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This e-newsletter is published by the Chronic Pain Research Alliance and developed to keep the medical-scientific and patient communities abreast of research advances on Chronic Overlapping Pain Conditions (COPCs). It contains abstracts of studies on the epidemiology, pathophysiology and clinical management of COPCs published between February and June 2018. Prior issues are available on our website, http://www.cpralliance.org. To read the CPRA's White Paper, click here . Please direct any questions or comments to the CPRA's Director, Christin Veasley - cveasley@cpralliance.org.

In this Issue...

PATHOPHYSIOLOGY STUDIES

Extracellular signal-regulated kinase activation in the spinal cord contributes to visceral hypersensitivity induced by craniofacial injury followed by stress.

Zhao YJ, ,Li JH, Hu B, Wang Y, Chang XF, Traub RJ, Cao DY.

Neurogastroenterol Motil. 2018 Feb;30(2). doi: 10.1111/nmo.13161.

BACKGROUND: We previously developed an animal model to examine mechanisms that underlie the emergence of visceral hypersensitivity modeling pain characteristics of temporomandibular disorder (TMD) patients with comorbid irritable bowel syndrome (IBS). In ovariectomized (OVx) rats with estradiol (E2) replacement, visceral hypersensitivity developed subsequent to masseter muscle inflammation followed by repeated forced swim (FS) stress. The purpose of this study was to investigate whether activation of extracellular signal-regulated kinase (ERK) in the spinal cord contributes to visceral hypersensitivity in this overlapping pain model. METHODS: In OVx with E2 replacement rats masseter muscle inflammation was followed by 3 day FS (comorbid condition). Depression-like behaviors were assessed by sucrose preference and in the elevated plus maze, and visceral sensitivity was measured by the visceromotor response (VMR) to colorectal distention. The protein level of ERK1/2 and phosphorylated ERK1/2 (p-ERK1/2) in the L6-S2 dorsal spinal cord was analyzed by western blot. KEY RESULTS: FS stress decreased sucrose consumption in E2 replaced rats in sucrose preference test. The expression of p-ERK1/2 in the L6-S2 dorsal spinal cord increased significantly in E2 with comorbid rats. Intrathecal injection of mitogen-activated protein kinase (MAPK) kinase (MEK) inhibitor PD98059

blocked the visceral hypersensitivity induced by masseter muscle inflammation combined with FS stress. CONCLUSIONS & INFERENCES: These data indicate that ERK1/2 activation contributes to the visceral hypersensitivity evoked by craniofacial inflammation pain combined with stress. The results may provide a new therapeutic avenue for alleviating overlapping pain conditions.

Evidence of altered trigeminal nociception in an animal model of fibromyalgia.
Nazeri M, Zarei MR, Pourzare AR, Ghahreh-Chahi HR, Abareghi F, Shabani M.
Pain Me. 2018 Feb 1;19(2):328-335. doi: 10.1093/pm/pnx114.

OBJECTIVE: Fibromyalgia (FM) is a debilitating chronic condition that significantly affects quality of life. A strong association has been demonstrated between FM and chronic pain in the trigeminal region in clinical studies. This study was performed to evaluate the response to acute and chronic noxious stimuli applied to the facial region. METHODS: Adult male Wistar rats (250-270 g, N=10 for each group) were used in the current study. A subchronic swim stress model was used as the animal model of FM. Anxiety-like behaviors and response to acute and chronic noxious stimuli were assayed using the elevated plus maze, eye wiping test, and orofacial formalin test, respectively. Balance and motor function were evaluated using rotarod and wire grip tests. RESULTS: An increased anxiety-like behavior was observed in swim stress rats in comparison with control and sham subjects. Response to acute and chronic noxious stimuli in the trigeminal region was increased in the stressed rats. Motor and balance function were not altered following stress. CONCLUSIONS: Results of the current study demonstrated a hyperalgesic state in the trigeminal region in a possible animal model of FM. This study provides a reliable animal model for further research on the possible mechanisms of orofacial pain in FM.

Salivary levels of interleukin-1beta in temporomandibular disorders and fibromyalgia.
Ce PS, Barreiro BB, Silva RB, Oliveira RB, Heitz C, Campos MM.
J Oral Facial Pain Headache. 2018 Mar 21. doi: 10.11607/ofph.1899.

AIMS: To evaluate salivary levels of the proinflammatory cytokine interleukin-1β (IL-1β) in patients with temporomandibular disorders (TMD), fibromyalgia, or both conditions in comparison to healthy individuals. METHODS: A total of 69 females (18 to 84 years of age) were assigned to one of four groups: (A) healthy controls (n = 27); (B) TMD only (n = 18); (C) fibromyalgia only (n = 15); and (D) fibromyalgia plus TMD (n = 9). Clinical data and salivary IL-1β levels were evaluated. Statistical analysis was performed by using Fischer exact test, unpaired Student t test, or one-way analysis of variance plus multiple comparisons Tukey test, depending on the variable. The correlation between age and IL-1β levels was assessed by using Pearson correlation coefficient. RESULTS: Most patients in groups B and D displayed clinical features of Group I (muscle disorders) and Group II (disc displacements) of the Axis I Research Diagnostic Criteria for Temporomandibular Disorders. The subjects in groups C and D presented values of > 7 on the Widespread Pain Index (WPI) and > 5 for Symptom Severity Score (SS) according to the Fibromyalgia Survey Diagnostic Criteria and Severity Scale. There were no significant differences when SS and WPI levels were compared between groups C and D. The patients with TMD showed significantly higher salivary IL-1β levels irrespective of a fibromyalgia diagnosis (groups B and D), whereas the fibromyalgia-only patients (group C) did not show any significant difference in relation to controls. CONCLUSION: This study provides novel evidence indicating that salivary IL-1β may be a biomarker for TMD.

Putative salivary biomarkers useful to differentiate patients with fibromyalgia.
Ciregia F, Giacomelli C, Giusti L, Boldrini C, Piga I, Pepe P, Consensi A, Gori S, Lucacchini A, Mazzoni MR, Bazzichi L.
J Proteomics. 2018 Apr 11. pii: S1874-3919(18)30172-6. doi: 10.1016/j.jprot.2018.04.012.

Fibromyalgia (FM) is a chronic pain disorder characterized by widespread pain and associated with unspecific symptoms. So far, no laboratory tests have been validated. The aim of the present study was to investigate the presence in saliva of potential diagnostic and/or prognostic biomarkers which could be useful for the management of FM patients. Specifically, the salivary profile of FM patients was compared with those of healthy subjects, subjects suffering migraine (model of non-inflammatory chronic pain), and patients affected by rheumatoid arthritis (model of

inflammatory chronic pain). For proteomics analysis 2-DE and SELDI-TOF-MS were applied. From 2-DE serotransferrin and alpha-enolase were found differentially expressed in FM. Hence, their expression was validated by ELISA together with phosphoglycerate-mutase-I and transaldolase, which were found in a previous work. Moreover, ROC curve was calculated by comparing FM patients versus control subjects (healthy plus migraine) to investigate the discriminative power of biomarkers. The best performance was obtained by combining alpha-enolase, phosphoglycerate-mutase-I and serotransferrin. On the other hand, none of the candidate proteins showed a statistical correlation with clinical features. Finally, preliminary SELDI analysis highlighted two peaks whose identification need to be validated. Overall, these results could be useful in supporting the clinical diagnosis of FM. SIGNIFICANCE: FM is one of the most common chronic pain condition which is associated with significant disability. The fibromyalgic pain is a peculiar characteristic of this disease and FM patients suffer from reduced quality of life, daily functioning and productivity. Considering the deep complexity of FM, the discovery of more objective markers is crucial for supporting clinical diagnosis. Therefore, the aim of the present study was the selection of biomarkers effectively associated with fibromyalgic pain which will enable clinicians to achieve an unambiguous diagnosis, and to improve approaches to patients' management. We defined a panel of 3 salivary proteins which could be one of the criteria to be taken into account. Consequently, the identification of disease salivary biomarkers could be helpful in detecting FM clusters and targeted treatment. Actually, our future perspective foresees to develop a simple, rapid and not invasive point-of-care testing which will be of use during the diagnostic process. In addition, the present results can offer a clue for shedding light upon the complex entity of such a disease like FM.

Painful neurotrophins and their role in visceral pain.
Lopez-Perez AE, Nurgali K, Abalo R.
Behav Pharmacol. 2018 Apr;29(2 and 3 - Special Issue):120-139. doi: 10.1097/FBP.0000000000000386.

Beyond their well-known role in embryonic development of the central and peripheral nervous system, neurotrophins, particularly nerve growth factor and brain-derived neurotrophic factor, exert an essential role in pain production and sensitization. This has mainly been studied within the framework of somatic pain, and even antibodies (tanezumab and fasinumab) have recently been developed for their use in chronic somatic painful conditions, such as osteoarthritis or low back pain. However, data suggest that neurotrophins also exert an important role in the occurrence of visceral pain and visceral sensitization. Visceral pain is a distressing symptom that prompts many consultations and is typically encountered in both 'organic' (generally inflammatory) and 'functional' (displaying no obvious structural changes in routine clinical evaluations) disorders of the gut, such as inflammatory bowel disease and irritable bowel syndrome, respectively. The present review provides a summary of neurotrophins as a molecular family and their role in pain in general and addresses recent investigations of the involvement of nerve growth factor and brain-derived neurotrophic factor in visceral pain, particularly that associated with inflammatory bowel disease and irritable bowel syndrome.

Neurobiologic features of fibromyalgia are also present among rheumatoid arthritis patients.
Basu N, Kaplan CM, Ichesco E, Larkin T, Harris RE, Murray A, Waiter G, Clauw DJ.
Arthritis Rheumatol. 2018 Jul;70(7):1000-1007. doi: 10.1002/art.40451.

OBJECTIVE: Many patients with rheumatoid arthritis (RA) report pain despite excellent control of inflammation with immunotherapies. Variable degrees of coexisting fibromyalgia (FM) may explain this disparity. FM has been characterized by aberrant brain functional connectivity, especially between the default mode network (DMN) and insula. We undertook this study to test the hypothesis that RA patients with the highest 2011 American College of Rheumatology FM survey criteria scores-a continuous measure of the degree of FM also known as "fibromyalgianess" (FMness)-would demonstrate functional connectivity abnormalities similar to those in FM. METHODS: RA patients underwent an 11-minute functional connectivity magnetic resonance imaging (MRI) brain scan and a clinical evaluation which included a measure of FMness. Brain networks were isolated from functional connectivity MRI data. Individual patient network-to-whole brain connectivity analyses were then conducted, followed by group-level regression, which correlated the connectivity of each network with FMness. Results were significant on the cluster level with a family-wise error (FWE) rate P value less than 0.05 derived from an uncorrected voxel-level P value less than 0.001. RESULTS: A total of 54 patients participated (mean age

54.9 years, 75.9% women, mean FMness score 13.2 [range 1-29]). From the whole brain analyses, a single significant positive correlation between DMN connectivity to the left mid/posterior insula and FMness (r = 0.58, FWE-corrected P = 0.001) was demonstrated. CONCLUSION: RA patients who have increased levels of FMness appear to share neurobiologic features consistently observed in FM patients. This study is the first to provide neuroimaging evidence that RA is a mixed pain state, with many patients' symptoms being related to the central nervous system rather than to classic inflammatory mechanisms.

Disease-related microstructural differences in the brain in women with provoked vestibulodynia.
Gupta A, Woodworth DC, Ellingston BM, Rapkin AJ, Naliboff B, Kilpatrick LA, Stains J, Masghati S, Tillisch K, Mayer EA, Labus JS.
J Pain. 2018 May;19(5):528.e1-528.e15. doi: 10.1016/j.jpain.2017.12.269.

