

The Pain and Interoception Imaging Network (PAIN) repository (painrepository.org) is a newly created NIH (NIDA/NCCAM) funded neuroimaging data repository that aims to accelerate scientific discovery regarding brain mechanisms in pain and to provide more rapid benefits to pain patients through the harmonization of efforts and data sharing. The PAIN Repository consists of two components, an Archived Repository and a Standardized Repository. Similar to other 'open' imaging repositories, neuroimaging researchers can deposit any dataset of chronic pain patients and healthy controls into the Archived Repository. Scans in the Archived Repository can be very diverse in terms of scanning procedures and clinical metadata, complicating the merging of datasets for analyses. The Standardized Repository overcomes these limitations through the use of standardized scanning protocols along with a standardized set of clinical metadata, allowing an unprecedented ability to perform pooled analyses. The Archived Repository currently includes 741 scans and is rapidly growing. The Standardized Repository currently includes 433 scans. Pain conditions currently represented in the PAIN repository include: irritable bowel syndrome, vulvodynia, migraine, chronic back pain, and inflammatory bowel disease. Both the PAIN Archived and Standardized Repositories promise to be important resources in the field of chronic pain research. The enhanced ability of the Standardized Repository to combine imaging, clinical and other biological datasets from multiple sites in particular make it a unique resource for significant scientific discoveries.

Painful bladder filling and painful urgency are distinct characteristics in men and women with urological chronic pelvic pain syndromes: A MAPP Research Network Study.

Lai HH, Krieger JN, Pontari MA, Buchwald D, Hou X, Landis JR; MAPP Research Network. J Urol. 2015 Jul 17. pii: S0022-5347(15)04413-4. doi: 10.1016/j.juro.2015.05.105. [Epub ahead of print]

PURPOSE: We describe bladder associated symptoms in patients with urological chronic pelvic pain syndromes. We correlated these symptoms with urological, nonurological, psychosocial and quality of life measures. **MATERIALS AND METHODS:** Study participants included 233 women and 191 men with interstitial cystitis/bladder pain syndrome or chronic prostatitis/chronic pelvic pain syndrome in a multicenter study. They completed a battery of measures, including items asking whether pain worsened with bladder filling (painful filling) or whether the urge to urinate was due to pain, pressure or discomfort (painful urgency). Participants were categorized into 3 groups, including group 1-painful filling and painful urgency (both), 2-painful filling or painful urgency (either) and 3) no painful filling or painful urgency (neither). **RESULTS:** Of the men 75% and 88% of the women were categorized as both or either. These bladder characteristics were associated with more severe urological symptoms (increased pain, frequency and urgency), a higher somatic symptom burden, depression and worse quality of life (3-group trend test each $p < 0.01$). A gradient effect was observed across the groups (both > either > neither). Compared to those in the neither group men categorized as both or either reported more frequent urological chronic pelvic pain syndrome symptom flares, catastrophizing and irritable bowel syndrome, and women categorized as both or either were more likely to have a negative affect and chronic fatigue syndrome. **CONCLUSIONS:** Men and women with bladder symptoms characterized as painful filling or painful urgency had more severe urological symptoms, more generalized symptoms and worse quality of life than participants who reported neither characteristic, suggesting that these symptom characteristics might represent important subsets of patients with urological chronic pelvic pain syndromes.

Relationship between chronic nonurological associated somatic syndromes and symptom severity in urological chronic pelvic pain syndromes: baseline evaluation of the MAPP study.

Krieger JN, Stephens AJ, Landis JR, Clemens JQ, Kreder K, Lai HH, Afari N, Rodríguez L, Schaeffer A, Mackey S, Andriole GL, Williams DA; MAPP Research Network. J Urol. 2015 Apr;193(4):1254-62. doi: 10.1016/j.juro.2014.10.086.

PURPOSE: We used MAPP data to identify participants with urological chronic pelvic pain syndromes only or a chronic functional nonurological associated somatic syndrome in addition to urological chronic pelvic pain syndromes. We characterized these 2 subgroups and explored them using 3 criteria, including 1) MAPP eligibility criteria, 2) self-reported medical history or 3) RICE criteria. **MATERIALS AND METHODS:** Self-reported cross-sectional data were collected on men and women with urological chronic pelvic pain syndromes, including predominant symptoms, symptom duration and severity, nonurological associated somatic syndrome symptoms and psychosocial factors. **RESULTS:** Of 424 participants with urological chronic pelvic pain syndromes 162 (38%) had a nonurological associated somatic syndrome, including irritable bowel syndrome in 93 (22%), fibromyalgia in 15 (4%), chronic fatigue syndrome in 13 (3%) and multiple syndromes in 41 (10%). Of 233 females 103 (44%) had a nonurological associated somatic syndrome compared to 59 of 191 males (31%) ($p = 0.006$). Participants with a nonurological associated somatic syndrome had more severe urological symptoms and more frequent depression and anxiety. Of 424 participants 228 (54%) met RICE criteria. Of 228 RICE positive participants 108 (47%) had a nonurological associated somatic syndrome compared to

54 of 203 RICE negative patients (28%) with a nonurological associated somatic syndrome ($p < 0.001$). **CONCLUSIONS:** Nonurological associated somatic syndromes represent important clinical characteristics of urological chronic pelvic pain syndromes. Participants with a nonurological associated somatic syndrome have more severe symptoms, longer duration and higher rates of depression and anxiety. RICE positive patients are more likely to have a nonurological associated somatic syndrome and more severe symptoms. Because nonurological associated somatic syndromes are more common in women, future studies must account for this potential confounding factor in urological chronic pelvic pain syndromes.

Unique microstructural changes in the brain associated with urological chronic pelvic pain syndrome (UCPPS) revealed by diffusion tensor MRI, super-resolution track density imaging, and statistical parameter mapping: A MAPP Network neuroimaging study.

Woodworth D, Mayer E, Leu K, Ashe-McNalley C, Naliboff BD, Labus JS, Tillisch K, Kutch JJ, Farmer MA, Apkarian AV, Johnson KA, Mackey SC, Ness TJ, Landis JR, Deutsch G, Harris RE, Clauw DJ, Mullins C, Ellingson BM; MAPP Research Network
PLoS One. 2015 Oct 13;10(10):e0140250. doi: 10.1371/journal.pone.0140250. eCollection 2015.

Studies have suggested chronic pain syndromes are associated with neural reorganization in specific regions associated with perception, processing, and integration of pain. Urological chronic pelvic pain syndrome (UCPPS) represents a collection of pain syndromes characterized by pelvic pain, namely Chronic Prostatitis / Chronic Pelvic Pain Syndrome (CP/CPSS) and Interstitial Cystitis/Painful Bladder Syndrome (IC/PBS), that are both poorly understood in their pathophysiology, and treated ineffectively. We hypothesized patients with UCPPS may have microstructural differences in the brain compared with healthy control subjects (HCs), as well as patients with irritable bowel syndrome (IBS), a common gastrointestinal pain disorder. In the current study we performed population-based voxel-wise DTI and super-resolution track density imaging (TDI) in a large, two-center sample of phenotyped patients from the multicenter cohort with UCPPS ($N = 45$), IBS ($N = 39$), and HCs ($N = 56$) as part of the MAPP Research Network. Compared with HCs, UCPPS patients had lower fractional anisotropy (FA), lower generalized anisotropy (GA), lower track density, and higher mean diffusivity (MD) in brain regions commonly associated with perception and integration of pain information. Results also showed significant differences in specific anatomical regions in UCPPS patients when compared with IBS patients, consistent with microstructural alterations specific to UCPPS. While IBS patients showed clear sex related differences in FA, MD, GA, and track density consistent with previous reports, few such differences were observed in UCPPS patients. Heat maps illustrating the correlation between specific regions of interest and various pain and urinary symptom scores showed clustering of significant associations along the cortico-basal ganglia-thalamic-cortical loop associated with pain integration, modulation, and perception. Together, results suggest patients with UCPPS have extensive microstructural differences within the brain, many specific to syndrome UCPPS versus IBS, that appear to be localized to regions associated with perception and integration of sensory information and pain modulation, and seem to be a consequence of longstanding pain.

PATHOPHYSIOLOGY STUDIES

Abnormal resting-state functional connectivity in patients with chronic fatigue syndrome: Results of seek and data-driven analyses.

Gay CW, Robinson ME, Lai S, O'Shea A, Craggs JG, Price DD, Staud R.
Brain Connect. 2015 Nov 10. [Epub ahead of print]

Although altered resting-state functional connectivity (FC) is a characteristic of many chronic pain conditions, it has not yet been evaluated in patients with chronic fatigue. Our objective was to investigate the association between fatigue and altered resting-state FC in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Thirty-six female subjects, 19 ME/CFS and 17 healthy controls, completed a fatigue inventory before undergoing functional magnetic resonance imaging. Two methods, (1) data driven and (2) model based, were used to estimate and compare the intraregional FC between both groups during the resting state (RS). The first approach using independent component analysis was applied to investigate five RS networks: the default mode network, salience network (SN), left frontoparietal networks (LFPN) and right frontoparietal networks, and the sensory motor network (SMN). The second approach used a priori selected seed regions demonstrating abnormal regional cerebral blood flow (rCBF) in ME/CFS patients at rest. In ME/CFS patients, Method-1 identified decreased intrinsic connectivity among regions within the LFPN. Furthermore, the FC of the left anterior midcingulate with the SMN and the connectivity of the left posterior cingulate cortex with the SN were significantly decreased. For Method-2, five distinct clusters within the right parahippocampus and occipital lobes, demonstrating significant rCBF reductions in ME/CFS patients, were used as seeds. The parahippocampal seed and three occipital lobe seeds showed altered FC with other brain regions. The degree of abnormal connectivity correlated with the level of self-reported fatigue. Our results confirm altered RS FC in patients with ME/CFS, which was significantly correlated with the severity of their chronic fatigue.

Disease-related differences in resting-state networks: a comparison between localized provoked vulvodynia, irritable bowel syndrome, and healthy control subjects.

Gupta A, Rapkin AJ, Gill Z, Kilpatrick L, Fling C, Stains J, Masghati S, Tillisch K, Mayer EA, Labus JS.

Pain. 2015 May;156(5):809-19. doi: 10.1097/01.j.pain.0000461289.65571.54.

Localized provoked vulvodynia (LPVD) affects approximately 16% of the female population, but biological mechanisms underlying symptoms remain unknown. Like in other often comorbid chronic pain disorders, altered sensory processing and modulation of pain, including central sensitization, dysregulation of endogenous pain modulatory systems, and attentional enhancement of pain perception, have been implicated. The aim of this study was to test whether regions of interest showing differences in LPVD compared to healthy control subjects (HCs) in structural and evoked-pain neuroimaging studies, also show alterations during rest when compared with HCs and a chronic pain control group (irritable bowel syndrome [IBS]). Functional magnetic resonance imaging was performed during resting state in 87 age-matched premenopausal females (29 LPVD, 29 HCs, and 29 IBS). Group-independent component analysis and general linear models were applied to investigate group differences in the intrinsic connectivity of regions comprising sensorimotor, salience, and default mode resting-state networks. Subjects with LPVD showed substantial alterations in the intrinsic connectivity of these networks compared with HCs and IBS. The intrinsic connectivity of many of the regions showing group differences during rest were moderately associated with clinical symptom reports in LPVD. Findings were robust to controlling for affect and medication usage. The current findings indicate that subjects with LPVD have alterations in the intrinsic connectivity of regions comprising the sensorimotor, salience, and default mode networks. Although shared brain mechanisms between different chronic pain disorders have been postulated, the current findings suggest that some alterations in functional connectivity may show disease specificity.

Neuroimaging of central sensitivity syndromes: Key insights from the scientific literature.

Walitt B, Ceko M, Gracely J, Gracely RH.
Curr Rheumatol Rev. 2015 Dec 30. [Epub ahead of print]

Central sensitivity syndromes are characterized by distressing symptoms, such as pain and fatigue, in the absence of clinically obvious pathology. The scientific underpinnings of these disorders are not currently known. Modern neuroimaging techniques promise new insights into mechanisms mediating these postulated syndromes. We review the results of neuroimaging applied to five central sensitivity syndromes: fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, temporomandibular joint disorder, and vulvodynia syndrome. Neuroimaging studies of basal metabolism, anatomic constitution, molecular constituents, evoked neural activity, and treatment effect are compared across all of these syndromes. Evoked sensory paradigms reveal sensory augmentation to both painful and non-painful stimulation. This is a transformative observation for these syndromes, which were historically considered to be completely of hysterical or feigned in origin. However, whether sensory augmentation represents the cause of these syndromes, a predisposing factor, an endophenotype, or an epiphenomenon cannot be discerned from the current literature. Further, the result from cross-sectional neuroimaging studies of basal activity, anatomy, and molecular constituency are extremely heterogeneous within and between the syndromes. A defining neuroimaging "signature" cannot be discerned for any of the particular syndromes or for an over-arching central sensitization mechanism common to all of the syndromes. Several issues confound initial attempts to meaningfully measure treatment effects in these syndromes. At this time, the existence of "central sensitivity syndromes" is based more soundly on clinical and epidemiological evidence. A coherent picture of a "central sensitization" mechanism that bridges across all of these syndromes does not emerge from the existing scientific evidence.

Lateral pterygoid muscle volume and migraine in patients with temporomandibular disorders.

Lopes SL, Costa AL, Gamba Tde O, Flores IL, Cruz AD, Min LL.
Imaging Sci Dent. 2015 Mar;45(1):1-5. doi: 10.5624/isd.2015.45.1.1.