Provoked vestibulodynia (PVD) is a chronic pelvic pain disorder affecting 16% of the female population. Neuroimaging studies have highlighted central abnormalities in PVD, similar to other chronic pelvic pain disorders, including brain regions involved in sensory processing and modulation of pain. The aim of the study was to determine alterations in the subvoxel, microstructural organization within tissues in PVD compared with healthy control participants (HCs) and a disease control group (irritable bowel syndrome [IBS]). Diffusion tensor imaging magnetic resonance imaging was conducted in 87 age-matched premenopausal women (29 PVD, 29 HCs, 29 IBS). Statistical parameter mapping of fractional anisotropy (FA) and mean diffusivity (MD) maps were used to identify microstructural difference in the brain specific to PVD or shared with IBS. PVD alterations in microstructural organization of the brain were predominantly observed in fibers associated with sensorimotor integration and pain processing that relay information between the thalamus, basal ganglia, sensorimotor, and insular cortex. PVD, compared with HCs, showed extensive increases in the FA of somatosensory and basal ganglia regions. In contrast, PVD and IBS subjects did not show any FA-related group differences. PVD subjects showed greater MD in the basal ganglia compared with HCs (higher MD in the internal capsule and pallidum) and IBS (higher MD in the putamen and pallidum). Increases in MD were associated with increased vaginal muscle tenderness and vulvar pain. The current findings highlight possible shared mechanisms between 2 different pelvic pain disorders, but also highlight the widespread alterations observed specifically in PVD compared with HCs. PERSPECTIVE: Alterations in microstructure in PVD were observed in fibers associated with sensorimotor integration and pain processing, which were also associated with increased vaginal muscle tenderness and vulvar pain. These alterations may be contributing to increased pain sensitivity and tenderness, highlighting the need for new therapies targeting the central nervous system.

Cortical thickness alterations in chronic pain disorder - an exploratory MRI study.
Magon S, Sprenger T, Otti A, Papadopoulou A, Gundel H, Noll-Hussong M.
Psychosom Med. 2018 May 21. doi: 10.1097/PSY.0000000000000605.

OBJECTIVE: Chronic pain disorder (CPD) has been associated with brain changes, especially in limbic circuits. However, in the majority of patients with chronic pain, depression or anxiety are common comorbidities. In this exploratory and naturalistic study, we investigated brain cortical thickness differences between patients with CPD and healthy controls, with consideration of concurrent psychiatric symptoms. METHODS: Twenty-three patients with CPD and 23 age- and sex-matched healthy volunteers were included in this study. Cortical thickness (CTh) was estimated using Freesurfer on high-resolution 3D T1-weighted images acquired with a 3Tesla scanner. Group differences were investigated using an ANCOVA model that included age, sex, and Beck Depression Inventory I (BDI-I) and Trait Anxiety Inventory (STAI-T) scores as covariates. The relationship between CTh and Toronto Alexithymia Scale (TAS-20) scores was also investigated in patients. Data were corrected for multiplicity using the False Discovery Rate (FDR) approach (q<.05). RESULTS: The comparison between groups using demographics and BDI-I scores as covariates showed thinner cortex in patients compared with controls, after correction for multiplicity in the left precentral (F(1,42)=21.9; p<.05) and postcentral gyri (F(1,42)=26.9; p<.05) and in the left inferior temporal sulcus (F(1,42)=19.6; p<.05). Moreover, using the STAI-T as covariate, a trend toward significance (p<.001 uncorrected) was seen for the left precentral gyrus (F(1,42)=13.8), right middle frontal (F(1,42)=14.3) and inferior parietal gyri (F(1,42)=13.4), and right anterior temporal pole (F(1,42)=15.9). CONCLUSION: The results indicate that brain

morphological differences between patients with chronic pain disorder and healthy controls are localized to regions that correspond to sensory as well as affective dimensions of pain processing.

Is migraine primarily a metaboloendocrine disorder?
Rainero I, Govone F, Gai A, Vacca A, Rubino E.
Curr Pain Headache Rep. 2018 Apr 4;22(5):36. doi: 10.1007/s11916-018-0691-7.

PURPOSE OF THE REVIEW: The goals of this review are to evaluate recent studies regarding comorbidity between migraine and different metabolic and endocrine disorders and to discuss the role of insulin resistance as a common pathogenetic mechanism of these diseases. RECENT FINDINGS: Recently, several studies showed that migraine is associated with insulin resistance, a condition in which a normal amount of insulin induces a suboptimal physiological response. All the clinical studies that used the oral glucose tolerance test to examine insulin sensitivity found that, after glucose load, there is in migraine patients a significant increase of both plasmatic insulin and glucose concentrations in comparison with controls. On the contrary, no association was found between migraine and type 2 diabetes, while type 1 diabetes seems to have a protective effect in the disease. Obesity and hypertension were shown to be risk factors for both episodic and chronic migraine. Metabolic syndrome has been recently associated mainly with migraine with aura and is now considered a risk factor also for medication overuse headache. Finally, a bidirectional association between migraine and hypothyroidism has been recently demonstrated, suggesting that common genetic or autoimmune mechanisms underlie both diseases. Recent studies showed that insulin receptor signaling and the related physiological responses are altered in migraine and may have a relevant pathogenic role in the disease. Further studies are warranted in order to better elucidate mechanisms underlying insulin resistance in migraine in order to develop new therapeutic strategies for this debilitating disease.

Shared genetics of temporomandibular disorder pain and neck pain: Results of a twin study.
Visscher CM, Schouten MJ, Ligthart L, van Houtem CM, de Jongh A, Boomsma DI.
J Oral Facial Pain Headache. 2018 Mar 6. doi: 10.11607/ofph.2016.

AIMS: (1) To examine the heritability of TMD pain and of neck pain; and (2) to estimate the potential overlap in genetic and environmental factors influencing TMD pain and neck pain. METHODS: Data from 2,238 adult female twins who completed a survey on TMD pain and neck pain were analyzed. The total variance of TMD pain and neck pain was decomposed into variance attributable to additive genetic effects and nonshared environmental effects. Bivariate structural equation modeling was applied to estimate trait-specific and genetic effects shared between traits. RESULTS: The prevalence of TMD pain and neck pain was 8.6% and 46.8%, respectively, while 6.7% of the twins reported both TMD pain and neck pain. The phenotypic correlation between TMD pain and neck pain, based on a liability threshold model, was 0.43 (95% confidence interval [CI] 0.34 to 0.51). The heritability for TMD was 0.35 (0.17 to 0.51), and for neck pain was 0.33 (0.23 to 0.43). The genetic correlation between TMD pain and neck pain was 0.64 (0.35 to 1.00), and the environmental correlation was 0.32 (0.14 to 0.48). CONCLUSION: This study shows that variation in TMD pain and neck pain can in part be attributed to genes. The comorbidity between them is partly explained by genes that influence both traits and partly by the same environmental factors.

Are migraine and tension-type headache genetically related? An investigation of twin family data.
Ligthart L, Huijgen A, Willemsen G, de Geus EJC, Boomsma DI.
Twin Res Hum Genet. 2018 Apr;21(2):112-118. doi: 10.1017/thg.2018.5.

Migraine and tension-type headache (TTH) are often viewed as distinct entities and defined as such in the International Classification of Headache Disorders, 2nd edition (ICHD-II) criteria, although there is also empirical evidence to suggest they may be etiologically similar. This study aims to investigate whether migraine and TTH are etiologically related conditions. First, we explored whether migraine and TTH were associated with the same environmental and lifestyle risk factors at the population level. Second, we examined comorbidity of migraine and TTH in a twin design. By comparing the associations in monozygotic (MZ) and dizygotic (DZ) twin pairs, we investigated whether the comorbidity can be explained by genetic factors that influence both conditions. Results indicated that migraine and TTH

were largely associated with the same environmental and lifestyle factors, including younger age, female sex, higher body mass index, more depression, stress at home, and less participation in regular exercise, with consistently stronger effects for migraine than for TTH. Migraine in one twin was significantly associated with TTH in the other twin. A stronger cross-trait, cross-twin association in MZ than DZ twins suggested that this comorbidity may also be partly due to shared genetic factors, although the difference in associations was not significant. In conclusion, our findings are consistent with the hypothesis that migraine and TTH have partly shared etiologies. For both treatment and research, it may be advisable not to make a rigid distinction, but to treat migraine and TTH as related conditions.

Is resolution of chronic pain associated with changes in blood pressure-related hypoalgesia?
de la Coba P, Bruehl S, Garber J, Smith CA, Walker LS.
Ann Behav Med. 2018 May 31;52(7):552-559. doi: 10.1093/abm/kax021.

BACKGROUND: In healthy individuals, elevated resting blood pressure (BP) is associated with reduced pain responsiveness and lower temporal summation. Prior work indicates that this BP-related hypoalgesia is reduced in individuals with chronic pain. PURPOSE: This study evaluated whether resolution of chronic pain was associated with greater BP-related hypoalgesia compared to nonresolution. METHODS: From a prospective sample of adolescents and young adults diagnosed with chronic functional abdominal pain an average of 9 years earlier, 99 individuals in whom the condition had resolved and 51 individuals with ongoing abdominal pain were studied. Resting systolic BP was assessed, followed by evaluation of thermal pain threshold and tolerance, and assessment of temporal summation to thermal pain stimuli. RESULTS: Higher resting systolic BP was significantly associated with higher pain threshold and tolerance, and lower temporal summation only in the group with resolved functional abdominal pain ($p < .05$). Hierarchical regressions revealed that interactions between BP and resolution of chronic pain were significant only for pain tolerance ($p < .05$). Analyses by sex indicated that interactions between BP and resolution status were significant for the temporal summation outcome in males but not in females. CONCLUSIONS: Results suggest that BP-related hypoalgesic mechanisms may be more effective in individuals in whom chronic pain has resolved compared to those with ongoing chronic pain. Findings hint at sex differences in the extent to which resolution of chronic pain is associated with BP-related hypoalgesia. Whether greater BP-related hypoalgesia is a consequence of, or alternatively a contributor to, resolution of chronic pain warrants further investigation.

"Motoring in idle": The default mode and somatomotor networks are overactive in children and adolescents with functional neurological symptoms.
Kozlowska K, Spooner CJ, Palmer DM, Harris A, Korgaonkar MS, Scher S, Williams LM.
Neuroimage Clin. 2018 Feb 17;18:730-743. doi: 10.1016/j.nicl.2018.02.003. eCollection 2018.

OBJECTIVE: Children and adolescents with functional neurological symptom disorder (FND) present with diverse neurological symptoms not explained by a disease process. Functional neurological symptoms have been conceptualized as somatoform dissociation, a disruption of the brain's intrinsic organization and reversion to a more primitive level of function. We used EEG to investigate neural function and functional brain organization in children/adolescents with FND. METHOD: EEG was recorded in the resting eyes-open condition in 57 patients (aged 8.5-18 years) and 57 age- and sex-matched healthy controls. Using a topographical map, EEG power data were quantified for regions of interest that define the default mode network (DMN), salience network, and somatomotor network. Source localization was examined using low-resolution brain electromagnetic tomography (LORETA). The contributions of chronic pain and arousal as moderators of differences in EEG power were also examined. RESULTS: Children/adolescents with FND had excessive theta and delta power in electrode clusters corresponding to the DMN-both anteriorly (dorsomedial prefrontal cortex [dmFPC]) and posteriorly (posterior cingulate cortex [PCC], precuneus, and lateral parietal cortex)-and in the premotor/supplementary motor area (SMA) region. There was a trend toward increased theta and delta power in the salience network. LORETA showed activation across all three networks in all power bands and localized neural sources to the dorsal anterior cingulate cortex/dmPFC, mid cingulate cortex, PCC/precuneus, and SMA. Pain and arousal contributed to slow wave power increases in all three networks. CONCLUSIONS: These findings suggest that children and adolescents with FND are characterized by overactivation of intrinsic resting brain networks involved in threat detection, energy regulation, and preparation for action.