PURPOSE: Lateral pterygoid muscle (LPM) plays an important role in jaw movement and has been implicated in Temporomandibular disorders (TMDs). Migraine has been described as a common symptom in patients with TMDs and may be related to muscle hyperactivity. This study aimed to compare LPM volume in individuals with and without migraine, using segmentation of the LPM in magnetic resonance (MR) imaging of the TMJ. **MATERIALS AND METHODS:** Twenty patients with migraine and 20 volunteers without migraine underwent a clinical examination of the TMJ, according to the Research Diagnostic Criteria for TMDs. MR imaging was performed and the LPM was segmented using the ITK-SNAP 1.4.1 software, which calculates the volume of each segmented structure in voxels per cubic millimeter. The chi-squared test and the Fisher's exact test were used to relate the TMD variables obtained from the MR images and clinical examinations to the presence of migraine. Logistic binary regression was used to determine the importance of each factor for predicting the presence of a migraine headache. **RESULTS:** Patients with TMDs and migraine tended to have hypertrophy of the LPM (58.7%). In addition, abnormal mandibular movements (61.2%) and disc displacement (70.0%) were found to be the most common signs in patients with TMDs and migraine. **CONCLUSION:** In patients with TMDs and simultaneous migraine, the LPM tends to be hypertrophic. LPM segmentation on MR imaging may be an alternative method to study this muscle in such patients because the hypertrophic LPM is not always palpable.

Imaging brain mechanisms in chronic visceral pain.

Mayer EA, Gupta A, Kilpatrick LA, Hong JY.

Pain. 2015 Apr;156 Suppl 1:S50-63. doi: 10.1097/j.pain.000000000000106.

Chronic visceral pain syndromes are important clinical problems with largely unmet medical needs. Based on the common overlap with other chronic disorders of visceral or somatic pain, mood and affect, and their responsiveness to centrally targeted treatments, an important role of central nervous system in their pathophysiology is likely. A growing number of brain imaging studies in irritable bowel syndrome, functional dyspepsia, and bladder pain syndrome/interstitial cystitis has identified abnormalities in evoked brain responses, resting state activity, and connectivity, as well as in gray and white matter properties. Structural and functional alterations in brain regions of the salience, emotional arousal, and sensorimotor networks, as well as in prefrontal regions, are the most consistently reported findings. Some of these changes show moderate correlations with behavioral and clinical measures. Most recently, data-driven machine-learning approaches to larger data sets have been able to classify visceral pain syndromes from healthy control subjects. Future studies need to identify the mechanisms underlying the altered brain signatures of chronic visceral pain and identify targets for therapeutic interventions.

Clinical value of serum neuroplasticity mediators in identifying the central sensitivity syndrome in patients with chronic pain with and without structural pathology.

Deitos A, Dussan-Sarria JA, de Souza A, Medeiros L, da Graca Tarrago M, Sehn F, Chassot M, Zanette S, Schwertner A, Fregni F, Torres IL, Caumo W.

Clin J Pain. 2015 Nov;31(11):959-67. doi: 10.1097/AJP.000000000000194.

Background and Objectives: Central sensitivity syndrome (CSS) encompasses disorders with overlapping symptoms in a spectrum of structural pathology from persistent somatic nociception (eg, osteoarthritis) to absence of tissue injury such as in fibromyalgia, chronic tension-type headache, and myofascial pain syndrome. Likewise, the spectrum of the neuroplasticity mediators associated with CSS might present a pattern of clinical utility. **Methods:** We studied the brain-derived neurotrophic factor (BDNF), tumor necrosis factor- α (TNF- α), and interleukins 6 (IL-6) and IL-10 in female patients with CSS absent of structural pathology (chronic tension-type headache [n=30], myofascial pain syndrome [n=29], fibromyalgia [n=22]); with CSS due to persistent somatic/visceral nociception (osteoarthritis [n=27] and endometriosis [n=32]); and in pain-free controls (n=37). **Results:** Patients with CSS absent of structural pathology presented higher serum TNF- α (28.61 \pm 12.74 pg/mL) and BDNF (49.87 \pm 31.86 ng/mL) than those with persistent somatic/visceral nociception (TNF- α =17.35 \pm 7.38 pg/mL; BDNF=20.44 \pm 8.30 ng/mL) and controls (TNF- α =21.41 \pm 5.74 pg/mL, BDNF=14.09 \pm 11.80 ng/mL). Moreover, CSS patients absent of structural pathology presented lower IL levels. Receiver operator characteristics analysis showed the ability of BDNF to screen CSS (irrespective of the presence of structural pathology) from controls (cutoff=13.31 ng/mL, area under the curve [AUC]=0.86, sensitivity=95.06%, specificity=56.76%); and its ability to identify persistent nociception in CSS patients when experiencing moderate-severe depressive symptoms (AUC=0.81; cutoff=42.83 ng/mL, sensitivity=56.80%, specificity=100%). When the level of pain measured on the visual analog scale was <5 and moderate-severe depressive symptoms were observed TNF- α discriminated structural pathology in the chronic pain conditions (AUC=0.97; cutoff=22.11 pg/mL, sensitivity=90%, specificity=91.3%). **Conclusion:** Neuroplasticity mediators could play a role as screening tools for pain clinicians, and as validation of the complex and diffuse symptoms of these patients.

Parasympathetic reactivity in fibromyalgia and temporomandibular disorder: Associations with sleep problems, symptom severity, and functional impairment.

Eisenlohr-Moul TA, Crofford LJ, Howard TW, Yepes JF, Carlson CR, de Leeuw R. J Pain. 2015 Mar;16(3):247-57. doi: 10.1016/j.jpain.2014.12.005.

Despite evidence of autonomic disturbances in chronic multisymptom illnesses such as temporomandibular disorder (TMD) and fibromyalgia, additional work is needed to characterize the role of parasympathetic reactivity in these disorders. Given the high levels of comorbidity with psychiatric disorders characterized by stronger parasympathetic decline than controls in safe contexts (leading to higher arousal), it was hypothesized that individuals with TMD and fibromyalgia would respond similarly. In this preliminary investigation, 43 women with TMD (n = 17), TMD + fibromyalgia (n = 11), or neither (controls; n = 15) completed a baseline assessment of respiratory sinus arrhythmia (a measure of parasympathetic activity) followed by ongoing parasympathetic assessment during a questionnaire period. As predicted, patients showed greater parasympathetic decline during psychosocial assessment, suggesting an autonomic stance that supports defensive rather than engagement behaviors. Individual differences in parasympathetic reduction during the questionnaire period were related to a variety of physical and psychosocial variables. Although this study has a number of key limitations, including a convenience sampling approach and small group sizes, if replicated in larger samples, the findings would have important implications for the treatment of patients with these disorders. PERSPECTIVE: Compared to controls, individuals with TMD or TMD and fibromyalgia demonstrated greater parasympathetic decline during psychosocial assessment, and individual differences in parasympathetic decline predicted negative patient outcomes. Such parasympathetic decline may demonstrate a tendency to readily perceive danger in safe environments.

The inflammatory hypothesis of mood spectrum broadened to fibromyalgia and chronic fatigue syndrome.

Dell'Osso L, Bazzichi L, Baroni S, Falaschi V, Conversano C, Carmassi C, Marazziti D. Clin Exp Rheumatol. 2015 Jan-Feb;33(1 Suppl 88):S109-16.

OBJECTIVES: The present paper aimed at reviewing literature data on the inflammatory hypothesis of mood spectrum, as well as the overlapping features with some chronic rheumatologic disorders, in particular fibromyalgia and chronic fatigue syndrome. METHODS: A literature search was carried out for English papers published in the years 2000-2014, while using the following words: mood spectrum, depression, bipolar disorders, fibromyalgia, chronic fatigue syndrome, neurotransmitters, inflammation, neuroinflammation, cytokines. RESULTS: Overlapping features were highlighted between mood spectrum, fibromyalgia and chronic fatigue syndrome suggesting common underlying mechanisms at pathophysiological level involving both central nervous and the immune systems. CONCLUSIONS: Taken together, the literature would suggest that the borders between different medical domains should be reconsidered in the light of common processes linking them.

Algo-dysfunctional syndromes: a critical digest of the recent literature.

Talotta R, Atzeni F, Bazzichi L, Giacomelli C, Di Franco M, Salaffi F, Sarzi-Puttini P. Clin Exp Rheumatol. 2015 Jan-Feb;33(1 Suppl 88):S102-8.

The etiopathogenesis of the algo-dysfunctional syndromes, which include chronic fatigue

syndrome, fibromyalgia and irritable bowel syndrome, is still debated, but it is widely accepted that it is best described by a multifactorial model that include genes, environmental factors such as external infections, inflammation, dietary habits, impaired endogenous cortisol production, the aberrant activation of some areas of the central nervous system, and small peripheral nervous fibre damage. This complexity suggests that they should be managed by means of a multidisciplinary approach involving the use of both pharmacological and non-pharmacological treatments. The aim of this review is to discuss the most recent scientific acquisitions concerning these syndromes and their treatment.

Mechanisms of visceral organ crosstalk: Importance of alterations in permeability in rodent models.

Greenwood-Van Meerveld B, Mohammadi E, Tyler K, Van Gordon S, Parker A, Towner R, Hurst R.

J Urol. 2015 Sep;194(3):804-11. doi: 10.1016/j.juro.2015.02.2944.

PURPOSE: The pathophysiology of painful bladder syndrome is poorly understood. However, there is evidence of female predominance and comorbidity with irritable bowel syndrome. Our hypothesis is that cross-sensitization between bladder and colon is due to altered permeability in 1 organ, which affects the other organ. **MATERIALS AND METHODS:** Experiments were performed in anesthetized, ovariectomized female rats. In separate groups protamine sulfate was infused in the bladder or trinitrobenzene sulfonic acid was infused in the colon. Untreated rats served as controls. Bladder and colonic tissue were harvested from all rats 1, 3 and 5 days after treatment. Permeability was assessed in vitro in Ussing chambers by measuring transepithelial electrical resistance and macromolecular flux of fluorescein isothiocyanate-dextran. **RESULTS:** Exposing the bladder to protamine sulfate induced a significant decrease in bladder transepithelial electrical resistance and an increase in the translocation of fluorescein isothiocyanate across the tissue compared to controls at 1 and 3 days ($p < 0.05$). Colonic tissue from rats with enhanced bladder permeability showed a significant decrease in transepithelial electrical resistance and increase in fluorescein isothiocyanate compared to untreated controls at all time points ($p < 0.05$). Conversely when colonic permeability was increased with trinitrobenzene sulfonic acid, we observed an increase in bladder permeability in the absence of any changes to the bladder urothelium. **CONCLUSIONS:** Changes in epithelial permeability may represent a novel mechanism for visceral organ crosstalk. It may explain the overlapping symptomatology of painful bladder syndrome and irritable bowel syndrome.

Somatosensory evaluation in Dysfunctional Syndrome patients.

Hilgenberg-Sydney PB, Kowacs PA, Conti PC.

J Oral Rehabil. 2015 Sep 4. doi: 10.1111/joor.12344.

Many chronic pain patients are refractory to treatment, which leads to the suspicion that somehow they are not fully effective and probably some mechanism of pain generation and/or maintenance is still unknown. The aim of this cross-sectional study was to provide evidence-based data on pain mechanisms in different types of chronic pain conditions. Eighty women, with 18-65 years old, were included, divided into four groups: myofascial pain of the masticatory muscles ($n = 20$), fibromyalgia ($n = 20$), chronic daily headache and healthy volunteers ($n = 20$). All patients were submitted to quantitative sensory tests: pressure pain threshold, mechanical detection threshold, mechanical pain threshold, ischemic pain tolerance, cold pain sensitivity, aftersensation, wind-up ratio and conditioned pain modulation. Current perception threshold was also determined (Neuromata CPT/C - Neutron (®)). Three different zones were evaluated: trigeminal (masseter muscle), cervical and extra trigeminal (thenar eminence). Data were

recorded and subjected to statistical analysis (anova, Tukey and Student's t-tests). Masticatory myofascial pain, fibromyalgia and chronic daily headache individuals presented lower pressure pain thresholds than healthy volunteers ($P = 0.00$). Chronic daily headache individuals had a significantly higher mechanical detection threshold than healthy volunteers ($P = 0.01$). Individuals of the symptomatic groups showed lower values for mechanical pain threshold and for ischemic pain tolerance ($P = 0.00$) than healthy volunteers. The ability to activate the mechanism of endogenous modulation is impaired in women with fibromyalgia and myofascial pain ($P = 0.00$). These results reinforce evidence of central sensitization and impaired endogenous modulation system in individuals with myofascial pain, fibromyalgia and chronic daily headache.

Gene expression factor analysis to differentiate pathways linked to fibromyalgia, chronic fatigue syndrome, and depression in a diverse patient sample.

Iacob E, Light AR, Donaldson GW, Okifuji A, Hughen RW, White AT, Light KC. *Arthritis Care Res (Hoboken)*. 2015 Jun 19. doi: 10.1002/acr.22639. [Epub ahead of print]

OBJECTIVE: To determine if independent candidate genes can be grouped into meaningful biological factors and if these factors are associated with the diagnosis of chronic fatigue syndrome (CFS) and fibromyalgia (FMS) while controlling for co-morbid depression, sex, and age. **METHODS:** We included leukocyte mRNA gene expression from a total of 261 individuals including healthy controls ($n=61$), patients with FMS only ($n=15$), CFS only ($n=33$), co-morbid CFS and FMS ($n=79$), and medication-resistant ($n=42$) or medication-responsive ($n=31$) depression. We used Exploratory Factor Analysis (EFA) on 34 candidate genes to determine factor scores and regression analysis to examine if these factors were associated with specific diagnoses. **RESULTS:** EFA resulted in four independent factors with minimal overlap of genes between factors explaining 51% of the variance. We labeled these factors by function as: 1) Purinergic and cellular modulators; 2) Neuronal growth and immune function; 3) Nociception and stress mediators; 4) Energy and mitochondrial function. Regression analysis predicting these biological factors using FMS, CFS, depression severity, age, and sex revealed that greater expression in Factors 1 and 3 was positively associated with CFS and negatively associated with depression severity (QIDS score), but not associated with FMS. **CONCLUSION:** Expression of candidate genes can be grouped into meaningful clusters, and CFS and depression are associated with the same 2 clusters but in opposite directions when controlling for co-morbid FMS. Given high co-morbid disease and interrelationships between biomarkers, EFA may help determine patient subgroups in this population based on gene expression.

Fibromyalgia and chronic fatigue: the underlying biology and related theoretical issues.

Romano GF, Tomassi S, Russell A, Mondelli V, Pariante CM. *Adv Psychosom Med*. 2015;34:61-77. doi: 10.1159/000369085.

There is an increasing interest in understanding the biological mechanism underpinning fibromyalgia (FM) and chronic fatigue syndrome (CFS). Despite the presence of mixed findings in this area, a few biological systems have been consistently involved, and the increasing number of studies in the field is encouraging. This chapter will focus on inflammatory and oxidative stress pathways and on the neuroendocrine system, which have been more commonly examined. Chronic inflammation, together with raised levels of oxidative stress and mitochondrial dysfunction, has been increasingly associated with the manifestation of symptoms such as pain, fatigue, impaired memory, and depression, which largely characterise at least some patients suffering from CFS and FM. Furthermore, the presence of blunted hypothalamic-pituitary-adrenal

axis activity, with reduced cortisol secretion both at baseline and in response to stimulation tests, suggests a role for the hypothalamic-pituitary-adrenal axis and cortisol in the pathogenesis of these syndromes. However, to what extent these systems' abnormalities could be considered as primary or secondary factors causing FM and CFS has yet to be clarified.

New concepts on functional chronic pelvic and perineal pain: pathophysiology and multidisciplinary management.

Ploteau S, Labat JJ, Riant T, Levesque A, Robert R, Nizard J.
Discov Med. 2015 Mar;19(104):185-92.

The management of chronic pelvic and perineal pain has been improved by a better understanding of the mechanisms of this pain and an optimized integrated multidisciplinary approach to the patient. The concept of organic lesions responsible for a persistent nociceptive factor has gradually been replaced by that of dysregulation of nociceptive messages derived from the pelvis and perineum. In this setting, painful diseases identified by organ specialists are usually also involved and share several common denominators (triggering factors, predisposing clinical context). These diseases include painful bladder syndrome, irritable bowel syndrome, vulvodynia, and chronic pelvic pain syndrome. The painful symptoms vary from one individual to another and according to his or her capacity to activate pain inhibition/control processes. Although the patient often attributes chronic pain to a particular organ (with the corollary that pain will persist until the organ has been treated), this pain is generally no longer derived from the organ but is expressed via this organ. Several types of clinical presentation of complex pelvic pain have therefore been pragmatically identified to facilitate the management of treatment failures resulting from a purely organ-based approach, which can also reinforce the patient's impression of incurability. These subtypes correspond to neuropathic pain, central sensitization (fibromyalgia), complex regional pain syndrome, and emotional components similar to those observed in post-traumatic stress disorder. These various components are also often associated and self-perpetuating. Consequently, when pelvic pain cannot be explained by an organ disease, this model, using each of these four components associated with their specific mechanisms, can be used to propose personalized treatment options and also to identify patients at high risk of postoperative pelvic pain (multi-operated patients, central sensitization, post-traumatic stress disorder, etc.), which constitutes a major challenge for prevention of these types of pain that have major implications for patients and society.

An insight into the gastrointestinal component of fibromyalgia: clinical manifestations and potential underlying mechanisms.

Slim M, Calandre EP, Rico-Villademoros F.
Rheumatol Int. 2015 Mar;35(3):433-44. doi: 10.1007/s00296-014-3109-9.

Fibromyalgia syndrome is characterized by chronic generalized pain accompanied by a broad symptomatologic spectrum. Besides chronic fatigue, sleep disturbances, headaches and cognitive dysfunction that are extensively described in the literature, a considerable proportion of patients with fibromyalgia experience gastrointestinal symptoms that are commonly overlooked in the studies that are not specifically dedicated to evaluate these manifestations. Nevertheless, various attempts were undertaken to explore the gastrointestinal dimension of fibromyalgia. Several studies have demonstrated an elevated comorbidity of irritable bowel syndrome (IBS) among patients with fibromyalgia. Other studies have investigated the frequency of presentation of gastrointestinal symptoms in fibromyalgia in a nonspecific approach describing several gastrointestinal complaints frequently reported by these patients such as abdominal pain, dyspepsia and bowel changes, among others. Several underlying mechanisms that require

further investigation could serve as potential explanatory hypotheses for the appearance of such manifestations. These include sensitivity to dietary constituents such as gluten, lactose or FODMAPs or alterations in the brain-gut axis as a result of small intestinal bacterial overgrowth or subclinical enteric infections such as giardiasis. The gastrointestinal component of fibromyalgia constitutes a relevant element of the multidisciplinary pathophysiologic mechanisms underlying fibromyalgia that need to be unveiled, as this would contribute to the adequate designation of relevant treatment alternatives corresponding to these manifestations.

EPIDEMIOLOGY STUDIES

Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.

Global Burden of Disease Study 2013 Collaborators.
Comment in Lancet. 2015 Aug 22;386(9995):721-2.

BACKGROUND: Up-to-date evidence about levels and trends in disease and injury incidence, prevalence, and years lived with disability (YLDs) is an essential input into global, regional, and national health policies. In the Global Burden of Disease Study 2013 (GBD 2013), we estimated these quantities for acute and chronic diseases and injuries for 188 countries between 1990 and 2013. **METHODS:** Estimates were calculated for disease and injury incidence, prevalence, and YLDs using GBD 2010 methods with some important refinements. Results for incidence of acute disorders and prevalence of chronic disorders are new additions to the analysis. Key improvements include expansion to the cause and sequelae list, updated systematic reviews, use of detailed injury codes, improvements to the Bayesian meta-regression method (DisMod-MR), and use of severity splits for various causes. An index of data representativeness, showing data availability, was calculated for each cause and impairment during three periods globally and at the country level for 2013. In total, 35620 distinct sources of data were used and documented to calculate estimates for 301 diseases and injuries and 2337 sequelae. The comorbidity simulation provides estimates for the number of sequelae, concurrently, by individuals by country, year, age, and sex. Disability weights were updated with the addition of new population-based survey data from four countries. **FINDINGS:** Disease and injury were highly prevalent; only a small fraction of individuals had no sequelae. Comorbidity rose substantially with age and in absolute terms from 1990 to 2013. Incidence of acute sequelae were predominantly infectious diseases and short-term injuries, with over 2 billion cases of upper respiratory infections and diarrhoeal disease episodes in 2013, with the notable exception of tooth pain due to permanent caries with more than 200 million incident cases in 2013. Conversely, leading chronic sequelae were largely attributable to non-communicable diseases, with prevalence estimates for asymptomatic permanent caries and tension-type headache of 2.4 billion and 1.6 billion, respectively. The distribution of the number of sequelae in populations varied widely across regions, with an expected relation between age and disease prevalence. YLDs for both sexes increased from 537.6 million in 1990 to 764.8 million in 2013 due to population growth and ageing, whereas the age-standardised rate decreased little from 114.87 per 1000 people to 110.31 per 1000 people between 1990 and 2013. Leading causes of YLDs included low back pain and major depressive disorder among the top ten causes of YLDs in every country. YLD rates per person, by major cause groups, indicated the main drivers of increases were due to musculoskeletal, mental, and substance use disorders, neurological disorders, and chronic respiratory diseases; however HIV/AIDS was a notable driver of increasing YLDs in sub-Saharan Africa. Also, the proportion of disability-adjusted life years due to YLDs increased globally from 21.1% in 1990 to 31.2% in 2013. **INTERPRETATION:** Ageing of the world's population is leading

to a substantial increase in the numbers of individuals with sequelae of diseases and injuries. Rates of YLDs are declining much more slowly than mortality rates. The non-fatal dimensions of disease and injury will require more and more attention from health systems. The transition to non-fatal outcomes as the dominant source of burden of disease is occurring rapidly outside of sub-Saharan Africa. Our results can guide future health initiatives through examination of epidemiological trends and a better understanding of variation across countries.

Irritable bowel syndrome subtypes: Clinical and psychological features, body mass index and comorbidities.

Kibune Nagasako C, Garvia Montes C, Silva Lorena SL, Mesquita MA

Rev Esp Enferm Dig. 2015 Nov 30;108. doi: 10.17235/reed.2015.3979/2015. [Epub ahead of print]

BACKGROUND: Irritable bowel syndrome (IBS) is classified into subtypes according to bowel habit. **OBJECTIVE:** To investigate whether there are differences in clinical features, comorbidities, anxiety, depression and body mass index (BMI) among IBS subtypes. **METHODS:** The study group included 113 consecutive patients (mean age: 48 ± 11 years; females: 94) with the diagnosis of IBS. All of them answered a structured questionnaire for demographic and clinical data and underwent upper endoscopy. Anxiety and depression were assessed by the Hospital Anxiety and Depression scale (HAD). **RESULTS:** The distribution of subtypes was: IBS-diarrhea (IBS-D), 46%; IBS-constipation (IBS-C), 32%, and mixed IBS (IBS-M), 22%. IBS overlap with gastroesophageal reflux disease (GERD), functional dyspepsia, chronic headache and fibromyalgia occurred in 65.5%, 48.7%, 40.7% and 22.1% of patients, respectively. Anxiety and/or depression were found in 81.5%. Comparisons among subgroups showed that bloating was significantly associated with IBS-M compared to IBS-D (odds ratio-OR-5.6). Straining was more likely to be reported by IBS-M (OR 15.3) and IBS-C (OR 12.0) compared to IBS-D patients, while urgency was associated with both IBS-M (OR 19.7) and IBS-D (OR 14.2) compared to IBS-C. In addition, IBS-M patients were more likely to present GERD than IBS-D (OR 6.7) and higher scores for anxiety than IBS-C patients (OR 1.2). BMI values did not differ between IBS-D and IBS-C. **CONCLUSION:** IBS-M is characterized by symptoms frequently reported by both IBS-C (straining) and IBS-D (urgency), higher levels of anxiety, and high prevalence of comorbidities. These features should be considered in the clinical management of this subgroup.

Incidence and risk factors for chronic pelvic pain after hysteroscopic sterilization.

Yunker AC, Ritch JM, Robinson EF, Golish CT.

J Minim Invasive Gynecol. 2015 Mar-Apr;22(3):390-4. doi: 10.1016/j.jmig.2014.06.007.

STUDY OBJECTIVE: To investigate the incidence of and preoperative risk factors for developing pelvic pain after hysteroscopic sterilization using the Essure microinserts. **DESIGN:** Retrospective cohort study (Canadian Task Force classification II-2). **SETTING:** University medical center. **PATIENTS:** A total of 458 patients who underwent hysteroscopic sterilization using Essure between January 1, 2005, and June 30, 2012. **INTERVENTION:** Hysteroscopic sterilization using Essure. **MEASUREMENTS AND MAIN RESULTS:** The incidence of acute pelvic pain after hysteroscopic sterilization was 8.1%, and of persistent pain at 3 months after the procedure was 4.2%. The range of presence of pain was 1 to 469 days (mean, 56 days). Of patients who developed chronic pelvic pain after the procedure, 75% reported it within 130 days of the procedure. Patients with previous diagnoses of any chronic pain (chronic pelvic pain, chronic low back pain, chronic headache, and fibromyalgia) were more likely to report both acute pain (odds ratio, 6.81; 95% confidence interval, 2.95-15.73) and chronic pain (odds ratio, 6.15;

95% confidence interval, 2.10-18.10) after hysteroscopic sterilization. **CONCLUSIONS:** Pelvic pain may develop after hysteroscopic sterilization. Patients with a diagnosis of preexisting chronic pain may be at increased risk of developing pelvic pain after the procedure. Fifty percent of new pelvic pain after Essure placement will resolve within 3 months.

A systematic review of the comorbidity between temporomandibular disorders and chronic fatigue syndrome.

Robinson LJ, Durham J, Newton JL

J Oral Rehabil. 2015 Nov 9. doi: 10.1111/joor.12367. [Epub ahead of print]

The most common cause of chronic oro-facial pain is a group of disorders collectively termed temporomandibular disorders (TMDs). Chronic painful TMD is thought to be a 'central sensitivity syndrome' related to hypersensitivity of the nervous system, but the cause is unknown. A similar understanding is proposed for other unexplained conditions, including chronic fatigue syndrome (CFS). Exploring the comorbidity of the two conditions is a valuable first step in identifying potential common aetiological mechanisms or treatment targets. **Method:** Systematic literature review. Studies were included if they recruited community or control samples and identified how many reported having both TMD and CFS, or if they recruited a sample of patients with either TMD or CFS and measured the presence of the other condition. **Results:** Six papers met inclusion criteria. In studies of patients with CFS ($n = 3$), 21-32% reported having TMD. In a sample of people with CFS and fibromyalgia, 50% reported having TMD. Studies in people with TMD ($n = 3$) reported 0-43% having CFS. Studies in samples recruited from oro-facial pain clinics ($n = 2$) reported a lower comorbidity with CFS (0-10%) than a study that recruited individuals from a TMD self-help organisation (43%). **Conclusion:** The review highlights the limited standard of evidence addressing the comorbidity between oro-facial pain and CFS. There is a valuable signal that the potential overlap in these two conditions could be high; however, studies employing more rigorous methodology including standardised clinical assessments rather than self-report of prior diagnosis are needed.

Temporomandibular disorder is more prevalent among patients with primary headaches in a tertiary outpatient clinic.

Tomaz-Morais JF, Lucena LB, Mota IA, Pereira AK, Lucena BT, Castro RD, Alves GA.

Arq Neuropsiquiatr. 2015 Nov;73(11):913-7. doi: 10.1590/0004-282X20150145.