Chronic diffuse pain and functional gastrointestinal disorders after traumatic stress: Pathophysiology through a polyvagal perspective.
Kolacz J, Porges SW.
Front Med (Lausanne). 2018 May 31;5:145. doi: 10.3389/fmed.2018.00145. eCollection 2018.

Chronic diffuse pain disorders, such as fibromyalgia, and functional gastrointestinal disorders (FGIDs), such as irritable bowel syndrome, place substantial burden on those affected and on the medical system. Despite their sizable impact, their pathophysiology is poorly understood. In contrast to an approach that focuses on the correlation between heart rate variability (HRV) and a specific organ or symptom, we propose that a bio-evolutionary threat-related autonomic response-as outlined in the Polyvagal Theory-may serve as a plausible explanation of how HRV, particularly respiratory sinus arrhythmia (RSA), would index the pathophysiology of these disorders. Evidence comes from: (1) the well-documented atypical autonomic regulation of the heart common to fibromyalgia and irritable bowel syndrome reflected in dampened RSA, (2) the neural architecture that integrates the heart, pain pathways, and the gastrointestinal tract, (3) the common physical co-morbidities shared by chronic diffuse pain and FGIDs, many of which are functionally regulated by the autonomic nervous system, (4) the elevated risk of chronic diffuse pain and FGIDs following traumatic stress or abuse, (5) and the elevated risk of chronic diffuse pain and FGIDs in individuals with anxiety and panic disorders. This novel conceptualization points to a pathogenesis rooted in changes to brain-body autonomic feedback loops in response to evolutionarily-salient threat cues, providing an integrated biopsychosocial model of chronic diffuse pain and FGIDs and suggesting new, non-pharmacological treatment strategies.

Irritable bowel syndrome and endometriosis: New insights for old diseases.
Viagno D, Zara F, Usai P.
Dig Liver Dis. 2018 Mar;50(3):213-219. doi: 10.1016/j.dld.2017.12.017.

Irritable bowel syndrome and endometriosis are two diseases affecting a significant part of the female population, either together or individually, with remarkable consequences in the quality of life. Several studies suggest an epidemiological association between them. Their association may not be just an epidemiological phenomenon, but the manifestation of a pathophysiological correlation, which probably generates a mutual promotion phenomenon. In particular, both clinical entities share the presence of a chronic low-grade inflammatory state at the basis of the disease persistence. Recognizing this association is highly significant due to their prevalence and the common clinical manifestation occurring with a chronic abdominal pain. A further multidisciplinary approach is suggested in these patients' management in order to achieve an adequate diagnostic work up and a targeted therapy. This paper analyses some common pathophysiological mechanisms, such as activation of mast cell line, neuronal inflammation, dysbiosis and impaired intestinal permeability. The aim was to investigate their presence in both IBS and endometriosis, and to show the complexity of their relationship in the generation and maintenance of chronic inflammation.

Visceral hypersensitivity is associated with GI symptom severity in functional GI disorders: consistent findings from five different patient cohorts.
Simren M, Tornblom H, Palsson OS, van Tilburg MAL, Van Oudenhove L, Tack J, Whitehead WE.
Gut. 2018 Feb;67(2):255-262. doi: 10.1136/gutjnl-2016-312361.

OBJECTIVE: Our aim was to evaluate the association between visceral hypersensitivity and GI symptom severity in large cohorts of patients with functional GI disorder (FGID) and to adjust for psychological factors and general tendency to report symptoms. DESIGN: We included five cohorts of patients with FGIDs (IBS or functional dyspepsia; n=1144), who had undergone visceral sensitivity testing using balloon distensions (gastric fundus, descending colon or rectum) and completed questionnaires to assess GI symptom severity, non-GI somatic symptoms, anxiety and depression. Subjects were divided into sensitivity tertiles based on pain/discomfort thresholds. GI symptom severity was compared between sensitivity tertiles in each cohort and corrected for somatisation, and anxiety and depression. RESULTS: In all five cohorts, GI symptom severity increased gradually with increasing visceral sensitivity, with significant differences in GI symptom severity between the sensitivity tertiles ($p<0.0001$), with small to medium effect sizes. The differences between sensitivity tertiles remained

significant in all cohorts after correction for anxiety and depression, and also after correction for non-GI somatic symptom reporting in all of the cohorts ($p<0.05$). CONCLUSIONS: A gradual increase in GI symptom severity with increasing GI sensitivity was demonstrated in IBS and functional dyspepsia, which was consistent across several large patient groups from different countries, different methods to assess sensitivity and assessments in different parts of the GI tract. This association was independent of tendency to report symptoms or anxiety/depression comorbidity. These findings confirm that visceral hypersensitivity is a contributor to GI symptom generation in FGIDs.

A unifying theory for cognitive abnormalities in functional neurological disorders, fibromyalgia and chronic fatigue syndrome: A systematic review.
Teodoro T, Edwards MJ, Isaacs JD.
J Neurol Neurosurg Psychiatry. 2018 May 7. pii: jnnp-2017-317823. doi: 10.1136/jnnp-2017-317823.

BACKGROUND: Functional cognitive disorder (FCD) describes cognitive dysfunction in the absence of an organic cause. It is increasingly prevalent in healthcare settings yet its key neuropsychological features have not been reported in large patient cohorts. We hypothesised that cognitive profiles in fibromyalgia (FM), chronic fatigue syndrome (CFS) and functional neurological disorders (FNDs) would provide a template for characterising FCD. METHODS: We conducted a systematic review of studies with cognition-related outcomes in FM, CFS and FND. RESULTS: We selected 52 studies on FM, 95 on CFS and 39 on FND. We found a general discordance between high rates of subjective cognitive symptoms, including forgetfulness, distractibility and word-finding difficulties, and inconsistent objective neuropsychological deficits. Objective deficits were reported, including poor selective and divided attention, slow information processing and vulnerability to distraction. In some studies, cognitive performance was inversely correlated with pain, exertion and fatigue. Performance validity testing demonstrated poor effort in only a minority of subjects, and patients with CFS showed a heightened perception of effort. DISCUSSION: The cognitive profiles of FM, CFS and non-cognitive FND are similar to the proposed features of FCD, suggesting common mechanistic underpinnings. Similar findings have been reported in patients with mild traumatic brain injury and whiplash. We hypothesise that pain, fatigue and excessive interoceptive monitoring produce a decrease in externally directed attention. This increases susceptibility to distraction and slows information processing, interfering with cognitive function, in particular multitasking. Routine cognitive processes are experienced as unduly effortful. This may reflect a switch from an automatic to a less efficient controlled or explicit cognitive mode, a mechanism that has also been proposed for impaired motor control in FND. These experiences might then be overinterpreted due to memory perfectionism and heightened self-monitoring of cognitive performance.

Gastrointestinal and hepatic disease in fibromyalgia.
Schatz RA, Moshiree B.
Rheum Dis Clin North Am. 2018 Feb;44(1):131-142. doi: 10.1016/j.rdc.2017.09.009.

Fibromyalgia (FM) has historically been associated with several diseases in gastroenterology and hepatology. The most substantiated evidence pertains to irritable bowel syndrome (IBS). The pathogeneses of FM and IBS remain unclear, but it is likely related to dysregulation within the brain-gut axis, resulting in a hyperalgesic state. IBS and FM share other similarities, including a female predominance, fatigue, insomnia, and susceptibility to psychiatric state. These common manifestations and pathogeneses serve as a foundation for overlapping, multidisciplinary treatment modalities.

Negative affectivity, depression, and resting heart rate variability (HRV) as possible moderators of endogenous pain modulation in functional somatic syndromes.
Van Den Houte M, Van Oudenhove L, Van Diest I, Bogaerts K, Persoons P, De Bie J, Van den Bergh O.
Front Psychol. 2018 Mar 6;9:275. doi: 10.3389/fpsyg.2018.00275. eCollection 2018.

Background: Several studies have shown that patients with functional somatic syndromes (FSS) have, on average, deficient endogenous pain modulation (EPM), as well as elevated levels of negative affectivity (NA) and high comorbidity with depression and reduced resting heart rate variability (HRV) compared to healthy controls (HC). The goals of this study were (1) to replicate these findings and (2) to investigate the moderating role of NA, depression, and resting HRV in EPM efficiency within a patient group with

fibromyalgia and/or chronic fatigue syndrome (CFS). Resting HRV was quantified as the root mean square of successive differences between inter-beat intervals (RMSSD) in rest, a vagally mediated time domain measure of HRV. Methods: Seventy-eight patients with fibromyalgia and/or CFS and 33 HC completed a counter-irritation paradigm as a measure of EPM efficiency. Participants rated the painfulness of electrocutaneous stimuli (of individually calibrated intensity) on the ankle before (baseline phase), during (counter-irritation phase) and after (recovery phase) the application of a cold pain stimulus on the forearm. A larger reduction in pain in the counter-irritation phase compared to the baseline phase reflects a more efficient EPM. Results: In contrast to our expectations, there was no difference between pain ratings in the baseline compared to counter-irritation phase for both patients and HC. Therefore, reliable conclusions on the moderating effect of NA, depression, and RMSSD could not be made. Surprisingly, patients reported more pain in the recovery compared to the counter-irritation and baseline phase, while HC did not. This latter effect was more pronounced in patients with comorbid depression, patients who rated the painfulness of the counter-irritation stimulus as high and patients who rated the painfulness of the electrocutaneous stimuli as low. We did not manage to successfully replicate the counter-irritation effect in HC or FSS patients. Therefore, no valid conclusions on the association between RMSSD, depression, NA and EPM efficiency can be drawn from this study. Possible reasons for the lack of the counter-irritation effect are discussed.

The association between vitamin D concentration and pain: A systematic review and meta-analysis.
Wu Z, Malihi Z, Stewart AW, Lawes CM, Scragg R.
Public Health Nutr. 2018 Mar 21:1-16. doi: 10.1017/S1368980018000551.

OBJECTIVE: Pain-related conditions, such as chronic widespread pain and fibromyalgia, are major burdens for individuals and the health system. Evidence from previous research on the association between circulating 25-hydroxyvitamin D (25(OH)D) concentrations and pain is conflicting. Thus, we aimed to determine if there is an association between mean 25(OH)D concentration (primary aim), or proportion of hypovitaminosis D (secondary aim), and pain conditions in observational studies. DESIGN: Published observational research on 25(OH)D concentration and pain-related conditions was systematically searched for in electronic sources (MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials) and a random-effects meta-analysis was conducted on included studies. RESULTS: Eighty-one observational studies with a total of 50 834 participants were identified. Compared with controls, mean 25(OH)D concentration was significantly lower in patients with arthritis (mean difference (MD): -12·34 nmol/l; P<0·001), muscle pain (MD: -8·97 nmol/l; P=0·003) and chronic widespread pain (MD: -7·77 nmol/l; P<0·001), but not in patients with headache or migraine (MD: -2·53 nmol/l; P=0·06). The odds of vitamin D deficiency was increased for arthritis, muscle pain and chronic widespread pain, but not for headache or migraine, compared with controls. Sensitivity analyses revealed similar results. CONCLUSIONS: A significantly lower 25(OH)D concentration was observed in patients with arthritis, muscle pain and chronic widespread pain, compared with those without. These results suggest that low25(OH)D concentrations may be associated with pain conditions.