Objective: The aim of this study was to estimate the prevalence of signs and symptoms of temporomandibular disorders (TMD) in patients with primary headaches attended in a tertiary neurology ambulatory. **Method:** Authorized by the Ethics Committee, the present cross-sectional study was conducted with a random sample of patients screened for orofacial pain and primary headaches at a tertiary hospital in Northeast of Brazil. **Results:** The sample consisted in 42 patients with primary headache, 59.5% male. The prevalence of > 6 TMD signs and symptoms was 54.8%. In those patients with migraine TMD was present in 71.4% and tension-type headache in 38.1% ($p = 0.030$; OR = 4.1). TMD was related to the clinical status of headache associated or attributed to medication overuse ($p = 0.001$). **Conclusion:** TMD has a high prevalence in patients with primary headaches (54.8%). Special attention must be given to patients with migraine and headache associated or attributed to medication overuse.

The prevalence of low back pain in hospital staff and its relationship with chronic fatigue syndrome and occupational factors.

Terzi R, Altın F.
Agri. 2015 Jul; 27(3):149-54. doi: 10.5505/agri.2015.26121.

OBJECTIVES: This study aimed to investigate the occurrence of low back pain in hospital employees during the previous year and its correlation with demographic data, occupational factors and chronic fatigue syndrome. **METHODS:** All participants provided information on their socio-demographic background, occupational characteristics, and their experience of low back pain during the previous year, and chronic fatigue syndrome. **RESULTS:** The study included 365 volunteers (221 male and 144 female). The mean age was 33.1±7.2. Of the 365 participants, 218 (59.7%) had experienced low back pain in the last year. No statistically significant difference was detected in age, height, weight, level of education, smoking habits, occupation, professional working hours, shift work or levels of income between the groups with and without low back pain. Low back pain was more frequent ($p<0.05$) in male workers. Chronic fatigue syndrome was statistically significant in the group suffering from low back pain ($p<0.05$), of whom 21.5% had chronic fatigue syndrome. We detected a statistically significant relationship ($p<0.05$) between chronic fatigue syndrome, occupational duration and shift work. **CONCLUSION:** To the best of our knowledge, this is the first to show the relationship between low back pain and chronic fatigue syndrome in hospital employees. Shift work and length of time in occupation are risk factors for chronic fatigue syndrome.

Musculoskeletal pain is associated with restless legs syndrome in young adults.

Hoogwout SJ, Paananen MV, Smith AJ, Beales DJ, O'Sullivan PB, Straker LM, Eastwood PR, McArdle N, Champion D.
BMC Musculoskelet Disord. 2015 Oct 14;16(1):294. doi: 10.1186/s12891-015-0765-1.

Background: In recent years, there is considerable evidence of a relationship between the sensorimotor disorder restless legs syndrome (RLS) and pain disorders, including migraine and fibromyalgia. An association between multi-site pain and RLS has been reported in adult women. In the current study, we explored the association between musculoskeletal (MSK) pain and RLS in a large cohort of young adults. **Methods:** Twenty two year olds, ($n=1072$) followed since birth of part of the Western Australian Pregnancy Cohort (Raine) Study, provided data on MSK pain (duration, severity, frequency, number of pain sites). RLS was considered present when 4 diagnostic criteria recommended by the International Restless Legs Syndrome Study Group were met (urge to move, dysaesthesia, relief by movement, worsening symptoms during the evening/night) and participants had these symptoms at least 5 times per month. Associations between MSK pain and RLS were analyzed by multivariable logistic regression with bias-corrected bootstrapped confidence intervals, with final models adjusted for sex, psychological distress and sleep quality. **Results:** The prevalence of RLS was 3.0 % and MSK pain was reported by 37.4 % of the participants. In multivariable logistic regression models, strong associations were found between RLS-diagnosis and long duration (three months or more) of MSK pain (odds ratio 3.6, 95 % confidence interval 1.4-9.2) and reporting three or more pain sites (4.9, 1.6-14.6). **Conclusions:** Different dimensions of MSK pain were associated with RLS in young adults, suggestive of shared pathophysiological mechanisms. Overlap between these conditions requires more clinical and research attention.

Clinical characteristics of dry eye patients with chronic pain syndromes.

Vehof J, Sillevius Smitt-Kamminga N, Kozareva D, Nibourg SA, Hammond CJ
Am J Ophthalmol. 2015 Nov 19. pii: S0002-9394(15)00705-9. doi: 10.1016/j.ajo.2015.11.017.
[Epub ahead of print]

PURPOSE: To investigate clinical characteristics of dry eye disease (DED) patients with a chronic pain syndrome. **DESIGN:** Cross-sectional study. **METHODS:** Four hundred twenty-five patients of a tertiary care DED patient cohort in the Netherlands were included. Chronic pain syndromes irritable bowel syndrome, chronic pelvic pain, and fibromyalgia were assessed by questionnaires. Outcome variables were the Ocular Surface Disease Index (OSDI) symptom questionnaire, tear osmolarity, Schirmer test, tear breakup time, conjunctival hyperemia, staining of the cornea and conjunctiva, and amount of mucus. Outcomes were cross-sectionally compared between DED patients with a chronic pain syndrome and those without. **RESULTS:** A total of 74 out of 425 DED patients (17%) had at least 1 chronic pain syndrome. The total symptom score was significantly higher in DED patients with a chronic pain syndrome than in those without (45.8 vs 33.8, $P < .0005$). Moreover, patients with a chronic pain syndrome scored higher on every single subscale of the 12-item OSDI symptom questionnaire. However, ocular signs were similar or even less severe in these patients. Similarly, in 64 DED patients from the population-based cohort Twins UK, patients with a chronic pain syndrome ($n = 24$, 38%) had higher subscale and total (34.1 vs 14.4, $P = .001$) symptom scores. **CONCLUSION:** In DED patients, chronic pain syndromes are common and are associated with increased severity of DED symptoms across all domains of the OSDI, even though objective ocular surface signs are no worse. In clinical practice, more awareness of chronic pain syndromes might help in understanding the discrepancy between signs and symptoms in DED.

Comorbidity is associated with pain-related activity limitations in multiple sclerosis.

Fiest KM, Fisk JD, Patten SB, Tremlett H, Wolfson C, Warren S, McKay KA, Berrigan L, Marrie RA; CIHR Team in the Epidemiology and Impact of Comorbidity on Multiple Sclerosis (ECoMS). *Mult Scler Relat Disord.* 2015 Sep; 4(5):470-6. Doi: 10.1016/j.msard.2015.07.014.

BACKGROUND: Comorbidities are common in multiple sclerosis (MS). The high prevalence of pain in MS is well-established but the influence of comorbidities on pain, specifically, pain-related interference in activity is not. **OBJECTIVE:** To examine the relationship between comorbidity and pain in MS. **METHODS:** We recruited 949 consecutive patients with definite MS from four Canadian centers. Participants completed the Health Utilities Index (HUI-Mark III) and a validated comorbidity questionnaire at 3 visits over 2 years. The HUI's pain scale was dichotomized into two groups: those with/without pain that disrupts normal activities. We used logistic regression to assess the association of pain with each comorbidity individually at baseline and over time. **RESULTS:** The incidence of disruptive pain over two years was 31.1 per 100 persons. Fibromyalgia, rheumatoid arthritis, irritable bowel syndrome, migraine, chronic lung disease, depression, anxiety, hypertension, and hypercholesterolemia were associated with disruptive pain ($p < 0.006$). Individual-level effects on the presence of worsening pain were seen for chronic obstructive pulmonary disease (odds ratio [OR]: 1.50 95% CI: 1.08-2.09), anxiety (OR: 1.49 95% CI: 1.07-2.08), and autoimmune thyroid disease (OR: 1.40 95% CI: 1.00-1.97). **CONCLUSION:** Comorbidity is associated with pain in persons with MS. Closer examination of these associations may provide guidance for better management of this disabling symptom in MS.

The incidence and prevalence of comorbid gastrointestinal, musculoskeletal, ocular, pulmonary, and renal disorders in multiple sclerosis: a systematic review.

Marrie RA, Reider N, Stuve O, Trojano M, Sorensen PS, Cutter GR, Reingold SC, Cohen J. *Mult Scler.* 2015 Mar;21(3):332-41. doi: 10.1177/1352458514564488.

BACKGROUND: As new disease-modifying therapies emerge a better knowledge of the risk of comorbid disease in multiple sclerosis (MS) is needed. **OBJECTIVE:** To estimate the incidence and prevalence of comorbid gastrointestinal, musculoskeletal, ocular, pulmonary, and renal disorders in MS. **METHODS:** We systematically reviewed the world literature by searching PUBMED, EMBASE, SCOPUS, the Web of Knowledge, and reference lists of retrieved articles. For selected articles, one reviewer abstracted data using a standardized form. The abstraction was verified by a second reviewer. The quality of all selected studies was assessed. For population-based studies we quantitatively assessed studies using the I² statistic, and conducted random effects meta-analyses. **RESULTS:** Study designs were heterogeneous with respect to populations, case definitions, and methods of ascertainment. Incidence of the studied comorbidities was rarely reported. Irritable bowel syndrome and chronic lung disease had a prevalence of more than 10% in the MS population. Irritable bowel syndrome, fibromyalgia, cataracts and glaucoma were more common than expected in the MS population. **CONCLUSION:** Although they have been the subject of less study than other comorbidities, irritable bowel syndrome, arthritis, and chronic lung disease are common in the MS population and occur more often than expected when compared to the general population.

Risk of associated conditions in relatives of subjects with interstitial cystitis.

Allen-Brady K, Norton PA, Cannon-Albright L.

Female Pelvic Med Reconstr Surg. 2015 Mar-Apr;21(2):93-8. doi: 10.1097/SPV.000000000000139.

OBJECTIVES: Urological chronic pelvic pain syndrome includes interstitial cystitis/painful bladder syndrome (IC/PBS), a chronic bladder pain condition of unknown etiology. Interstitial cystitis/painful bladder syndrome can co-occur with a number of associated conditions such as irritable bowel syndrome and fibromyalgia. The purpose of this study was to estimate the heritability of approximately 20 associated conditions in first-degree relatives (and if appropriate, second- and third-degree relatives) of patients with IC/PBS to identify shared genetic contributions for the disease combinations. **METHODS:** We used the Utah Population Database, a unique population-based genealogical database that has been linked to electronic health records for the University of Utah Health Sciences Center back in 1994. Interstitial cystitis/painful bladder syndrome probands were identified by the International Classification of Diseases, Ninth Revision code for chronic interstitial cystitis and had genealogy information for 12 of their 14 immediate ancestors. We calculated excess risk of an associated condition in relatives of patients with IC/PBS using relative risk estimates. **RESULTS:** We identified 248 IC/PBS probands. We found that 2 associated conditions, myalgia and myositis/unspecified (fibromyalgia) as well as constipation, were in significant excess in the patients with IC/PBS themselves, their first-degree relatives, and their second-degree relatives. The excess risk among relatives between IC/PBS and these associated conditions also held in the converse direction. Excess risk of IC/PBS was observed in the first- and second-degree relatives in probands with myalgia and myositis/unspecified (fibromyalgia) and in probands with constipation. **CONCLUSIONS:** These results suggest that myalgia and myositis/unspecified (fibromyalgia) as well as constipation are likely to share underlying genetic factors with IC/PBS.

Gastrointestinal symptoms among endometriosis patients--A case-cohort study.

Ek M, Roth B, Ekström P, Valentin L, Bengtsson M, Ohlsson B.

BMC Womens Health. 2015 Aug 13;15:59. doi: 10.1186/s12905-015-0213-2.

BACKGROUND: Women with endometriosis often experience gastrointestinal symptoms. Gonadotropin-releasing hormone (GnRH) analogs are used to treat endometriosis; however, some patients develop gastrointestinal dysmotility following this treatment. The aims of the present study were to investigate gastrointestinal symptoms among patients with endometriosis and to examine whether symptoms were associated with menstruation, localization of endometriosis lesions, or treatment with either opioids or GnRH analogs, and if hormonal treatment affected the symptoms. **METHODS:** All patients with diagnosed endometriosis at the Department of Gynecology were invited to participate in the study. Gastrointestinal symptoms were registered using the Visual Analogue Scale for Irritable Bowel Syndrome (VAS-IBS); socioeconomic and medical histories were compiled using a clinical data survey. Data were compared to a control group from the general population. **RESULTS:** A total of 109 patients and 65 controls were investigated. Compared to controls, patients with endometriosis experienced significantly aggravated abdominal pain ($P = 0.001$), constipation ($P = 0.009$), bloating and flatulence ($P = 0.000$), defecation urgency ($P = 0.010$), and sensation of incomplete evacuation ($P = 0.050$), with impaired psychological well-being ($P = 0.005$) and greater intestinal symptom influence on their daily lives ($P = 0.001$). The symptoms were not associated with menstruation or localization of endometriosis lesions, except increased nausea and vomiting ($P = 0.010$) in patients with bowel-associated lesions. Half of the patients were able to differentiate between abdominal pain from endometriosis and from the gastrointestinal tract. Patients using opioids experienced more severe symptoms than patients not using opioids, and patients with current or previous use of GnRH analogs had more severe abdominal pain than the other patients ($P = 0.024$). Initiation of either combined oral contraceptives or progesterone for endometriosis had no effect on gastrointestinal symptoms when the patients were followed prospectively. **CONCLUSIONS:** The majority of endometriosis patients experience more severe gastrointestinal symptoms than controls. A poor association between symptoms and lesion localization was found, indicating existing comorbidity between endometriosis and irritable bowel syndrome (IBS). Treatment with opioids or GnRH analogs is associated with aggravated gastrointestinal symptoms.

Menstrual-cycle and menstruation disorders in episodic vs chronic migraine: An exploratory study.

Spierings EL, Padamsee A.

Pain Med. 2015 Jul;16(7):1426-32. doi: 10.1111/pme.12788.

OBJECTIVE: Migraine is a chronic condition of recurring moderate-to-severe headaches that affects an estimated 6% of men and 18% of women. The highest prevalence is in those 18-49 years of age, generally when women menstruate. It is divided into episodic and chronic migraine depending on the total number of headache days per month being 14 or less or 15 or more, respectively. Migraine has been associated with menorrhagia, dysmenorrhea, and endometriosis, the latter particularly in chronic migraine. **METHODS:** We conducted a questionnaire survey of 96 women with migraine, 18-45 years old, to determine the occurrence of the menstrual-cycle disorders, oligomenorrhea, polymenorrhea, and irregular cycle, and the menstruation disorders, dysmenorrhea and menorrhagia, in episodic vs chronic migraine. **RESULTS:** The prevalence of menstrual-cycle disorders in general (41.2 vs 22.2%) and dysmenorrhea (51.0 vs 28.9%) was statistically significantly higher in the women with chronic migraine than in those with episodic migraine ($P \leq 0.05$) (not corrected for multiple comparisons). Whether the migraine was menstruation sensitive, that is, the headaches consistently occurred or worsened with menstruation, did not impact the prevalence of menstrual disorders. **CONCLUSION:** We conclude that chronic migraine is possibly more often than episodic migraine associated with menstrual-cycle disorders in general and dysmenorrhea, without impact on menstruation sensitivity of the headaches.

Case-control study of craniomandibular disorders in patients with fibromyalgia.

García-Moya EJ, Montiel-Company JM, Almerich-Silla JM.

J Clin Exp Dent. 2015 Apr 1;7(2):e293-8. doi: 10.4317/jced.51816. eCollection 2015.

BACKGROUND: Fibromyalgia is a clinical syndrome characterized by chronic widespread pain, which is non-articular and is predominantly experienced in the muscles and vertebral column, and by extensive heightened sensitivity to local pressure at many specific points. The purpose of this study was to measure differences in the level of painful symptoms and in the movements of the mandible in a group of patients who had been diagnosed as suffering from fibromyalgia, in comparison with a control group. The anxiety and subjective pain levels and their relation with mandibular mobility were also compared. **MATERIAL AND METHODS:** A case-control study was designed. The temporomandibular joints and masticatory muscles of the cases (n=20) and controls (n=18) were examined, anxiety was assessed by the STAI index and subjective pain was measured on a visual analogue scale. The data analysis was carried out with SPSS v.19.0 software. The descriptive data were expressed as means and proportions at a 95% confidence interval. The proportions were compared with the chi-square test and the means with the Mann-Whitney U test. Pearson's correlation coefficient was used to measure the association between quantitative variables. **RESULTS:** The fibromyalgia patients (the case group) presented a higher level of pain following the musculoskeletal examination and significantly greater symptoms at the examination points. Regarding joint mobility, significant differences in mandibular opening were found (cases 43.4 mm vs controls 47.2 mm, $p = 0.042$). The mean pain score of the cases was significantly higher than that of the controls (4.03 vs 1.8, $p = 0.001$) but no significant differences were found in the anxiety index (23.8 vs 23.4). **CONCLUSIONS:** Patients with fibromyalgia are affected to a greater extent by craniomandibular disorders, with lower mouth opening and higher pain levels than healthy persons. However, the anxiety levels of the two groups are similar.

Functional gastrointestinal disorders are associated with the joint hypermobility syndrome in secondary care: a case-control study.

Fikree A, Aktar R, Grahame R, Hakim AJ, Morris JK, Knowles CH, Aziz Q.

Neurogastroenterol Motil. 2015 Apr;27(4):569-79. doi: 10.1111/nmo.12535.

BACKGROUND: The overlap of unexplained gastrointestinal (GI) and somatic symptoms is well established in patients with functional gastrointestinal disorders (FGID). Joint hypermobility syndrome (JHS) is a non-inflammatory connective tissue disorder associated with GI and somatic symptoms. We aimed to determine whether there is an association between diagnosis of JHS and FGID and the impact of this association on comorbidities and quality of life (QOL). **METHODS:** Prospective case-control study in secondary care GI clinics over 2 years. JHS was assessed by the first author prior to consultation in 641 consecutive new patients. Diagnosis of FGID (cases, $n = 336$) or organic disorders (controls, $n = 305$) was established blind to JHS status. JHS prevalence was compared in cases (FGID patients) and controls (organic disorders patients). Extra-intestinal comorbidity and QOL were compared in FGID patients with and without JHS. **KEY RESULTS:** JHS prevalence was higher in FGID compared to organic GI disorders (39.0% vs 27.5%, ORadj: 1.51, CI: 1.07-2.12, $p = 0.02$), and particularly associated with functional gastroduodenal disorders (44.1%, ORadj: 2.08, CI: 1.25-3.46, $p = 0.005$), specifically postprandial distress syndrome (51%, ORadj: 1.99, CI: 1.06-3.76, $p = 0.03$). FGID patients with JHS had increased chronic pain (23.2% vs 11.9%, $p = 0.01$), fibromyalgia (10.5% vs 3.1%, $p = 0.01$), somatization scores (13 vs 10, $p < 0.001$), urinary autonomic scores (30.5 vs 20.7, $p = 0.03$), and worse pain-related QOL scores (45.0 vs 63.5, $p = 0.004$). **CONCLUSIONS &**

INFERENCES: JHS is significantly associated with FGID, and this subgroup of patients have increased comorbidity and decreased QOL. Further research is required to understand the pathophysiological basis of this association.

Chronic fatigue syndrome and fibromyalgia in Canada: prevalence and associations with six health status indicators.

Rusu C, Gee ME, Lagacé C, Parlor M.

Health Promot Chronic Dis Prev Can. 2015 Mar;35(1):3-11.

INTRODUCTION: Few studies have considered the factors independently associated with chronic fatigue syndrome (CFS) and/or fibromyalgia (FM) or considered the impact of these conditions on health status using population-based data. METHODS: We used data from the nationally representative 2010 Canadian Community Health Survey (n = 59 101) to describe self-reported health professional-diagnosed CFS and/or FM, and their associations with 6 health status indicators. RESULTS: In 2010, diagnosed CFS and FM are reported by 1.4% (95% confidence interval [CI]: 1.3%-1.6%) and 1.5% (1.4%-1.7%), respectively, of the Canadian household population aged 12 years and over, with comorbid CFS and FM affecting 0.3% (0.3%-0.4%) of that population. Prevalent CFS and/or FM were more common among women, adults aged 40 years and over, those with lowest income, and those with certain risk factors for chronic disease (i.e. obesity, physical inactivity and smoking). After controlling for differences between the groups, people with CFS and/or FM reported poorer health status than those with neither condition on 5 indicators of health status, but not on the measure of fair/poor mental health. Having both CFS and FM and having multiple comorbid conditions was associated with poorer health status. CONCLUSION: Co-occurrence of CFS and FM and having other chronic conditions were strongly related to poorer health status and accounted for much of the differences in health status. Understanding factors contributing to improved quality of life in people with CFS and/or FM, particularly in those with both conditions and other comorbidities, may be an important area for future research.

Gender differences in chronic fatigue syndrome.

Faro M, Sàez-Francás N, Castro-Marrero J, Aliste L, Fernández de Sevilla T, Alegre J.

Reumatol Clin. 2015 Jul 16. pii: S1699-258X(15)00081-9. doi: 10.1016/j.reuma.2015.05.007.

[Epub ahead of print]

BACKGROUND AND OBJECTIVES: Chronic fatigue syndrome (CFS) is a chronic condition that predominantly affects women. To date, there are few epidemiologic studies on CFS in men. The objective of the study was to assess whether there are gender-related differences in CFS, and to define a clinical phenotype in men. PATIENTS AND METHODS: A prospective, cross-sectional cohort study was conducted including CFS patients at the time of diagnosis. Sociodemographic data, clinical variables, comorbid phenomena, fatigue, pain, anxiety/depression, and health quality of life, were assessed in the CFS population. A comparative study was also conducted between genders. RESULTS: The study included 1309 CFS patients, of which 119 (9.1%) were men. The mean age and symptoms onset were lower in men than women. The subjects included 30% single men vs. 15% single women, and 32% of men had specialist work vs. 20% of women. The most common triggering factor was an infection. Widespread pain, muscle spasms, dizziness, sexual dysfunction, Raynaud's phenomenon, morning stiffness, migratory arthralgias, drug and metals allergy, and facial oedema were less frequent in men. Fibromyalgia was present in 29% of men vs. 58% in women. The scores on physical function, physical role, and overall physical health of the SF-36 were higher in men. The sensory and affective dimensions of pain were lower in men. CONCLUSIONS: The clinical phenotype of the men with CFS was young,

single, skilled worker, and infection as the main triggering agent. Men had less pain and less muscle and immune symptoms, fewer comorbid phenomena, and a better quality of life.

Specific and number of comorbidities are associated with increased levels of temporomandibular pain intensity and duration.

Dahan H, Shir Y, Velly A, Allison P.

J Headache Pain. 2015 Dec;16:528. doi: 10.1186/s10194-015-0528-2.

BACKGROUND: Temporomandibular pain disorder (TMD) is a common pain condition in the face. People with TMD report multiple pain comorbidities. The presence of fibromyalgia and migraine in people with TMD is associated with an increase in TMD pain intensity and duration. However, data on the relationship between increasing number of pain comorbidities and TMD pain are rare. The aims of this study were: firstly to evaluate the extent to which increasing number of comorbidities is associated with increasing TMD pain intensity and duration; and secondly to evaluate the extent to which the presence of specific comorbidities is associated with increasing TMD pain intensity and duration. **METHODS:** The sample included 180 people seeking TMD treatment at Boston and Montreal clinics. TMD was diagnosed using the Research Diagnostic Criteria for TMD. A Numerical Pain Rating Scale assessed TMD pain intensity and participants provided their TMD pain duration in a study questionnaire. The comorbidities of migraine, chronic fatigue syndrome, irritable bowel syndrome, interstitial cystitis and restless leg syndrome were diagnosed by 5 validated diagnostic questionnaires. The associations were analyzed by linear regression, controlling for confounders. **RESULTS:** There was a positive association between the number of comorbidities present and TMD pain intensity ($p < 0.01$) and between the number of comorbidities present and TMD pain duration ($p < 0.01$). Also, the presence of migraine was positively associated with TMD pain intensity ($p < 0.01$) and the presence of chronic fatigue syndrome was positively associated with TMD pain intensity ($p < 0.05$) and with TMD pain duration ($p < 0.01$). When TMD patients were separated into groups, these associations did not change for the myofascial pain group, whereas in the non-myofascial pain group, the relationship between number of comorbidities and TMD pain duration was the only one still present. **CONCLUSION:** This study shows that the number of comorbidities is positively associated with TMD pain duration and intensity. The presence of specific conditions, such as migraine and chronic fatigue syndrome, is associated with an increase in TMD intensity and duration.

Frequency of migraine headaches in patients with fibromyalgia.

Vij B, Whipple MO, Tepper SJ, Mohabbat AB, Stillman M, Vincent A.

Headache. 2015 Jun;55(6):860-5. doi: 10.1111/head.12590.

OBJECTIVE: The purpose of this study was to evaluate the frequency of migraine headache in a large cohort of patients with fibromyalgia using a brief migraine headache-screening tool. **BACKGROUND:** Several studies report a high prevalence of fibromyalgia among patients with migraine headaches, but there is a dearth of research evaluating the frequency of migraine headaches in patients with fibromyalgia, despite clinical observations suggesting that migraine headaches are common in patients with fibromyalgia. **DESIGN AND METHODS:** This was a cross-sectional survey study. Patients ($N=3717$) with a previous diagnosis of fibromyalgia who were members of the Mayo Clinic Fibromyalgia Registry were contacted by electronic survey and asked to complete a brief demographic and medical history questionnaire and the validated ID-Migraine screener. **RESULTS:** A total of 1730 patients (46.5%) completed the electronic survey. The majority of participants were white (97.2%), female (92.5%), with a mean age of 56.2 (± 13.1) years. Of the respondents, 966 (55.8%) met criteria for migraine headaches. Hypertension (309

[32.3%] vs. 294 [40.1%], $P=.004$), asthma (312 [32.5%] vs. 189 [25.9%], $P=.011$), irritable bowel syndrome (520 [54.6%] vs. 348 [47.6], $P=.017$), chronic fatigue syndrome (486 [50.7%] vs. 271 [37.1], $P<.0001$), depression (634 [66.5%] vs. 413 [56.7%], $P=.0002$), anxiety (415 [43.5%] vs. 252 [34.7%], $P=.0011$), and post-traumatic stress disorder (172 [18.0%] vs. 96 [13.2%], $P=.006$) were all significantly more common in those who met criteria for migraine headaches than those who did not. **CONCLUSION:** The results of this study suggest that migraine headaches are common in patients with fibromyalgia. Clinicians who care for either population must be aware that these conditions commonly overlap and can significantly increase a patient's cumulative disease burden.

The risk of irritable bowel syndrome in patients with endometriosis during a 5-year follow-up: a nationwide population-based cohort study.

Wu CY, Chang WP, Chang YH, Li CP, Chuang CM.

Int J Colorectal Dis. 2015 Jul;30(7):907-12. doi: 10.1007/s00384-015-2218-6.

PURPOSE: Studies have suggested that endometriosis may coexist with irritable bowel syndrome (IBS). Using a population-based cohort study, we followed subjects for a 5-year period to identify the risk of IBS after a diagnosis of endometriosis. **METHODS:** This cohort study used the Taiwan National Health Insurance Database as a source of subjects. A total of 6076 patients with endometriosis from 2000 to 2005 were identified. Their data were compared with those of 30,380 age-matched controls without endometriosis who were randomly selected from the same database. All subjects were tracked for 5 years from the date of cohort entry to identify the risk of IBS. The Cox model was used to evaluate the 5-year event occurrence of IBS. **RESULTS:** Nine hundred twenty-six patients were diagnosed with IBS, including 256 in the case cohort (4.2%) and 670 in the control cohort (2.2%). The Kaplan-Meier survival curves demonstrated significantly lower event-free rates in the case cohort than in the control cohort ($P=0.001$). After adjusting for urbanization level, monthly income, residential region and comorbidities, the hazard ratio (HR) within 5 years revealed a 1.79-fold (95% confidence interval [CI] 1.55-2.07) greater risk among the cases than the controls. The HR was higher within the first year of follow-up (HR 1.90, 95% CI 1.42-2.55) and in those women aged 25-34 years (HR 2.17, 95% CI 1.61-2.92). **CONCLUSIONS:** The risk of IBS among endometriosis patients persisted over 5 years of follow-up. The association detected in this study might have proceeded through shared risk and pathogenic factors.