The distribution of pain activity across the human neonatal brain is sex dependent.
Verriotis M, Jones L, Whitehead K, Laudiano-Dray M, Panayotidis I, Patel H, Meek J, Fabrizi L, Fitzgerald M.
Neuroimage. 2018 May 12;178:69-77. doi: 10.1016/j.neuroimage.2018.05.030. [Epub ahead of print]

In adults, there are differences between male and female structural and functional brain connectivity, specifically for those regions involved in pain processing. This may partly explain the observed sex differences in pain sensitivity, tolerance, and inhibitory control, and in the development of chronic pain. However, it is not known if these differences exist from birth. Cortical activity in response to a painful stimulus can be observed in the human neonatal brain, but this nociceptive activity continues to develop in the postnatal period and is qualitatively different from that of adults, partly due to the considerable cortical maturation during this time. This research aimed to investigate the effects of sex and prematurity on the magnitude and spatial distribution pattern of the long-latency nociceptive event-related potential (nERP) using electroencephalography (EEG). We measured the cortical response time-locked to a clinically required heel lance in 81 neonates born between 29 and 42 weeks gestational age (median postnatal age 4 days). The results show that heel lance results in a spatially widespread nERP response in the majority of newborns. Importantly, a widespread pattern is significantly more

likely to occur in females, irrespective of gestational age at birth. This effect is not observed for the short latency somatosensory waveform in the same infants, indicating that it is selective for the nociceptive component of the response. These results suggest the early onset of a greater anatomical and functional connectivity reported in the adult female brain, and indicate the presence of pain-related sex differences from birth.

Sex differences in how inflammation affects behavior: What we can learn from experimental inflammatory models in humans.
Lasselin J, Lekander M, Axelsson J, Karshikoff B.
Front Neuroendocrinol. 2018 Jun 20. pii: S0091-3022(18)30047-5. doi: 10.1016/j.yfrne.2018.06.005.

Human models demonstrate that experimental activation of the innate immune system has profound effects on brain activation and behavior, inducing fatigue, worsened mood and pain sensitivity. It has been proposed that inflammation is a mechanism involved in the etiology and maintenance of depression, chronic pain and long-term fatigue. These diseases show a strong female overrepresentation, suggesting that a better understanding of sex differences in how inflammation drives behavior could help the development of individualized treatment interventions. For this purpose, we here review sex differences in studies using experimental inflammatory models to investigate changes in brain activity and behavior. We suggest a model in which inflammation accentuates sex differences in brain networks and pre-existing vulnerability factors. This effect could render women more vulnerable to the detrimental effects of immune-to-brain communication over time. We call for systematic and large scale investigations of vulnerability factors for women in the behavioral response to inflammation.

miR-34a-mediated regulation of XIST in female cells under inflammation.
Shenoda BB, Tian Y, Alexander GM, Aradillas-Lopez E, Schwartzman RJ, Ajit SK.
J Pain Res. 2018 May 8;11:935-945. doi: 10.2147/JPR.S159458. eCollection 2018.

BACKGROUND: Evidence is overwhelming for sex differences in pain, with women representing the majority of the chronic pain patient population. There is a need to explore novel avenues to elucidate this sex bias in the development of chronic inflammatory pain conditions. Complex regional pain syndrome (CRPS) is a chronic neuropathic pain disorder, and the incidence of CRPS is greater in women than in men by ~4:1. Since neurogenic inflammation is a key feature of CRPS, dysregulation of inflammatory responses can be a factor in predisposing women to chronic pain. METHODS: Our studies investigating alterations in circulating microRNAs (miRNAs) in whole blood from female CRPS patients showed significant differential expression of miRNAs between responders and poor responders to ketamine treatment. Several of these miRNAs are predicted to target the long noncoding RNA, X-inactive-specific transcript (XIST). XIST mediates X-chromosome inactivation and is essential for equalizing the expression of X-linked genes between females and males. Based on the well-established role in inflammatory process, we focused on miR-34a, one of the miRNAs predicted to target *XIST*, and downregulated in CRPS patients responding poorly to ketamine. RESULTS: Our in vitro and in vivo models of acute inflammation and data from patients with CRPS showed that miR-34a can regulate *XIST* under inflammation directly, and through pro-inflammatory transcription factor Yin-Yang 1 (YY1). *XIST* was significantly upregulated in a subset of CRPS patients responding poorly to ketamine. CONCLUSION: Since dysregulation of XIST can result in genes escaping inactivation or reactivation in female cells, further investigations on the role of XIST in the predominance of chronic inflammatory and pain disorders in women is warranted.

Spinal inhibition of P2XR or p38 signaling disrupts hyperalgesic priming in male, but not female, mice.
Paige C, Maruthy GB, Mejia G, Dussor G, Price T.
Neuroscience. 2018 Jun 18. pii: S0306-4522(18)30423-8. doi: 10.1016/j.neuroscience.2018.06.012.

Recent studies have demonstrated sexual dimorphisms in the mechanisms contributing to the development of chronic pain. Here we tested the hypothesis that microglia might preferentially regulate hyperalgesic priming in male mice. We based this hypothesis on evidence that microglia preferentially contribute to neuropathic pain in male mice via ionotropic purinergic receptor (P2XR) or p38 mitogen-activated protein kinase (p38) signaling. Mice given a single-priming injection of the soluble human

interleukin-6 receptor (IL-6r) and then a second injection of prostaglandin E2 (PGE_2), which unmasks hyperalgesic priming, shows a significant increase in levels of activated microglia at 3 hours following the PGE_2 injection in both male and female mice. There was no change in microglia following PGE_2. Intrathecal injection of the P2X3/4 inhibitor TNP-ATP blocked the initial response to IL-6r in both males and females, but only blocked hyperalgesic priming in male mice. Intrathecally applied p38 inhibitor, skepinone, had no effect on the initial response to IL-6r but attenuated hyperalgesic priming in males only. Neither TNP-ATP nor skepinone could reverse priming once it had already been established in male mice suggesting that these pathways must be inhibited early in the development of hyperalgesic priming to have an effect. Our work is consistent with previous findings that P2XR and p38 inhibition can lead to male-specific effects on pain behaviors in mice. However, given that we did not observe microglial activation at time points where these drugs were effective, our work also questions whether these effects can be completely attributed to microglia.

Differential gene expression in trigeminal ganglia of male and female rates following chronic constriction of the infraorbital nerve.
Korczeniewska OA, Husain S, Khan J, Eliav E, Soteropoulos P, Benoliel R.
Eur J Pain. 2018 May;22(5):875-888. doi: 10.1002/ejp.1174.

BACKGROUND: The mechanisms underlying sex-based differences in pain and analgesia are poorly understood. In this study, we investigated gene expression changes in trigeminal ganglia (TG) of male and female rats exposed to infraorbital nerve chronic constriction injury (IoN-CCI). METHODS: Somatosensory assessments were performed prior to IoN-CCI and at selected time points postsurgery. Selected gene expression changes were examined with real-time quantitative polymerase chain reaction (RT-PCR) in ipsilateral TG at 21 days postsurgery. RESULTS: Rats exposed to IoN-CCI developed significant mechanical allodynia and hyperalgesia on days 19 and 21 postsurgery. During this period, females developed significantly more allodynia but not hyperalgesia compared to males. At 21 days postsurgery, expression levels of 44 of the 84 investigated pain-related genes in ipsilateral TG were significantly regulated relative to naïve rats in either sex. Csf1 and Cx3cr1 were up-regulated in both sexes, but the magnitude of regulation was significantly higher in females ($p = 0.02$ and $p = 0.001$, respectively). Htr1a and Scn9a were down-regulated in both sexes, but the down-regulation was significantly more pronounced in males ($p = 0.04$ and $p = 0.02$, respectively). Additionally, Cck, Il1a, Pla2g1b and Tnf genes were significantly regulated in females but not in males, and Chrna4 gene was significantly down-regulated in males but not in females. CONCLUSIONS: Our findings suggest sex-dependent gene regulation in response to nerve injury, which may contribute to sex dimorphism of trigeminal neuropathic pain. Further studies are needed to establish gene expression changes over time and correlate these with hormonal and other physiological parameters in male and female. SIGNIFICANCE: We present novel sex-specific transcriptional regulation in trigeminal ganglia that may contribute to male-/female-based differences in trigeminal neuropathic pain. These findings are expected to open new research horizons, particularly in male versus female targeted therapeutic regimens.

EPIDEMIOLOGY STUDIES

Persistent, consistent, and extensive: The trend of increasing pain prevalence in older Americans.
Zimmer Z, Zajacova A.
J Gerontol B Psychol Sci Soc Sci. 2018 Mar 20. doi: 10.1093/geronb/gbx162.

OBJECTIVES: Assess trends in pain prevalence from 1992 to 2014 among older U.S. adults and by major population subgroups, and test whether the trends can be explained by changes in population composition. METHODS: Health and Retirement Study data include information on any pain, pain intensity, and limitations in usual activities due to pain. Average annual percent change in prevalence is calculated for any and for 2 levels of pain-mild/moderate and nonlimiting and severe and/or limiting-across demographic and socioeconomic characteristics, and for those with and without specific chronic conditions. Generalized linear latent and mixed models examine trends adjusting for covariates. RESULTS: Linear and extensive increases in pain prevalence occurred across the total population and subgroups. The average annual percent increase was in the 2%-3% range depending upon age and sex.

Increases were consistent across subgroups, persistent over time, and not due to changes in population composition. Without increases in educational attainment over time, pain prevalence increases would be even higher. DISCUSSION: The increases in pain prevalence among older Americans are alarming and potentially of epidemic proportions. Population-health research must monitor and understand these worrisome trends.

Is there an association between diabetes and neck pain and lower back pain? Results of a population-based study.
Jimenez-Garcia R, Del Barrio JL, Hernandez-Barrera V, de Miguel-Diez J, Jimenez-Trujillo I, Martinez-Huedo MA, Lopez-de-Andres A.
J Pain Res. 2018 May 24;11:1005-1015. doi: 10.2147/JPR.S158877. eCollection 2018.

BACKGROUND: The objective of the study was to study the association between low back pain (LBP), neck pain (NP), and diabetes while controlling for many sociodemographic characteristics, comorbidities, and lifestyle variables. The study also aimed to identify which of these variables is independently associated with LBP and NP among diabetes sufferers. METHODS: A case-control study using data taken from the European Health Interview Surveys for Spain was conducted in 2009/2010 (n=22,188) and 2014 (n=22,842). We selected subjects ≥40 years of age. Diabetes status was self-reported. One non-diabetic control was matched by the year of survey, age, and sex for each diabetic case. The presence of LBP and NP was defined as the affirmative answer to both of the questions: "Have you suffered chronic LBP/NP over the last 12 months?" and "Has your physician confirmed the diagnosis?" Independent variables included demographic and socioeconomic characteristics, health status variables, lifestyles, and pain characteristics. RESULTS: The prevalence of NP (32.2% vs 26.8%) and LBP (37.1% vs 30.3%) was significantly higher among those suffering from diabetes. Multivariable analysis showed that diabetes was associated with a 1.19 (95% CI 1.04-1.36) and 1.20 (95% CI 1.06-1.35) higher risk of NP and LBP. Among diabetic subjects, being female, concomitant mental or respiratory disorders, being obese, and physically inactive are variables associated with suffering from these pains. Those suffering NP had 8 times higher risk of reporting LBP than those without NP and the same association is found among those suffering from LBP. CONCLUSION: The prevalence and intensity of NP and LBP are high among people with diabetes, affecting them significantly more than their age- and sex-matched non-diabetic controls. Specific preventive and educational strategies must be implemented to reduce the incidence, severity, and negative effect on the quality of NP and LBP among diabetic patients.