Comorbid conditions do not differ in children and young adults with functional disorders with or without postural tachycardia syndrome.

Chelimsky G, Kovacic K, Nugent M, Mueller A, Simpson P, Chelimsky TC.

J Pediatr. 2015 Jul;167(1):120-4. doi: 10.1016/j.jpeds.2015.03.039.

OBJECTIVE: To determine if several multisystem comorbid conditions occur more frequently in subjects with tilt-table defined postural tachycardia syndrome (POTS) compared with those without. **STUDY DESIGN:** Retrospective chart review of 67 subjects aged 6-24 years, referred to a tertiary care neurogastroenterology and autonomic disorders clinic for a constellation of functional gastrointestinal, chronic pain, and autonomic complaints. All patients underwent formal autonomic testing, Beighton scores assessment for joint hypermobility (0-9), and fibromyalgia tender points (0-18) (43 subjects). **RESULTS:** Twenty-five subjects (37%) met tilt table criteria for POTS. The median age of 16 years (range, 12-24 years) in the POTS group differed from 15 years (range, 6-21 years) in the no-POTS group ($P = .03$). Comorbidities including chronic fatigue, sleep disturbances, dizziness, syncope, migraines, functional gastrointestinal disorders, chronic nausea, fibromyalgia, and joint hypermobility did not differ between groups. All subjects

with fibromyalgia by tender point-examination had a Beighton score ≥ 4 ($P = .002$).
CONCLUSIONS: Comorbid conditions are equally prevalent in children and young adults with and without tilt-table defined POTS, suggesting that POTS itself is not a cause of the other comorbidities. Instead, POTS likely reflects another comorbid condition in children with functional disorders. Dizziness and syncope, classically associated with POTS, are not predictive of a diagnosis of POTS by tilt table, a test that is still required for formal diagnosis. These results suggest a paradigm shift in the concept of POTS as the physiological basis of many functional symptoms.

Painful temporomandibular disorders are common in patients with postural orthostatic tachycardia syndrome and impact significantly upon quality of life.

Durham J, McDonald C, Hutchinson L, Newton JL.

J Oral Facial Pain Headache. 2015 Spring;29(2):152-7. doi: 10.11607/ofph.1396

AIMS: To explore the point prevalence of painful temporomandibular disorders (TMD) in a well-characterized clinical cohort of postural orthostatic tachycardia syndrome (PoTS) sufferers and to understand the functional and physiologic impact of this comorbidity on the patient. METHODS: Patients with PoTS were retrospectively recruited from a previous study conducted in a UK hospital setting. Data had previously been collected on several parameters, including sociodemographic, physiologic, and functional. The participants were mailed a highly sensitive (99%) and specific (97%) self-report screening instrument for painful TMD. Simple descriptive statistics with Fisher Exact and Kruskal-Wallis tests were used to examine the data and draw inferences from it. RESULTS: A total of 36 individuals responded (69% response rate). Just under half (47%) of the sample screened positive for painful TMD. There was no significant difference between the screening result for TMD or previously reported headaches or joint pain ($P < .05$). Chronic fatigue syndrome (CFS) was diagnosed by the Fukuda Criteria in 44% of the total sample and in 56% of those with painful TMD. There were no significant differences in physiologic parameters in CFS and TMD. TMD caused a significant decrease in quality of life as measured by the Patient-Reported Outcomes Measurement Information System, Health Assessment Questionnaire ($P < .05$). CONCLUSION: TMD are common in patients with PoTS. They have a significant, additional impact on patients' quality of life and should therefore be screened for at an early stage in PoTS.

Mood and anxiety disorders in chronic fatigue syndrome, fibromyalgia, and irritable bowel syndrome: Results from the LifeLines cohort study.

Janssens KA, Zijlema WL, Joustra ML, Rosmalen JG.

Psychosom Med. 2015 May;77(4):449-57. doi: 10.1097/PSY.000000000000161.

OBJECTIVE: Functional somatic syndromes (FSSs) have often been linked to psychopathology. The aim of the current study was to compare prevalence rates of psychiatric disorders among individuals with chronic fatigue syndrome (CFS), fibromyalgia (FM), and irritable bowel syndrome (IBS). METHODS: This study was conducted in 94,516 participants (mean [standard deviation] age = 44.6 [12.5] years, 58.7% women) of the general-population cohort LifeLines. FSSs were assessed by self-reports. Mood disorders (i.e., major depressive disorder and dysthymia) and anxiety disorders (i.e., generalized anxiety disorder, social phobia, panic disorder with/without agoraphobia, and agoraphobia) were assessed by means of the Mini International Neuropsychiatric Interview. Risks on psychiatric disorders were compared for individuals with CFS, FM, and IBS by using logistic regression analyses adjusted for age and sex. RESULTS: Prevalence rates of CFS, FM, and IBS were 1.3%, 3.0%, and 9.7%, respectively. Individuals with

CFS, FM, and IBS had significantly more mood (odds ratios [ORs] = 1.72-5.42) and anxiety disorders (ORs = 1.52-3.96) than did individuals without FSSs, but prevalence rates were low (1.6%-28.6%). Individuals with CFS more often had mood (ORs = 2.00-4.08) and anxiety disorders (ORs = 1.63-2.32) than did individuals with FM and IBS. Major depressive disorder was more common in FM than in IBS (OR = 1.58, 95% confidence interval = 1.24-2.01), whereas these groups did not differ on dysthymia or anxiety disorders. CONCLUSIONS: Mood and anxiety disorders are more prevalent in individuals with FSSs, and particularly CFS, than in individuals without FSSs. However, most individuals with FSSs do not have mood or anxiety disorders.

Chronic multisymptom illness among female Veterans deployed to Iraq and Afghanistan.

Mohanty AF, Muthukutty A, Carter ME, Palmer MN, Judd J, Helmer D, McAndrew LM, Garvin JH, Samore MH, Gundlapalli AV.

Med Care. 2015 Apr;53(4 Suppl 1):S143-8. doi: 10.1097/MLR.0000000000000314.

BACKGROUND: Chronic multisymptom illness (CMI) may be more prevalent among female Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND) deployed Veterans due to deployment-related experiences. OBJECTIVES: To investigate CMI-related diagnoses among female OEF/OIF/OND Veterans. RESEARCH DESIGN: We estimated the prevalence of the International Classification of Disease-9th edition-Clinical Modification coded CMI-related diagnoses of chronic fatigue syndrome, fibromyalgia (FM), and irritable bowel syndrome (IBS) among female OEF/OIF/OND Veterans with Veterans Health Administration (VHA) visits, FY2002-2012 (n=78,435). We described the characteristics of female Veterans with and without CMI-related diagnoses and VHA settings of first CMI-related diagnoses. RESULTS: The prevalence of CMI-related diagnoses among female OEF/OIF/OND Veterans was 6397 (8.2%), over twice as high as the prevalence 95,424 (3.9%) among the totality of female Veterans currently accessing VHA (P<0.01). There were statistically significant differences in age, education, marital status, military component, service branch, and proportions of those with depression and/or post-traumatic stress disorder diagnoses across females with and without CMI-related diagnoses. Diagnoses were mainly from primary care, women's health, and physical medicine and rehabilitation clinics. CONCLUSIONS: CMI-related diagnoses were more prevalent among female OEF/OIF/OND Veterans compared with all female Veterans who currently access VHA. Future studies of the role of mental health diagnoses as confounders or mediators of the association of OEF/OIF/OND deployment and CMI are warranted. These and other factors associated with CMI may provide a basis for enhanced screening to facilitate recognition of these conditions. Further work should evaluate models of care and healthcare utilization related to CMI in female Veterans.

Early menopause and other gynecologic risk indicators for chronic fatigue syndrome in women.

Boneva RS, Lin JM, Unger ER.

Menopause. 2015 Aug;22(8):826-34. doi: 10.1097/GME.0000000000000411.

OBJECTIVE: This study aims to examine whether gynecologic conditions are associated with chronic fatigue syndrome (CFS). METHODS: This study includes a subset of 157 women from a population-based case-control study in Georgia, United States, conducted in 2004-2009. Gynecologic history was collected using a self-administered questionnaire. Crude odds ratios (ORs) with 95% CIs and ORs adjusted for body mass index and other covariates, where relevant, were estimated for gynecologic conditions between 84 CFS cases and 73 healthy controls.

RESULTS: Cases and controls were of similar age. Women with CFS reported significantly more gynecologic conditions and surgical operations than controls: menopause status (61.9% vs 37.0%; OR, 2.37; 95% CI, 1.21-4.66), earlier mean age at menopause onset (37.6 vs 48.6 y; adjusted OR, 1.22; 95% CI, 1.09-1.36), excessive menstrual bleeding (73.8% vs 42.5%; adjusted OR, 3.33; 95% CI, 1.66-6.70), bleeding between periods (48.8% vs 23.3%; adjusted OR, 3.31; 95% CI, 1.60-6.86), endometriosis (29.8% vs 12.3%; adjusted OR, 3.67; 95% CI, 1.53-8.84), use of noncontraceptive hormonal preparations (57.1% vs 26.0%; adjusted OR, 2.95; 95% CI, 1.36-6.38), nonmenstrual pelvic pain (26.2% vs 2.7%; adjusted OR, 11.98; 95% CI, 2.57-55.81), and gynecologic surgical operation (65.5% vs 31.5%; adjusted OR, 3.33; 95% CI, 1.66-6.67), especially hysterectomy (54.8% vs 19.2%; adjusted OR, 3.23; 95% CI, 1.46-7.17). Hysterectomy and oophorectomy occurred at a significantly younger mean age in the CFS group than in controls and occurred before CFS onset in 71% of women with records of date of surgical operation and date of CFS onset. **CONCLUSIONS:** Menstrual abnormalities, endometriosis, pelvic pain, hysterectomy, and early/surgical menopause are all associated with CFS. Clinicians should be aware of the association between common gynecologic problems and CFS in women. Further work is warranted to determine whether these conditions contribute to the development and/or perpetuation of CFS in some women.

Disease history and risk of comorbidity in women's life course: a comprehensive analysis of the Japan Nurses' Health Study baseline survey.

Nagai K, Hayashi K, Yasui T, Katanoda K, Iso H, Kiyohara Y, Wakatsuki A, Kubota T, Mizunuma H.

BMJ Open. 2015 Mar 11;5(3):e006360. doi: 10.1136/bmjopen-2014-006360.

OBJECTIVE: To classify diseases based on age at peak incidence to identify risk factors for later disease in women's life course. **DESIGN:** A cross-sectional baseline survey of participants in the Japan Nurses' Health Study. **SETTING:** A nationwide prospective cohort study on the health of Japanese nurses. The baseline survey was conducted between 2001 and 2007 (n=49,927). **MAIN OUTCOME MEASURES:** Age at peak incidence for 20 diseases from a survey of Japanese women was estimated using the Kaplan-Meier method with the Kernel smoothing technique. The incidence rate and peak incidence for diseases whose peak incidence occurred before the age of 45 years or before the perimenopausal period were selected as early-onset diseases. The OR and 95% CI were estimated to examine the risk of comorbidity between early-onset and other diseases. **RESULTS:** Four early-onset diseases (endometriosis, anaemia, migraine headache and uterine myoma) were significantly correlated with one another. Late-onset diseases significantly associated (OR>2) with early-onset diseases included comorbid endometriosis with ovarian cancer (3.65 (2.16 to 6.19)), endometrial cancer (2.40 (1.14 to 5.04)) and cerebral infarction (2.10 (1.15 to 3.85)); comorbid anaemia with gastric cancer (3.69 (2.68 to 5.08)); comorbid migraine with transient ischaemic attack (3.06 (2.29 to 4.09)), osteoporosis (2.11 (1.71 to 2.62)), cerebral infarction (2.04 (1.26 to 3.30)) and angina pectoris (2.00 (1.49 to 2.67)); and comorbid uterine myoma with colorectal cancer (2.31 (1.48 to 3.61)). **CONCLUSIONS:** While there were significant associations between four early-onset diseases, women with a history of one or more of the early-onset diseases had a higher risk of other diseases later in their life course. Understanding the history of early-onset diseases in women may help reduce the subsequent risk of chronic diseases in later life.

Risk for irritable bowel syndrome in fibromyalgia patients: a national database study.

Yang TY, Chen CS, Lin CL, Lin WM, Kuo CN, Kao CH.

Medicine (Baltimore). 2015 Mar;94(10):e616. doi: 10.1097/MD.0000000000000616.

Various studies have shown that irritable bowel syndrome (IBS) is highly associated with other pathologies, including fibromyalgia (FM). The objective of this study was to analyze the differences among risk factors associated with IBS following FM in a nationwide prospective cohort study. We propose that a relationship exists between FM and IBS. This article presents evidence obtained from a cohort study in which we used data from the Taiwan National Health Insurance Research Database to clarify the relationship between FM and IBS. The follow-up period ran from the start of FM diagnosis to the date of the IBS event, censoring, or December 31, 2011. We analyzed the risk of IBS using Cox proportional hazard regression models, including sex, age, and comorbidities. During the follow-up period, from 2000 to 2011, the overall incidence of IBS was higher in FM patients than in non-FM patients (7.47 vs 4.42 per 1000 person-years), with a crude hazard ratio=1.69 (95% confidence interval [CI] 1.45-1.63). After adjustment for age, sex, and comorbidities, FM was associated with a 1.54-fold increased risk for IBS. Mutually risk factors may influence the relationship between FM and IBS. We recommend that physiologists conduct annual examinations of FM patients to reduce the incidence of IBS progression.

Chronic fatigue syndrome and fibromyalgia in diagnosed sleep disorders: a further test of the 'unitary' hypothesis.

Pejovic S, Natelson BH, Basta M, Fernandez-Mendoza J, Mahr F, Vgontzas AN.
BMC Neurol. 2015 Apr 12;15:53. doi: 10.1186/s12883-015-0308-2.

BACKGROUND: Since chronic fatigue syndrome (CFS) and fibromyalgia (FM) often co-exist, some believe they reflect the same process, somatization. Against that hypothesis are data suggesting FM but not CFS was common in patients with sleep-disordered breathing (SDB). The presence of discrete case definitions for CFS and FM allowed us to explore rates of CFS alone, CFS with FM, and FM alone in SDB patients compared to those with sleep complaints that fulfilled criteria for insomnia. **METHODS:** Participants were 175 sequential patients with sleep-related symptoms (122 had SDB and 21 had insomnia) and 39 healthy controls. Diagnoses were made by questionnaires, tender point count, and rule out labs; sleepiness was assessed with Epworth Sleepiness Scale and mood with Beck Depression Inventory. **RESULTS:** Rates of CFS, FM or CFS+FM were high: 13% in SDB and 48% in insomnia. CFS occurred frequently in SDB and insomnia, but FM occurred frequently only in insomnia. SDB patients with CFS and/or FM had higher daytime sleepiness than those without these disorders. **CONCLUSION:** CFS patients should complete Epworth scales, and sleep evaluation should be considered for those with scores \geq 16 before receiving the diagnosis of CFS; the coexistence of depressed mood in these patients suggests some may be helped by treatment of their depression. That FM was underrepresented in SDB suggests FM and CFS may have different underlying pathophysiological causes.

Prevalence of smoking in adults with chronic pain.

Orhurhu VJ, Pittelkow TP, Hooten WM.
Tob Induc Dis. 2015 Jul 17;13(1):17. doi: 10.1186/s12971-015-0042-y. eCollection 2015.

INTRODUCTION: Cigarette smoking is common among adults with chronic pain. The primary objective of this study was to determine the period prevalence of smoking in patients with chronic pain. A secondary objective was to determine the prevalence of smoking among patients with commonly occurring pain diagnoses including fibromyalgia, low back pain, and headache. **METHODS:** This population study included 5350 patients (1256 smokers, 4094 nonsmokers)

admitted to the Mayo Comprehensive Pain Rehabilitation Center from January 1998 through December 2012. Smoking status was determined using a self-report questionnaire. **RESULTS:** During the 15 year study period, the overall prevalence of smoking was 23.5 % (95 % CI 22.4 - 24.6). The prevalence of smoking in 2000, 2005, and 2010 was 24.2, 25.7, and 28.3 % respectively. The overall prevalence of smoking in patients with fibromyalgia, low back pain, and headache was 25.2 % (95 % CI 22.8 - 28.3), 22.8 % (95 % CI 21.3 - 25.9), and 21.2 % (95 % CI 17.9 - 24.7), respectively. In a multiple variable logistic model adjusted for age and sex, opioid use was significantly associated with status as a current smoker. **CONCLUSION:** The prevalence of smoking in patients with chronic pain has not declined when compared to the general population. The higher prevalence of smoking was consistently observed in commonly occurring pain diagnoses including fibromyalgia, back pain, and headache. Further research is needed to identify the potential factors that contribute to the high prevalence of smoking in this patient population.

FUNCTIONAL STATUS / QUALITY OF LIFE STUDIES

Neurocognitive complaints and functional status among patients with chronic fatigue syndrome and fibromyalgia.

Schmaling KB, Betterton KL.

Qual Life Res. 2015 Oct 15. [Epub ahead of print]

Purpose: The purpose of this study was to conduct a longitudinal examination of cognitive complaints and functional status in patients with chronic fatigue syndrome (CFS) alone and those who also had fibromyalgia (CFS/FM). **Methods:** A total of 93 patients from a tertiary care fatigue clinical were evaluated on four occasions, each 6 months apart. Each evaluation included a tender point assessment, and self-reported functional status and cognitive complaints. **Results:** Patients with CFS/FM reported significantly worse physical functioning, more bodily pain, and more cognitive difficulties (visuo-perceptual ability and verbal memory) than patients with CFS alone. Over time, bodily pain decreased only for participants with CFS alone. Verbal memory problems were associated with more bodily pain for both patient groups, whereas visuo-perceptual problems were associated with worse functional status for patients with CFS alone. **Conclusions:** This study adds to the literature on functional status, longitudinal course, and cognitive difficulties among patients with CFS and those with CFS and FM. The results suggest that patients with CFS/FM are more disabled, have more cognitive complaints, and improve more slowly over time than patients with CFS alone. Specific cognitive difficulties are related to worse functional status, which supports the addition of cognitive difficulties to the FM case criteria.

Suicide risk in patients with migraine and comorbid fibromyalgia.

Liu HY, Fuh JL, Lin YY, Chen WT, Wang SJ.

Neurology. 2015 Aug 21. pii: 10.1212/WNL.0000000000001943. [Epub ahead of print]

OBJECTIVES: To identify the frequency, clinical effects, and suicide risk in comorbid fibromyalgia (FM) among patients with migraine. **METHODS:** We surveyed patients with migraine who attended a headache clinic. All patients completed questionnaires containing demographics, headache profiles based on the International Classification of Headache Disorders, 2nd edition, FM questionnaires based on the modified 2010 American College of Rheumatology preliminary diagnostic criteria, Migraine Disability Assessment, Hospital Anxiety and Depression Scale, and Pittsburgh Sleep Quality Index. Suicide risk was evaluated by self-report of lifetime suicidal ideation and attempts. **RESULTS:** Of the 1,318 recruited patients with migraine (aged 42.6 ± 12.7 years; female/male = 4.5), 10.1% (aged 44.3 ± 12.6 years; female/male = 7.9) had comorbidity of

FM. Patients with migraine and comorbid FM had higher headache frequency and headache-related disability, poor sleep quality, and were more depressed/anxious than those with migraine only ($p < 0.001$). Suicidal ideation and attempts were reported in 27.3% and 6.9% of patients with migraine, respectively, and were higher in patients with comorbid FM than in those without (ideation: 58.3% vs 24%; attempt: 17.6% vs 5.7%; $p < 0.001$). In addition, comorbidity of FM was associated with a higher suicide risk in 3 different migraine subgroups, i.e., migraine without aura, migraine with aura, and chronic migraine. After controlling for covariates, comorbidity of FM remained as a predictor of suicidal ideation and attempts (odds ratio 2.61 and 1.99, respectively, $p < 0.05$) in patients with migraine. **CONCLUSIONS:** Comorbidity with FM is associated with a high suicide risk in patients with migraine.

Disability in children and adolescents with irritable bowel syndrome and/or fibromyalgia.

Otu-Nyarko CG, Gedalia A, Karpinski AC, Kolomensky A, Hyman PE.
J Pediatr Gastroenterol Nutr. 2015 Jun 23. [Epub ahead of print]

To compare disability and emotional health in individuals with irritable bowel syndrome (IBS), fibromyalgia or both, patients completed the Questionnaire for Pediatric Gastrointestinal Symptoms-Rome III, Childhood Functional Disability Inventory (FDI), and Behavior Assessment System for Children Second Edition (BASC-2). Patients' (age range 8-18 years, 19 IBS, 12 fibromyalgia, and 12 both) FDI scores showed greater disability than scores from historically healthy patients. Fibromyalgia (FDI 22.5+12.7, $p=0.018$) and patients with both (FDI 26.2+13.8, $p=0.001$) averaged greater disability than those with IBS (FDI 10.6 7.9). Disability correlated with anxiety and depression symptoms. Disability and psychological symptoms are important when evaluating individuals with fibromyalgia and IBS.

Functional limitations in functional somatic syndromes and well-defined medical diseases. Results from the general population cohort LifeLines.

Joustra ML, Janssens KA, Bültmann U, Rosmalen JG.
J Psychosom Res. 2015 Aug;79(2):94-9. doi: 10.1016/j.jpsychores.2015.05.004.

OBJECTIVE: Functional somatic syndromes (FSS), defined as physical syndromes without known underlying organic pathology, are sometimes regarded as less serious conditions than well-defined medical diseases (MD). The aims of this study were to evaluate functional limitations in FSS, and to compare the results to MD patients with the same core symptoms. **METHODS:** This study was performed in 89,585 participants (age: 44.4 ± 12.4 years, 58.5% female) of the general-population cohort LifeLines. Quality of Life (QoL) and work participation were examined as indicators of functional limitations. QoL was assessed with two summary scales of the RAND-36: the physical component summary (PCS) and the mental component summary (MCS). Work participation was assessed with a self-reported questionnaire. QoL and work participation were compared between FSS and MD patients, using Chi-squared tests and ANCOVA-analyses, adjusted for age, sex, educational level, and mental disorders. **RESULTS:** Of the participants, 11.0% ($n=9861$) reported a FSS, and 2.7% ($n=2395$) reported a MD. Total QoL, PCS and MCS were significantly lower in all separate FSS and MD compared to controls ($P \leq .001$). Clinically relevant differences in QoL were found between chronic fatigue syndrome and multiple sclerosis patients, and between fibromyalgia syndrome and rheumatoid arthritis patients. Compared to controls, FSS and MD patients reported a comparably reduced working percentage, increased sick absence, early retirement due to health-related reasons, and disability percentage ($P \leq .001$). **CONCLUSION:** Functional limitations in FSS patients are common, and as severe as those in patients with MD when looking at QoL and work participation, emphasizing that FSS are serious

health conditions.

CLINICAL STUDIES

Diagnosing and treating chronic musculoskeletal pain based on the underlying mechanism(s).

Clauw DJ.

Best Pract Res Clin Rheumatol. 2015 Feb;29(1):6-19. doi: 10.1016/j.berh.2015.04.024.

Until recently, most clinicians considered chronic pain to be typically due to ongoing peripheral nociceptive input (i.e., damage or inflammation) in the region of the body where the individual is experiencing pain. Clinicians are generally aware of a few types of pain (e.g., headache and phantom limb pain) where chronic pain is not due to such causes, but most do not realize there is not a single chronic pain state where any radiographic, surgical, or pathological description of peripheral nociceptive damage has been reproducibly shown to be related to the presence or severity of pain. The primary reason for this appears to be that both the peripheral and central nervous systems play a critical role in determining which nociceptive input being detected by sensory nerves in the peripheral tissues will lead to the perception of pain in humans. This manuscript reviews some of the latest findings regarding the neural processing of pain, with a special focus on how clinicians can use information gleaned from the history and physical examination to assess which mechanisms are most likely to be responsible for pain in a given individual, and tailors therapy appropriately. A critical construct is that, within any specific diagnostic category (e.g., fibromyalgia (FM), osteoarthritis (OA), and chronic low back pain (CLBP) are specifically reviewed), individual patients may have markedly different peripheral/nociceptive and neural contributions to their pain. Thus, just as low back pain has long been acknowledged to have multiple potential mechanisms, so also is this true of all chronic pain states, wherein some individuals will have pain primarily due to peripheral nociceptive input, whereas in others peripheral (e.g., peripheral sensitization) or central nervous system factors ("central sensitization" or "centralization" of pain via augmented pain processing in spinal and brain) maybe playing an equally or even more prominent role in their pain and other symptoms.

Migraine and central sensitization: clinical features, main comorbidities and therapeutic perspectives.

de Tommaso M, Sciricchio V

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BACKGROUND Migraine is a disorder of neuro-vascular origin, being amongst the 20 most disabling disease. Migraine attacks are characterized by severe throbbing headache, associated to nausea, vomiting, photophobia, and phonophobia. **PATHOPHYSIOLOGY AND ROLE OF CENTRAL SENSITIZATION** Abnormal neuronal excitability may subtend altered processing of sensory stimuli, leading to cortical spreading depression and trigeminal activation. A dysfunction of pain modulation enhances central sensitization phenomena, contributing to acute allodynia and headache persistence. The peculiarity of migraine pain facilitates the use of analgesics, and causes an adjunctive invalidating tendency toward drug over-use. **COMORBIDITY** Chronic migraine patients are frequently affected by diffuse pain, framed in fibromyalgia diagnosis. This comorbidity seems to be supported by common pathophysiological mechanisms. It may aggravate migraine invalidity being worth of consideration for therapeutic management. **MIGRAINE MANAGEMENT** Acute and preventive treatments need to be tailored to single cases. Main comorbidity and factors facilitating central sensitization should be taken into account. The management of migraine patients should include a link between headache centers and general

practitioner, in order to provide for a better patient information and treatment just at the onset of the disease. **CONCLUSIONS** Despite its high epidemiologic impact, migraine is frequently underestimated and destined to evolve into chronic form and drugs abuse. A more focused attention to factors facilitating central sensitization and invalidating comorbidities, should reduce the global burden of the disease.

The Evidence-Based Vulvodynia Assessment (EVA) Project. A national registry for the study of vulvodynia.

Lamvu G, Nguyen RH, Burrows LJ, Rapkin A, Witzeman K, Marvel RP, Hutchins D, Witkin SS, Veasley C, Fillingim R, Zolnoun D.
J Reprod Med. 2015 May-Jun;60(5-6):223-35.

OBJECTIVE: To create a national registry for the study of vulvodynia in order to enhance classification of vulvodynia based on multiple phenotypic domains such as pain characteristics, clinical examination, sexual function, psychological functioning, and distress. **STUDY DESIGN:** Methodology for this prospective cohort registry was institutional review board approved and implemented at 8 enrollment sites starting in 2009. Women underwent gynecologic evaluation and pressure sensory testing for assessment of pain sensitivity in the vaginal mucosa and vaginal muscles. Psychometric questionnaires were used to assess self-described pain, distress, sexual function, and quality of life. **RESULTS:** More than 300 women were enrolled and 176 charts were analyzed. This cohort had a median age of 29 years and median pain duration of 25.5 months. A total of 84% of participants were previously or currently sexually active in spite of pain. The most common pain comorbidities reported by the women were migraines (34%), chronic pelvic pain (22%), and irritable bowel syndrome (20%). Anxiety affected 41% of the cohort. More than 90% presented with localized vestibular pain, and 90% had muscular examination abnormalities. **CONCLUSION:** A national registry for the study of vulvodynia was established with successful enrollment of participants at 8 sites. In addition to the cotton swab evaluation for vulvar allodynia, women with vulvar chronic pain should also be routinely screened for musculoskeletal dysfunction, emotional distress with specific emphasis on anxiety, and comorbid pain conditions.