Increased pain sensitivity in migraine and tension-type headache coexistent with low back pain: A cross-sectional population study.
Ashina S, Lipton RB, Bendtsen L, Hajiyeva N, Buse DC, Lyngberg AC, Jensen R.
Eur J Pain. 2018 May;22(5):904-914. doi: 10.1002/ejp.1176.

BACKGROUND: Low back pain is common in the general population and in individuals with primary headaches. We assessed the relative frequency of self-reported back pain in persons with and without primary headaches and examined pain sensitivity. METHOD: A population of 796 individuals completed a headache interview based on ICHD criteria and provided data of interest in a self-administered questionnaire. Headache cases were classified into chronic (≥15) (CH) or episodic (<15 headache days/month) (EH). A total of 495 had a pericranial total tenderness score (TTS), and 494 had cephalic and extracephalic pressure pain thresholds (PPTs) assessed. RESULTS: Adjusted for age, gender, education and poor self-rated health, 1-year relative frequency of back pain was higher in individuals with CH (82.5%) and EH (80.1%) compared to no headache group (65.7%). In persons with back pain, TTS was higher in CH, (26.3 ± 12.1) than in EH, (18.5 ± 10.0; $p < 0.001$) and higher in both groups than in those with no headache, 10.8 ± 8.5 ($p < 0.001$ and $p < 0.001$, respectively). In persons with back pain, temporalis PPT were lower in CH, 169.3 ± 57.8, than in EH, 225.2 ± 98.1, and in no headache group, 244.3 ± 105.4 ($p = 0.02$ and $p = 0.01$, respectively). In persons with back pain, finger PPT were lower in CH, 237.1 ± 106.7, than in EH, 291.3 ± 141.3, or in no headache group, 304.3 ± 137.4 ($p = 0.02$ and $p < 0.001$, respectively). CONCLUSION: Back pain is highly frequent in individuals with CH, followed by EH and no headache. In persons with CH, back pain is associated with lower cephalic and extracephalic PPTs suggesting central sensitization may be a substrate or consequence of comorbidity. SIGNIFICANCE: We found that back pain has high relative frequency in individuals with CH followed EH

and no headache. Back pain is associated with low cephalic and extracephalic PPTs in individuals with CH. Central sensitization may be a substrate or consequence of this comorbidity of back pain and CH.

Prevalence of comorbid diseases in patients with fibromyalgia: A retrospective cross-sectional study.
Bilge U, Sari YE, Balcioglu H, Yasar Bilger NS, Kasifoglu T, Kayhan M, Unloglu I.
J Pak Med Assoc. 2018 May;68(5):729-732.

OBJECTIVE: To examine the prevalence of comorbid conditions in patients diagnosed with fibromyalgia. METHODS: The retrospective cross-sectional study was conducted at Eskisehir Osmangazi University, Eskisehir, Turkey, and comprised data of fibromyalgia patients aged 18 years or more admitted between January 1, 2012 and August 15, 2016. Hospital's database was investigated using the International Classification of Diseases, 10th Revision codes to identify fibromyalgia cases and predetermined comorbid conditions. SPSS 21 was used for data analysis. RESULTS: Of 509 patients, 51(10%) were males and 458(90%) were females with an overall mean age of 50.24±12.32 years. Of the total, 345(67.8%) patients had at least one comorbid disease, while 164 (32.2%) had no comorbid disease. The most prevalent condition was cardiovascular diseases in 187(36.7%) patients followed by endocrine diseases in 157(30.8%). CONCLUSIONS: Fibromyalgia is a disease that is seen to be increasing in frequency in recent years. It is useful to evaluate fibromyalgia patients with their comorbid conditions on their follow-up.

The relationship with restless legs syndrome, fibromyalgia, and depressive symptoms in migraine patients.
Akdag Uzun Z, Kurt S, Karaer Unaldi H.
Neurol Sci. 2018 May 18. doi: 10.1007/s10072-018-3438-7.

OBJECTIVE: In this study, we aimed to investigate restless legs syndrome, depression, frequency of fibromyalgia and possible causes of its frequencies, and the relationships among these synergies and migraine's prodrome, aura, pain, and postdrome symptoms in patients with migraine. SUBJECTS AND METHODS: The study group included 200 patients previously or recently diagnosed with definite migraine and according to International Headache Society criteria and 200 healthy volunteers. All subjects underwent a medical interview to confirm restless legs syndrome and fibromyalgia, and they were asked to complete Beck Depression and Anxiety Inventory and "severity of restless legs syndrome inventory." RESULTS: The frequencies of depressive symptoms and fibromyalgia in the patients with migraine were higher than those of the control group. The mean age of the migraine patients with restless legs syndrome was also higher, and this group had migraine headache for a longer time. There was a statistically significant difference with regard to only generalized anxiety and traveler's distress, which were features of the migraine, between migraine patients with and without restless legs syndrome. Restless legs syndrome was more common in migraine patients with and without aura and in those with nonspecific white matter lesions in the cranial MRI. CONCLUSIONS: In our study, the greater frequency of restless legs syndrome, depressive symptoms, and fibromyalgia in the patients with migraine supports the role of dopamine, which is common to all three disorders. Interviews focused on these problems among migraine patients may help to decide on the best available treatment modality.

Fatigue - a symptom in endometriosis.
Ramin-Wright A, Kohl Schwartz AS, Geraedts K, Rauchfuss M, Wolfler MM, Haeberlin F, von Orelli S, Eberhard M, Imthurn B, Imesch P, Fink D, Leeners B.
Hum Reprod. 2018 Jun 26. doi: 10.1093/humrep/dey115. [Epub ahead of print]

STUDY QUESTION: Is fatigue a frequent symptom of endometriosis? SUMMARY ANSWER: Fatigue is an underestimated symptom of endometriosis as it affects the majority of women with endometriosis, but it is not widely discussed in literature. WHAT IS KNOWN ALREADY: Fatigue can be a symptom of endometriosis causing major distress impacting the daily activities and quality of life of women with endometriosis. However, few studies with large sample sizes have investigated fatigue as a symptom of endometriosis. STUDY DESIGN, SIZE, DURATION: The study was designed as a multi-center matched case-control study. Recruitment took place at hospitals and private practices in Switzerland, Germany and Austria between 2010 and 2016. Data was collected from 1120 women, 560 of them

with endometriosis. The women with endometriosis were matched to 560 control women in regard to age ±3 years and ethnic background. PARTICIPANTS/MATERIALS, SETTING, METHODS: Diagnosis of women with endometriosis had to be surgically and histologically confirmed. Surgical exclusion or absence of any endometriosis-identifying symptoms was required for control subjects. Materials included surgical and histological reports as well as data retrieved from a self-administered questionnaire. This study focused on the symptom fatigue in endometriosis. Relationships of variables were established by regression analysis and associations were quantified as odds ratios. MAIN RESULTS AND THE ROLE OF CHANCE: Frequent fatigue was experienced by a majority of women diagnosed with endometriosis (50.7% versus 22.4% in control women, P < 0.001). Fatigue in endometriosis was associated with insomnia (OR: 7.31, CI: 4.62-11.56, P < 0.001), depression (OR: 4.45, CI: 2.76-7.19, P < 0.001), pain (OR: 2.22, CI: 1.52-3.23, P < 0.001), and occupational stress (OR: 1.45, CI: 1.02-2.07, P = 0.037), but was independent of age, time since first diagnosis and stage of the disease. LIMITATIONS, REASONS FOR CAUTION: Women with symptomatic endometriosis cannot be excluded in the control group which would lead to underestimation of our results. The study's design allows no evaluation of causal effects. WIDER IMPLICATIONS OF THE FINDINGS: As fatigue is experienced by numerous women with endometriosis, it needs to be addressed in the discussion of management and treatment of the disease. In addition to treating endometriosis, it would be beneficial to reduce insomnia, depression, pain and occupational stress in order to better manage fatigue. STUDY FUNDING/COMPETING INTERESTS: There was no additional funding received for this study and no conflict of interest.

Painful musculoskeletal disorders and depression among working aged migraineurs.
Sumelahti ML, Mattila K, Sumanen M.
Acta Neurol Scand. 2018 Jul;138(1):93-98. doi: 10.1111/ane.12919.

OBJECTIVE: Musculoskeletal disorders and depression are common among migraineurs. The aim of our study was to evaluate the occurrence of these disorders among working aged migraineurs. MATERIAL AND METHODS: The risk for fibromyalgia, rheumatoid arthritis (RA), osteoarthrosis (OA), sciatic syndrome, and the occurrence of depression was studied among cases who reported about these conditions and migraine in working aged Finnish population in The Health and Social Support Study (HeSSup) based on postal questionnaire in 2012. Group differences were tested by chi-square test. Odds ratios (ORs with 95% CI) adjusted for age, gender, education level and depression were calculated with logistic regression analysis. RESULTS: Total of 1505 migraineurs (13%) and 8092 controls were included among the 11 596 responders in 2012. Age and gender adjusted ORs, 2.37 (95% CI 1.81-3.09) for fibromyalgia, 1.46 (1.10-1.95) for RA, 1.58 (1.38-1.80) for OA, and 2.09 (1.84-2.37) for sciatic syndrome, were significant. At least moderate depression was more common among migraineurs (7.3%) than among controls (3.4%) (P < .001). CONCLUSION: Recognition of comorbid musculoskeletal disorders and mood disorders among migraineurs needs targeted outreach in working aged population. The acute and preventive treatments to control for neuronal sensitization in migraine and comorbid pain disorders may benefit of individual treatment plan and tailored use of antidepressants.

Prevalence and clinical characteristics of headache in juvenile myoclonic epilepsy: experience from a tertiary epilepsy center.
Dedei Daryan M, Guveli BT, Baslo SA, Mulhan K, Sari H, Balcik ZE, Atakli D.
Neurol Sci. 2018 Mar;39(3):519-525. doi: 10.1007/s10072-017-3232-y.

The comorbidity of headache and epilepsy is often seen in neurological practice. The objective of this study was to assess the prevalence, types of, and risk factors for headache in juvenile myoclonic epilepsy (JME). We assessed a total of 200 patients and 100 healthy controls in our study. Headache was classified in participants using a self-administered questionnaire. Demographical, clinical features and headache characteristics were recorded. Seizure and headache temporal profiles were noted. Headache was present in 111 (56%) patients and 50 (50%) healthy participants. From these patients, 47 (42.3%) JME patients had migraine [30 (27%) migraine without aura (MO), 17 (15.3%) migraine with aura (MA)], 52 (46.8%) had tension type headache (TTH), 4 (3.6%) had both migraine and TTH, and 8 (7.2%) had other non-primary headaches. In the healthy control group, migraine was detected in 16 (32%) subjects, TTH in 33 (66%), both migraine and TTH in 1 (2%) subject. A positive migraine family history and symptom relief with sleep were more frequent in JME patients (p=0.01). Headache was classified as inter-ictal in 82 (79.6%) patients and peri-ictal in 21

(20.4%) patients. In conclusion, the present study revealed that headache frequency was not significantly different between JME patients and healthy controls (p>0.05). However, migraine frequency was higher in JME patients than healthy controls. Some migraine and TTH characteristics were different in between groups. We suggest that our results support both genetic relationship and shared underlying hypothetical pathopysiological mechanisms between JME and headache, especially migraine.