The effect of relaxation therapy on autonomic functioning, symptoms and daily functioning, in patients with chronic fatigue syndrome or fibromyalgia: a systematic review.

Meeus M, Nijs J, Vanderheiden T, Baert I, Descheemaeker F, Struyf F.
Clin Rehabil. 2015 Mar;29(3):221-33. doi: 10.1177/0269215514542635.

OBJECTIVE: To establish the effects of relaxation therapy on autonomic function, pain, fatigue and daily functioning in patients with chronic fatigue syndrome or fibromyalgia. **METHOD:** A systematic literature study was performed. Using specific keywords related to fibromyalgia or chronic fatigue syndrome and relaxation therapy, the electronic databases PubMed and Web of Science were searched. Included articles were assessed for their risk of bias and relevant information regarding relaxation was extracted. The review was conducted and reported according to the PRISMA-statement. **RESULTS:** Thirteen randomized clinical trials of sufficient quality were included, resulting in a total of 650 fibromyalgia patients (11 studies) and 88 chronic fatigue syndrome patients (3 studies). None of the studies reported effects on autonomic function. Six studies reported the effect of guided imagery on pain and daily functioning in fibromyalgia. The acute effect of a single session of guided imagery was studied in two studies and seems beneficial for pain relief. For other relaxation techniques (eg. muscle relaxation, autogenic training) no conclusive evidence was found for the effect on pain and functioning in

fibromyalgia patients comparison to multimodal treatment programs. For fatigue a multimodal approach seemed better than relaxation, as shown in the sole three studies on chronic fatigue syndrome patients. **CONCLUSION:** There is moderate evidence for the acute effect of guided imagery on pain, although the content of the visualization is a matter of debate. Other relaxation formats and the effects on functionality and autonomic function require further study.

Effect of local estrogen therapy on urinary and sexual symptoms in premenopausal women with interstitial cystitis/bladder pain syndrome.

Gardella B, Iacobone AD, Porru D, Musacchi V, Dominoni M, Tinelli C, Spinillo A, Nappi RE. *Gynecol Endocrinol.* 2015 Aug 10:1-5. [Epub ahead of print]

The association between vulvodynia and interstitial cystitis/bladder pain syndrome (IC/BPS), a chronic, debilitating disease of unknown etiology, may involve sex hormone-dependent mechanisms regulating vulvo-vaginal health. We aimed to prospectively investigate the effects of 12 weeks of local estrogen therapy (LET) on urinary/bladder and sexual symptoms in premenopausal women with IC/BPS. Thirty-four women (mean age: 36.1±8.4) diagnosed with IC/BPS were treated vulvo-vaginally three-times/week with estriol 0.5mg cream and tested by validated questionnaires (ICSI/ICPI, pain urgency frequency [PUF], female sexual function index [FSFI]) and by cotton swab testing, vaginal health index (VHI) and maturation index (MI) before and after treatment. Vulvodynia was present in 94.1% of IC/BPS women. A significant positive effect of LET was evident on urinary and sexual function ($p<0.001$, for both) following 12 weeks, as well as an improvement of the VHI ($p<0.001$) and the MI ($p<0.04$). The results of this open study indicate that 12 weeks of local estriol cream at vaginal and vestibular level may ameliorate urinary/bladder pain symptoms, as well as may improve domains of sexual function. The association between vulvar pain and bladder pain could, therefore, be related to a vaginal environment carrying signs of hypoestrogenism, but further studies are needed to clarify this issue.

Deconstructing chronic low back pain in the older adult-Step by step evidence and expert-based recommendations for evaluation and treatment part III: Fibromyalgia syndrome.

Fatemi G, Fang MA, Breuer P, Cherniak PE, Gentili A, Hanlon JT, Karp JF, Morone NE, Rodriguez E, Rossi MI, Schmader K, Weiner DK. *Pain Med.* 2015 Sep;16(9):1709-19. doi: 10.1111/pme.12863.

OBJECTIVE: To present the third in a series of articles designed to deconstruct chronic low back pain (CLBP) in older adults. The series presents CLBP as a syndrome, a final common pathway for the expression of multiple contributors rather than a disease localized exclusively to the lumbosacral spine. Each article addresses one of 12 important contributors to pain and disability in older adults with CLBP. This article focuses on fibromyalgia syndrome (FMS). **METHODS:** A modified Delphi approach was used to create the evaluation and treatment algorithm, the table discussing the rationale behind each of the algorithm components, and the stepped-care drug recommendations. The team involved in the creation of these materials consisted of a principal investigator, a 5-member content expert panel, and a 9-member primary care panel. The evaluation and treatment recommendations were based on availability of medications and other resources within the Veterans Health Administration (VHA) facilities. However, non-VHA panelists were also involved in the development of these materials, which can be applied to both VA and civilian settings. The illustrative clinical case was taken from the clinical practice of the principal investigator. **RESULTS:** Following expert consultations and a review of the literature, we developed an evaluation and treatment algorithm with supporting materials to aid in the care of

older adults with CLBP who have concomitant FMS. A case is presented that demonstrates the complexity of pain evaluation and management in older patients with CLBP and concomitant FMS. CONCLUSIONS: Recognition of FMS as a common contributor to CLBP in older adults and initiating treatment targeting both FMS and CLBP may lead to improved outcomes in pain and disability.

Hydrodistension with or without fulguration of Hunner lesions for interstitial cystitis: Long-term outcomes and prognostic predictors.

Niimi A, Nomiya A, Yamada Y, Suzuki M, Fujimura T, Fukuhara H, Kume H, Igawa Y, Homma Y. *Neurourol Urodyn*. 2015 Jul 24. doi: 10.1002/nau.22837. [Epub ahead of print]

AIMS: Hydrodistension of the bladder, with optional fulguration of Hunner lesions, is one of the recommended therapies for interstitial cystitis (IC). The aims of this study are to evaluate long-term outcomes of hydrodistension and identify outcome predictors. METHODS: The study cohort was 191 newly diagnosed IC patients (155 women and 36 men) who underwent hydrodistension with fulguration of Hunner lesions if detected between 2007 and 2013 at our institution. The primary outcome was therapeutic failure, which was defined as repeat hydrodistension, bladder instillation therapy, or narcotic use for pain control. Clinical features, including comorbidities and endoscopic findings, were analyzed along with the outcome. RESULTS: The cohort comprised 126 patients of Hunner type IC and 65 patients of non-Hunner type IC. The mean time to therapeutic failure was 28.5 months in Hunner type IC and 25.2 months in non-Hunner type IC. The therapeutic failure rate was higher in non-Hunner type IC at 17.3 months; however, the long-term outcomes reversed thereafter. The mean time to therapeutic failure was shorter in patients with lumbar spinal stenosis (LSS) or irritable bowel syndrome (IBS). Multivariate analysis identified LSS as a predictor for failure in Hunner type IC and non-Hunner type IC (HR=18.8, P=0.001; HR=3.8, P=0.028, respectively) and IBS in non-Hunner type IC (HR=18.0, P=0.008). CONCLUSIONS: Bladder hydrodistension, with fulguration of the Hunner lesions, improved IC symptoms. The outcome was worse in non-Hunner type IC shortly after hydrodistension but eventually comparable across the two types. Concomitant LSS and IBS were predictors for poor outcome.

Light therapy modulates serotonin levels and blood flow in women with headache. A preliminary study.

Tomaz de Magalhães M, Núñez SC, Kato IT, Ribeiro MS. *Exp Biol Med* (Maywood). 2015 Jul 22. pii: 1535370215596383. [Epub ahead of print]

In this study, we looked at the possible effects of low-level laser therapy (LLLT) on blood flow velocity, and serotonin (5-HT) and cholinesterase levels in patients with chronic headache associated with temporomandibular disorders (TMD). LLLT has been clinically applied over the past years with positive results in analgesia and without the report of any side effects. The understanding of biological mechanisms of action may improve clinical results and facilitate its indication. Ten patients presenting headache associated with TMD completed the study. An 830-nm infrared diode laser with power of 100mW, exposure time of 34s, and energy of 3.4J was applied on the tender points of masseter and temporal muscle. Blood flow velocity was determined via ultrasound Doppler velocimetry before and after laser irradiation. The whole blood 5-HT and cholinesterase levels were evaluated three days before, immediately, and three days after laser irradiation. Pain score after treatment decreased to a score of 5.8 corresponding to 64% of pain reduction (P<0.05). LLLT promoted a decrease in the blood flow velocity (P<0.05). In addition, the 5-HT levels were significantly increased three days after LLLT (P<0.05). The cholinesterase levels remained unchanged at the analyzed time points (P>0.05). Our findings

indicated that LLLT regulates blood flow in the temporal artery after irradiation and might control 5-HT levels in patients suffering with tension-type headache associated to TMD contributing to pain relief.

Effects of exercise training and photobiomodulation therapy (EXTRAPHOTO) on pain in women with fibromyalgia and temporomandibular disorder: study protocol for a randomized controlled trial.

da Silva MM, Albertini R, Leal-Junior EC, de Tarso Camillo de Carvalho P, Silva JA Jr, Bussadori SK, de Oliveira LV, Casarin CA, Andrade EL, Bocalini DS, Serra AJ. *Trials*. 2015 Jun 4;16:252. doi: 10.1186/s13063-015-0765-3.

BACKGROUND: Fibromyalgia (FM) is a syndrome most prevalent in women, in whom it is characterized mainly by chronic pain. An important issue is that many patients with FM are reported to have temporomandibular dysfunction (TMD), and the coexistence of these pathologies generates a clinical outcome of high complexity. The literature is unclear regarding an effective therapy for reducing pain in patients with both comorbidities. Exercise training and phototherapy (low-level laser therapy with light-emitting diode) are two of the approaches used to treat pain. Thus, the aim of this study is to assess the potential role of exercise training plus phototherapy in reducing chronic pain in women with FM and TMD. A further aim is to determine whether the interventions can improve quality of life and modulate endogenous serotonin.

METHODS/DESIGN: A randomized controlled clinical trial will be conducted. It will involve 60 women \geq 35 years of age with a diagnosis of FM and TMD. After recruitment, patients will be randomly allocated to one of four groups: a control group (no intervention), a group that will receive a phototherapy intervention (PHO), a group that will be prescribed muscle-stretching, aerobic, and facial exercises (EXT), or a group that will receive phototherapy plus exercise interventions (PHO + EXT). The trial will last 10 weeks, and the following outcomes will be evaluated on two separate occasions (baseline and within 24 h after the last day of the protocol). Pain intensity will be analyzed using a visual analogue scale and the McGill Pain Questionnaire, and pain thresholds will be punctuated using a digital algometer. FM symptoms will be assessed using the Fibromyalgia Impact Questionnaire, and quality of life will be determined with the 36-item Short Form Health Survey. Serotonin levels will be evaluated in salivary samples using a competitive enzyme-linked immunosorbent assay.

DISCUSSION: This is the first randomized controlled trial in which the role of phototherapy, exercise training, and a combination of these interventions will be evaluated for chronic pain in patients with FM and TMD. The results will offer valuable clinical evidence for objective assessment of the potential benefits and risks of procedures.

Changes in illness perceptions mediated the effect of cognitive behavioural therapy in severe functional somatic syndromes.

Christensen SS, Frostholt L, Ørnbøl E, Schröder A. *J Psychosom Res*. 2015 Apr;78(4):363-70. doi: 10.1016/j.jpsychores.2014.12.005.

OBJECTIVE: Although there is substantial evidence that cognitive behavioural therapy alleviates symptoms in functional somatic syndromes, the mechanisms of change are less investigated. This study examined whether changes in illness perceptions mediated the effect of cognitive behavioural therapy.

METHODS: We analysed additional data from a randomised controlled trial comparing completers of cognitive behavioural group therapy (46 patients) to an enhanced usual care group (66 patients). Proposed mediators (illness perceptions) and primary (physical health) and secondary (somatic symptoms and illness worry) outcomes were assessed by means of

questionnaires at referral, baseline, end of treatment, and 10 and 16 months after randomisation. Multiple mediation analysis determined whether (1) changes in specific illness perceptions during treatment mediated the effect of cognitive behavioural therapy (primary analysis), and (2) whether changes in illness perceptions during the whole trial period were associated with improved outcome (secondary analysis). RESULTS: Improvements in illness perceptions during treatment partially mediated the effect of cognitive behavioural therapy on physical health one year after treatment (sum of indirect effects 1.556, BCa 95% CI (0.006; 3.620)). Improving perceived control was particularly important. Changes in illness perceptions from baseline to 16 months after randomisation were associated with clinically meaningful improvements in physical health, somatic symptoms and illness worry during the same period. CONCLUSION: Our results suggest that changing patients' illness perceptions is an important process in cognitive behavioural therapy for functional somatic syndromes. Challenging patients' own understanding of their illness may hence be a key element of successful treatment.

About the Chronic Pain Research Alliance

The Chronic Pain Research Alliance (CPRA) is the *only* research-led collaborative advocacy effort dedicated to improving the lives of those affected by multiple pain conditions, termed *Chronic Overlapping Pain Conditions* (COPCs), which include vulvodynia, temporomandibular disorders, fibromyalgia, irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, migraine and tension-type headache, endometriosis, myalgic encephalomyelitis/chronic fatigue syndrome and chronic low back pain.

The CPRA envisions and is working towards a future where individuals with COPCs will receive a timely diagnosis, followed by comprehensive medical care, which includes the use of safe and effective approved treatments, informed by the latest and most rigorous scientific evidence.

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