Comorbidity between pain and mental illness - Evidence of a bidirectional relationship.
Bondesson E, Larrosa Pardo F, Stigmar K, Ringqvist A, Petersson IF, Joud A, Schelin MEC.
Eur J Pain. 2018 Mar 25. doi: 10.1002/ejp.1218.

BACKGROUND: Pain from various locations in the body and mental illness are common and the comorbidity between the two is well-known although the temporal relationship remains to be determined. Our aim was to follow patients over time to study if pain (here dorsalgia/abdominal pain) or fibromyalgia lead to an increased risk of developing mental illness (here depression/anxiety) and/or the reverse, that is whether patients with mental illness have an increased risk to develop pain or fibromyalgia, compared to the rest of the population. METHODS: This prospective cohort study used the Skåne Healthcare Register, covering all care in the region of Skåne, southern Sweden (population ~1.3 million). The cohort included healthcare consultations in primary care, outpatient specialized care and inpatient care between 2007 and 2016 for all patients without prior registered diagnosis of mental illness or pain, aged 18 or older (n = 504,365). RESULTS: The incidence rate ratio (IRR) for developing mental illness after pain was 2.18 (95% CI = 2.14-2.22) compared to without pain. IRR for developing pain after mental illness was 2.02 (95% CI = 1.98-2.06) compared to without mental illness. Corresponding IRR for developing mental illness after fibromyalgia was 4.05 (95% CI = 3.58-4.59) and for developing fibromyalgia after mental illness 5.54 (95% CI = 4.99-6.16). CONCLUSIONS: This study shows a bidirectional influence of similar magnitude of pain and mental illness, respectively. In monitoring patients with pain or mental illness, a focus on both conditions is thus important to develop appropriate, targeted interventions and may increase the likelihood of improved outcomes. SIGNIFICANCE: We followed a population-based cohort over a period of 10 years, including incident cases of both exposure and outcome and found a bidirectional relationship between pain and mental illness. Clinicians need to pay attention on both conditions, in patients seeking care due to mental illness or pain.

A population-based examination of the co-occurrence and functional correlates of chronic pain and generalized anxiety disorder.
Csupak B, Sommer JL, Jacobsohn E, El-Gabalawy R.
J Anxiety Disord. 2018 May;56:74-80. doi: 10.1016/j.janxdis.2018.04.005.

OBJECTIVES: This study aimed to: 1) Establish the prevalence of co-occurring chronic pain conditions (i.e., arthritis, back pain, and migraines) and generalized anxiety disorder (GAD), and 2) Examine levels of pain, severity, disability, and work absenteeism among comorbid chronic pain conditions and GAD. METHODS: Data were analyzed from the 2012 Canadian Community Health Survey-Mental Health (CCHS-MH; N=25,113). Chi-square analyses assessed whether significant differences existed in pain severity in those with comorbid chronic pain and GAD versus pain conditions alone. Multivariable regressions examined the association between comorbid chronic pain and GAD with functional outcomes. RESULTS: The weighted prevalence of GAD among those with chronic migraines, arthritis and back pain was 6.9%, 4.4%, and 6.1% respectively, compared to 2.6% among the entire sample. Severity of pain was increased among those with comorbid chronic pain and GAD compared with chronic pain conditions alone. Migraine was the only pain condition that was significantly associated with disability in our most stringent adjustment model. After controlling for other psychiatric disorders, comorbid GAD and chronic pain was not associated with work absenteeism. CONCLUSION: Chronic pain is common among the Canadian population and is associated with substantial disability. Results demonstrated that GAD is prevalent among chronic pain conditions, and comorbidity is associated with greater pain severity. GAD in the context of migraines, in particular, may represent an important treatment target to reduce disability.

Back pain and co-occurring conditions: Findings from a nationally representative sample.

Badley EM, Millstone DB, Perruccio AV.
Spine (Phila Pa 1976). 2018 Feb 16. doi: 10.1097/BRS.0000000000002590.

STUDY DESIGN: Cross-sectional population-level health survey. OBJECTIVE: To describe the frequency of co-occurring conditions with back pain; to identify risk factors for back pain controlling for co-occurring conditions; and to examine the association between back pain and individual co-occurring conditions. SUMMARY OF BACKGROUND DATA: Back pain shares risk factors with a range of other conditions. Most studies have considered risk factors for back pain without taking into account the potential influence of co-occurring conditions. METHODS: Analysis of the 2013 Canadian Community Health Survey (n=61,854, age, 15 years or older). Back pain status and co-occurring conditions were determined from questions about long term health conditions diagnosed by a health profession. Multivariable log-Poisson regression analysis was used to assess the adjusted association of back pain with demographic and lifestyle characteristics and co-occurring conditions. RESULTS: The population prevalence of reported back pain was 19.3%. Most (71%) reported at least one co-occurring condition. Most frequently reported were arthritis (35%), high blood pressure (26%), migraine (18%), and mood disorders (14%). Following the addition of co-occurring condition count to the regression model, being female and being overweight/obese were no longer significantly associated with back pain, and the associations with ages 45-54 years and older, low income, smoking and being physical inactive were significantly attenuated. The highest prevalence ratio, 3.32 (95% CI: 3.06-3.59), was for 3+ co-occurring conditions. In multi-variable regression all but a few individual chronic conditions remained significant associated with back pain. CONCLUSIONS: Established risk factors for back pain may be largely a reflection of shared risk factors with co-occurring conditions. The high frequency of co-occurring conditions likely reflects diverse mechanisms related to heterogeneity of back pain. The extent of association of co-occurring conditions with back pain has implications for clinical management and need for further research to characterise sub-groups. LEVEL OF EVIDENCE: 2.

Comorbidity between idiopathic overactive bladder and chronic migraine.
Ramos ML, Garcia-Cabo C, Leira R, Dominguez C, Pozo-Rosich P, Vila C, Lainez MJ, Pascual J.
Cephalgia. 2018 Mar;38(3):581-584. doi: 10.1177/0333102417690127.

Objective: We tested whether overactive bladder (OAB) and chronic migraine (CM) could be comorbid. Patients and methods: CM women, aged 40-69 years, answered a validated OAB questionnaire. Prevalence data were compared with those reported in our country in the general population (GP) using the same questionnaire. Results: We interviewed 231 CM women. Eighty-four met OAB criteria. OAB prevalence in CM patients was significantly higher than that found in the GP (36.4% vs. 21.8% in the GP; p=0.0001). There were 34 CM women aged 40-49 years (34.3% vs. 15.2%; p=0.001), 35 aged 50-59 years (38.9% vs. 21.7%; p=0.004) and 15 aged 60-69 years (35.7% vs. 24.5%; p=0.15) meeting OAB criteria. Seventy-seven (33% vs. 9.9%; p=0.002) needed more than eight micturitions/24 hours, 61 (26.4% vs. 8.1%; p=0.002) experienced nocturia and 43 (18.6% vs. 8.1%; p=0.001) urinary incontinence. Conclusion: In this exploratory study, at least in women, OAB and CM are comorbid, which suggests shared mechanisms.

Prevalence of migraines in adolescents with endometriosis.
Miller JA, Missmer SA, Vitonis AF, Sarda V, Laufer MR, DiVasta AD.
Fertil Steril. 2018 Apr;109(4):685-690. doi: 10.1016/j.fertnstert.2017.12.016.

OBJECTIVE: To determine the prevalence and experience of migraines in adolescents with surgically confirmed endometriosis compared with those without endometriosis. DESIGN: Cross-sectional study conducted within The Women's Health Study: From Adolescence to Adulthood-an ongoing longitudinal cohort. SETTING: Boston Center for Endometriosis. PATIENT(S): Adolescent females enrolled November 2012 through November 2016. The case group included adolescents surgically diagnosed with endometriosis. The control group included adolescents without endometriosis, recruited from the local community and clinics. INTERVENTIONS: Not available. MAIN OUTCOME MEASURES: An extensive online health questionnaire regarding medical history, lifestyle, medication use, anthropometrics, and symptom experience and treatments. Migraine diagnosis was self-reported. Migraine pain and noncyclic pelvic pain severity were rated using an 11-point numerical rating scale. Cyclic pelvic pain was categorized. RESULTS: Adolescents with endometriosis were more likely to experience migraines (69.3%)

than those without endometriosis (30.7%) (multivariable odds ratio = 4.77, 95% confidence interval 2.53, 9.02). For each 1-point increase in the migraine numerical rating scale, the odds of endometriosis increased by 22% (multivariable odds ratio = 1.22, 95% confidence interval 1.03, 1.44; P(trend)= .02). Among those with endometriosis, age of menarche was associated inversely with the odds of migraines. Participants with endometriosis and migraines have more dysmenorrhea than those without migraines. CONCLUSION(S): Adolescents with endometriosis are more likely to experience migraines than adolescents without endometriosis. A linear relationship exists between migraine pain severity and the odds of endometriosis, suggesting heightened pain sensitivity for adolescents with endometriosis. Due to the strong correlation, patients who present with either condition should be screened for comorbidity to maximize the benefits of care.

Association of risk factors with temporomandibular disorders in the Northern Finland Birth Cohort 1966.
Jussila P, Knuutila J, Salmela S, Napankangas R, Pakkila J, Pirttiniemi P, Raustia A.
Acta Odontol Scand. Jun 19:1-5. doi: 10.1080/00016357.2018.1479769.

OBJECTIVE: To investigate the association between risk factors and pain-related symptoms and clinical signs of temporomandibular disorders (TMD) in Northern Finland Birth Cohort (NFBC) 1966. MATERIAL AND METHODS: A total of 1962 subjects (1050 women, 912 men) attended the follow-up study. The questionnaires included the subjects' background information concerning living conditions and general health, socioeconomic factors, and dental health. The clinical examination was performed using the modified protocol of Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) presented at the International Association for Dental Research (IADR) Conference in 2010. Cross-tabulation, a chi-square test and Fisher's exact test were used to analyze differences between groups.
RESULTS: Female gender showed statistically significant association with symptoms and signs of TMD, while marital status, living conditions, and socioeconomic group showed no association. A strong association was found between self-reported health condition as well as general health problems [i.e. depression, migraine, fibromyalgia (FM), gastrointestinal diseases] and TMD pain-related symptoms and pain on palpation in the masticatory muscles and TMJs. CONCLUSION: In conclusion, general health problems and female gender had a strong association with pain-related symptoms and clinical signs of TMD. These findings are important to take into account when diagnosing and treating TMD patients. Conversely to earlier presented results, no statistically significant association was shown here between marital status, living conditions or socioeconomic group and pain-related symptoms and clinical signs of TMD.

Incidence of irritable bowel syndrome and chronic fatigue following GI infection: a population-level study using routinely collected claims data.
Donnachie E, Schneider A, Mehring M, Enck P.
Gut. 2018 Jun;67(6):1078-1086. doi: 10.1136/gutjnl-2017-313713.

OBJECTIVES: To investigate the occurrence of postinfectious IBS in routine outpatient care, comparing different types of GI infection and its interaction with psychosomatic comorbidity. DESIGN: Retrospective cohort study using routinely collected claims data covering statutorily insured patients in Bavaria, Germany. Cases were defined as patients without prior record of functional intestinal disorder with a first-time diagnosis of GI infection between January 2005 and December 2013 and classed according to the type of infection. Each case was matched by age, sex and district of residence to a patient without history of GI infection. Prior psychological disorder (depression, anxiety or stress reaction disorder) was assessed in the 2 years prior to inclusion. Proportional hazards regression models were used to estimate the HRs for GI infection and psychological disorder. Chronic fatigue syndrome (CFS) was assessed as a comparator outcome. RESULTS: A total of 508 278 patients with first diagnosis of GI infection were identified, resulting in a matched cohort of 1 016 556 patients. All infection types were associated with an increased risk of IBS (HR: 2.19-4.25) and CFS (HR 1.35-1.82). Prior psychological disorder was a distinct risk factor for IBS (HR: 1.73) and CFS (HR: 2.08). Female sex was a further risk factor for both conditions. CONCLUSION: Psychological disorder and GI infections are distinct risk factors for IBS. The high incidence of non-specific GI infection suggests that postinfectious IBS is a common clinical occurrence in primary care. Chronic fatigue is a further significant sequela of GI infection.

Prevalence of irritable bowel syndrome and chronic fatigue 10 years after Giardia infection.
Litleskare S, Rortveit G, Eide GE, Hanevik K, Langeland N, Wensaas KA.
Clin Gastroenterol Hepatol. 2018 Jul;16(7):1064-1072.e4. doi: 10.1016/j.cgh.2018.01.022

BACKGROUND & AIMS: Irritable bowel syndrome (IBS) is a complication that can follow gastrointestinal infection, but it is not clear if patients also develop chronic fatigue. We investigated the prevalence and odds ratio of IBS and chronic fatigue 10 years after an outbreak of Giardia lamblia, compared with a control cohort, and changes in prevalence over time. METHODS: We performed a prospective follow-up study of 1252 laboratory-confirmed cases of giardiasis (exposed), which developed in Bergen, Norway in 2004. Statistics Norway provided us with information from 2504 unexposed individuals from Bergen, matched by age and sex (controls). Questionnaires were mailed to participants 3, 6, and 10 years after the outbreak. Results from the 3- and 6-year follow-up analyses have been published previously. We report the 10-year data and changes in prevalence among time points, determined by logistic regression using generalized estimating equations. RESULTS: The prevalence of IBS 10 years after the outbreak was 43% (n = 248) among 576 exposed individuals and 14% (n = 94) among 685 controls (adjusted odds ratio for development of IBS in exposed individuals, 4.74; 95% CI, 3.61-6.23). At this time point, the prevalence of chronic fatigue was 26% (n = 153) among 587 exposed individuals and 11% (n = 73) among 692 controls (adjusted odds ratio, 3.01; 95% CI, 2.22-4.08). The prevalence of IBS among exposed persons did not change significantly from 6 years after infection (40%) to 10 years after infection (43%; adjusted odds ratio for the change 1.03; 95% CI, 0.87-1.22). However, the prevalence of chronic fatigue decreased from 31% at 6 years after infection to 26% at 10 years after infection (adjusted odds ratio for the change 0.74; 95% CI, 0.61-0.90). CONCLUSION: The prevalence of IBS did not change significantly from 6 years after an outbreak of Giardia lamblia infection in Norway to 10 years after. However, the prevalence of chronic fatigue decreased significantly from 6 to 10 years afterward. IBS and chronic fatigue were still associated with giardiasis 10 years after the outbreak.

Gender differences in pain experience and treatment after motor vehicle collisions: A secondary analysis of the CRASH Injury Study.
Madsen TE, McLean S, Zhai W, Linnstaedt S, Kurz MC, Swor R, Hendry P, Peak D, Lewandowski C, Pearson C, O'Neil B, Datner E, Lee D, Beaudoin F.
Clin Ther. 2018 Feb;40(2):204-213.e2. doi: 10.1016/j.clinthera.2017.12.014.

PURPOSE: Little is known about gender differences in the treatment of pain after motor vehicle collisions (MVCs) in an emergency department (ED). We aimed to describe gender differences in pain experiences and treatment, specifically the use of opioids and benzodiazepines after ED discharge, for MVC-related pain. METHODS: This was a secondary analysis of previously collected data from the CRASH Injury studies. We included patients who were seen and discharged from an ED after an MVC and who were enrolled in 1 of 2 multicenter longitudinal prospective cohort studies (1 black/non-Hispanic and 1 white/non-Hispanic). First, we compared the experience of pain as defined by self-reported moderate-to-severe axial pain, widespread pain, number of somatic symptoms, pain catastrophizing, and peritraumatic distress between women and men using bivariate analyses. We then determined whether there were gender differences in the receipt of prescription medications for post-MVC pain symptoms (opioids and benzodiazepines) using multivariate logistic regression adjusting for demographic characteristics, pain, and collision characteristics. FINDINGS: In total, 1878 patients were included: 61.4% were women. More women reported severe symptoms on the pain catastrophizing scale (36.8% vs 31.0%; P = 0.032) and peritraumatic distress following the MVC (59.7% vs 42.5%; P < 0.001), and women reported more somatic symptoms than men (median, 3.9; interquartile range, 3.7-4.0 vs median, 3.3; interquartile range, 3.1-3.5; P < 0.001). Unadjusted, similar proportions of women and men were given opioids (29.2% vs 29.7%; P = 0.84). After adjusting for covariates, women and men remained equally likely to receive a prescription for opioids (relative risk = 0.83; 95% confidence interval, 0.58-1.19). Women were less likely than men to receive a benzodiazepine at discharge from an ED (relative risk = 0.53; 95% confidence interval, 0.32-0.88). IMPLICATIONS: In a large, multicenter study of ED patients treated for MVC, there were gender differences in the acute psychological response to MVC with women reporting more psychological and somatic symptoms. Women and men were equally likely to receive opioid prescriptions at discharge. Future research should investigate potential gender-specific interventions to reduce both posttraumatic distress and the risk of developing negative long-term

outcomes like chronic pain.

Migraine and associated comorbidities are three times more frequent in children with ADHD and their mothers.
Kutuk MO, Tufan AE, Guler G, Yalin OO, Altintas E, Bag HG, Uluduz D, Toros F, Aytan N, Kutuk O, Ozge A.
Brain Dev. 2018 Jun 16. pii: S0387-7604(18)30253-5. doi: 10.1016/j.braindev.2018.06.001. [Epub ahead of print]

OBJECTIVE: Attention deficit and hyperactivity disorder (ADHD) is a neuro-developmental disorder related to internalizing and externalizing disorders as well as somatic complaints and disorders. This study was conducted to evaluate the prevalence of headache subtypes, epilepsy, atopic disorders, motion sickness and recurrent abdominal pain among children and adolescents with ADHD and their parents. METHODS: In a multi-center, cross-sectional, familial association study using case-control design, treatment naïve children and adolescents between 6 and 18 years of age diagnosed with ADHD accroding to the DSM-5 criteria as well as age- and gender-matched healthy controls and their parents were evaluated by a neurologist and analyzed accordingly. RESULTS: 117 children and adolescents with ADHD and 111 controls were included. Headache disorder diagnosis was common for both patients and healthy controls (59.0% vs. 37.8%), with a significantly elevated rate in the ADHD group (p=0.002). Migraine was found in 26% of ADHD patients and 9.9% of healthy controls. Tension headache was found in 32.4% of ADHD patients and 27.9% of healthy controls. Headache diagnosis was also found to be significantly more common in mothers of children with ADHD than control group mothers (90.5% vs. 36.6%, p=0.001). CONCLUSION: Headache diagnoses and specifically migraines were significantly more common among children with ADHD and their mothers, while recurrent abdominal pain was elevated in both parents and ADHD patients. Migraine is an important part of ADHD comorbidity, not only for children but also for mothers. Motion sickness may be reduced among families of ADHD probands.

CLINICAL STUDIES

The X-Y factor: females and males with urological chronic pelvic pain syndrome present distinct clinical phenotypes.
Hosier GW, Doiron RC, Tolls V, Nickel JC.
Can Urol Assoc J. 2018 Jun;12(6):E270-E275. doi: 10.5489/cuaj.4798.

INTRODUCTION: Urological chronic pelvic pain syndrome (UCPPS) in females is often attributed to the bladder (interstitial cystitis/ bladder pain syndrome), while UCPPS in males is often attributed to the prostate (chronic prostatitis/chronic pelvic pain syndrome). However, there is increasing awareness that bladder pain plays a role in both males and females and the degree of overlap of clinical characteristics in males and females with UCPPS is not well known. Our objective was to compare clinical phenotypes of females and males with UCPPS. METHODS: We conducted a retrospective analysis of prospectively collected data from a single-centre patient population presenting between 1998 and 2016 to our UCPPS clinic. Demographics, symptom scores, pain scales, retrospectively described clinical UPOINT (urinary, psychosocial, organ-specific, infection, neurogenic, and tenderness) scoring, and presence of comorbid medical conditions were compared between females and males using comparative analyses. RESULTS: We identified 2007 subjects (1523 males, 484 females) with UCPPS. Females had increased prevalence of irritable bowel syndrome (25% vs. 11.2%), chronic fatigue syndrome (13.6% vs. 1.6%), fibromyalgia (16.9% vs. 1.6%), drug allergies (56.6% vs. 13.5%), diabetes (20.2% vs. 3.9%), depression (31% vs. 18.4%), and alcohol use (44.2% vs. 10.8%) compared to males with UCPPS (all p<0.001). In respect to UPOINT domains, females had a higher "total" (3.2 vs. 2.4), "urinary" (92.8% vs. 67.6%), "organ-specific" (90.1% vs. 51.4%), and "neurogenic" (44.7% vs. 30%) prevalence compared to males (all p<0.001). CONCLUSIONS: Females with UCPPS have greater prevalence of systemic disorders/symptoms and worse urinary symptoms than males with UCPPS. These findings demonstrate that females and males with UCPPS have distinct and different clinical phenotypes.

The role of genetic polymorphisms in chronic pain patients.
Knezevic NN, Tverdohleb T, Knezevic I, Candido KD.
Int J Mol Sci. 2018 Jun 8;19(6). pii: E1707. doi: 10.3390/ijms19061707.

It is estimated that the total annual financial cost for pain management in the U.S. exceeds 100 billion dollars. However, when indirect costs are included, such as functional disability and reduction in working hours, the cost can reach more than 300 billion dollars. In chronic pain patients, the role of pharmacogenetics is determined by genetic effects on various pain types, as well as the genetic effect on drug safety and efficacy. In this review article, we discuss genetic polymorphisms present in different types of chronic pain, such as fibromyalgia, low back pain, migraine, painful peripheral diabetic neuropathy and trigeminal neuralgia. Furthermore, we discuss the role of CYP450 enzymes involved in metabolism of drugs, which have been used for treatment of chronic pain (amitriptyline, duloxetine, opioids, etc.). We also discuss how pharmacogenetics can be applied towards improving drug efficacy, shortening the time required to achieve therapeutic outcomes, reducing risks of side effects, and reducing medical costs and reliance upon polypharmacy.

Clinical course and prognostic factors across different musculoskeletal pain sites: A secondary analysis of individual patient data from randomized clinical trials.
Green DJ, Lewis M, Mansell G, Artus M, Dziedzic KS, Hay EM, Foster NE, van der Windt DA.
Eur J Pain. 2018 Jul;22(6):1057-1070. doi: 10.1002/ejp.1190.

BACKGROUND: Previous research has identified similar prognostic factors in patients with musculoskeletal (MSK) conditions regardless of pain presentation, generating opportunities for management based on prognosis rather than specific pain presentation. METHODS: Data from seven RCTs (2483 participants) evaluating a range of primary care interventions for different MSK pain conditions were used to investigate the course of symptoms and explore similarities and differences in predictors of outcome. The value of pain site for predicting changes in pain and function was investigated and compared with that of age, gender, social class, pain duration, widespread pain and level of anxiety/depression. RESULTS: Over the initial three months of follow-up, changes in mean pain intensity reflected an improvement, with little change occurring after this period. Participants with knee pain due to osteoarthritis (OA) showed poorer long-term outcome (mean difference in pain reduction at 12 months -1.85, 95% CI -2.12 to -1.57, compared to low back pain). Increasing age, manual work, longer pain duration, widespread pain and increasing anxiety/depression scores were significantly associated with poorer outcome regardless of pain site. Testing of interactions showed some variation between pain sites, particularly for knee OA, where age, manual work and pain duration were most strongly associated with outcome. CONCLUSIONS: Despite some differences in prognostic factors for trial participants with knee OA who were older and had more chronic conditions, similarity of outcome predictors across regional MSK pain sites provides evidence to support targeting of treatment based on prognostic factors rather than site of pain. SIGNIFICANCE: Individual patient data analysis of trials across different regional musculoskeletal pain sites was used to evaluate course and prognostic factors associated with pain and disability. Overall, similarity of outcome predictors across these different pain sites supports targeting of treatment based on prognostic factors rather than pain site alone.

A new clinical model for facilitating the development of pattern recognition skills in clinical pain assessment.
Waslton DM, Elliott JM.
Musculoskelet Sci Pract. 2018 Aug;36:17-24. doi: 10.1016/j.msksp.2018.03.006.

Common, enigmatic musculoskeletal conditions such as whiplash-associated disorder, myofascial pain syndrome, low back pain, headache, fibromyalgia, osteoarthritis, and rotator cuff pathology, account for significant social, economic, and personal burdens on a global scale. Despite their primacy (and shared sequelae) there remains a paucity of available and effective management options for patients with both acute and chronic conditions. Establishing an accurate prognostic or diagnostic profile on a patient-by-patient basis can challenge the insight of both novice and expert clinicians. Questions remain on how and when to choose the right tool(s), at the right time(s), for the right patient(s), for the right problem(s). The aim of this paper is to introduce a new clinical reasoning framework that is simple in presentation but allows interpretation of complex clinical patterns, and is adaptable across patient populations with acute or chronic, traumatic or non-traumatic pain. The concepts of clinical phenotyping (e.g. identifying observable characteristics of an individual resulting from the interaction

of his/her genotype and their environment) and triangulation serve as the foundation for this framework. Based on our own clinical and research programs, we present these concepts using two patient cases; a) whiplash-associated disorder (WAD) following a motor vehicle collision and b) mechanical low back pain.

Potential mechanisms underlying centralized pain and emerging therapeutic interventions.
Eller-Smith OC, Nicol AL, Christianson JA.
Front Cell Neurosci. 2018 Feb 13;12:35. doi: 10.3389/fncel.2018.00035. eCollection 2018.

Centralized pain syndromes are associated with changes within the central nervous system that amplify peripheral input and/or generate the perception of pain in the absence of a noxious stimulus. Examples of idiopathic functional disorders that are often categorized as centralized pain syndromes include fibromyalgia, chronic pelvic pain syndromes, migraine, and temporomandibular disorder. Patients often suffer from widespread pain, associated with more than one specific syndrome, and report fatigue, mood and sleep disturbances, and poor quality of life. The high degree of symptom comorbidity and a lack of definitive underlying etiology make these syndromes notoriously difficult to treat. The main purpose of this review article is to discuss potential mechanisms of centrally-driven pain amplification and how they may contribute to increased comorbidity, poorer pain outcomes, and decreased quality of life in patients diagnosed with centralized pain syndromes, as well as discuss emerging non-pharmacological therapies that improve symptomology associated with these syndromes. Abnormal regulation and output of the hypothalamic-pituitary-adrenal (HPA) axis is commonly associated with centralized pain disorders. The HPA axis is the primary stress response system and its activation results in downstream production of cortisol and a dampening of the immune response. Patients with centralized pain syndromes often present with hyper- or hypocortisolism and evidence of altered downstream signaling from the HPA axis including increased Mast cell (MC) infiltration and activation, which can lead to sensitization of nearby nociceptive afferents. Increased peripheral input via nociceptor activation can lead to "hyperalgesic priming" and/or "wind-up" and eventually to central sensitization through long term potentiation in the central nervous system. Other evidence of central modifications has been observed through brain imaging studies of functional connectivity and magnetic resonance spectroscopy and are shown to contribute to the widespreadness of pain and poor mood in patients with fibromyalgia and chronic urological pain. Non-pharmacological therapeutics, including exercise and cognitive behavioral therapy (CBT), have shown great promise in treating symptoms of centralized pain.

Measurement properties of the central sensitization inventory: A systematic review.
Scerbo T, Colasurdo J, Dunn S, Unger J, Nijs J, Cook C.
Pain Pract. 2018 Apr;18(4):544-554. doi: 10.1111/papr.12636.

BACKGROUND AND OBJECTIVE: Central sensitization (CS) is a phenomenon associated with several medical diagnoses, including postcancer pain, low back pain, osteoarthritis, whiplash, and fibromyalgia. CS involves an amplification of neural signaling within the central nervous system that results in pain hypersensitivity. The purpose of this systematic review was to gather published studies of a widely used outcome measure (the Central Sensitization Inventory [CSI]), determine the quality of evidence these publications reported, and examine the measurement properties of the CSI. DATABASES AND DATA TREATMENT: Four databases were searched for publications from 2011 (when the CSI was developed) to July 2017. The Consensus-Based Standards for the Selection of Health Measurement Instruments (COSMIN) checklist was applied to evaluate methodological quality and risk of bias. In instances when COSMIN did not offer a scoring system for measurement properties, qualitative analyses were performed. RESULTS: Fourteen studies met inclusion criteria. Quality of evidence examined with the COSMIN checklist was determined to be good to excellent for all studies for their respective measurement property reports. Interpretability measures were consistent when publications were analyzed qualitatively, and construct validity was strong when examined alongside other validated measures relating to CS. CONCLUSIONS: An assessment of the published measurement studies of the CSI suggest the tool generates reliable and valid data that quantify the severity of several symptoms of CS.

Research design characteristics of published pharmacologic randomized clinical trials for irritable

bowel syndrome and chronic pelvic pain conditions: An ACTTION systematic review.
Gewandter JS, Chaudari J, Iwan KB, Kitt R, As-Sanie S, Bachmann G, Clemens Q, Lai HH, Tu F, Verne GN, Vincent K, Wesselmann U, Zhou Q, Turk DC, Dworkin RH, Smith SM.
J Pain. 2018 Feb 2. pii: S1526-5900(18)30055-5. doi: 10.1016/j.jpain.2018.01.007.

Chronic pain conditions occurring in the lower abdomen and pelvis are common, often challenging to manage, and can negatively affect health-related quality of life. Methodological challenges in designing randomized clinical trials (RCTs) for these conditions likely contributes to the limited number of available treatments. The goal of this systematic review of RCTs of pharmacologic treatments for irritable bowel syndrome and 3 common chronic pelvic pain conditions are to: 1) summarize the primary end points and entry criteria, and 2) evaluate the clarity of reporting of important methodological details. In total, 127 RCTs were included in the analysis. The most common inclusion criteria were a minimum pain duration (81%), fulfilling an established diagnostic criteria (61%), and reporting a minimum pain intensity (42%). Primary end points were identified for only 57% of trials. These end points, summarized in this article, were highly variable. The results of this systematic review can be used to inform future research to optimize the entry criteria and outcome measures for pain conditions occurring in the lower abdomen and pelvis, to increase transparency in reporting to allow for proper interpretation of RCT results for clinical and policy applications, and to facilitate the aggregation of data in meta-analyses. PERSPECTIVE: This article summarizes entry criteria and outcome measures and the clarity of reporting of these important design features in RCTs of irritable bowel syndrome and 3 common chronic pelvic pain conditions. These results can be used to improve design of future trials of these largely unaddressed pain conditions.

Recent insights into 3 underrecognized conditions: Myalgic encephalomyelitis-chronic fatigue syndrome, fibromyalgia, and environmental sensitivities-multiple chemical sensitivity.
Hu H, Baines C.
Can Fam Physician. 2018 Jun;64(6):413-415.

No abstract available.

Effects of a physical therapy protocol in patients with chronic migraine and temporomandibular disorders: A randomized, single-blinded, clinical trial.
Garrigos-Pedron M, La Touche R, Navarro-Sesentre P, Gracia-Naya M, Segura-Orti E.
Oral Facial Pain Headache. 2018 Spring;32(2):137-150. doi: 10.11607/ofph.1912.

AIMS: To investigate the effects of adding orofacial treatment to cervical physical therapy in patients with chronic migraine and temporomandibular disorders (TMD). METHODS: A total of 45 participants with chronic migraine and TMD aged 18 to 65 years were randomized into two groups: a cervical group (CG) and a cervical and orofacial group (COG). Both groups continued their medication regimens for migraine treatment and received physical therapy. The CG received physical therapy only in the cervical region, and the COG received physical therapy in both the cervical and orofacial regions. Both groups received six sessions of treatment that consisted of manual therapy and therapeutic exercise in the cervical region or the cervical and orofacial regions. Scores on the Craniofacial Pain and Disability Inventory (CF-PDI) and the Headache Impact Test (HIT-6) were primary outcome variables, and the secondary outcome variables were scores on the Tampa Scale for Kinesiophobia (TSK-11), pain intensity measured on a visual analog scale (VAS), pressure pain thresholds (PPTs) in the temporal, masseter (2 points, M1 and M2) and extratrigeminal (wrist) regions, and maximal mouth opening (MMO). Data were recorded at baseline, posttreatment, and after 12 weeks of follow-up. The α level was set at .05 for all tests and two-way repeated-measures analysis of variance (ANOVA) for within- and between-group interactions. RESULTS: There were 22 CG participants (13.6% men and 86.4% women) and 23 COG participants (13% men and 87% women). The ANOVA analysis revealed statistically significant differences for group × time interaction in CF-PDI, HIT-6 in the last follow-up, pain intensity, PPTs in the trigeminal region, and MMO ($P < .05$), with a medium-large magnitude of effect. No statistically significant differences were found in the PPTs of the extratrigeminal region or in the TSK-11 ($P > .05$). CONCLUSION: Both groups reported a significant improvement in CF-PDI, HIT-6, and pain intensity. Cervical and orofacial treatment was more effective than cervical treatment alone for increasing PPTs in the trigeminal region and producing pain-free MMO. Physical therapy alone was not

effective for increasing the PPTs in the extratrigeminal region (wrist) or decreasing the level of TSK-11.

"Brave men" and "emotional women": A theory-guided literature review on gender bias in health care and gendered norms towards patients with chronic pain.
Samulowitz A, Gremyr I, Eriksson E, Hensing G.
Pain Res Manag. 2018 Feb 25;2018:6358624. doi: 10.1155/2018/6358624. eCollection 2018.

BACKGROUND: Despite the large body of research on sex differences in pain, there is a lack of knowledge about the influence of gender in the patient-provider encounter. The purpose of this study was to review literature on gendered norms about men and women with pain and gender bias in the treatment of pain. The second aim was to analyze the results guided by the theoretical concepts of hegemonic masculinity and andronormativity. METHODS: A literature search of databases was conducted. A total of 77 articles met the inclusion criteria. The included articles were analyzed qualitatively, with an integrative approach. RESULTS: The included studies demonstrated a variety of gendered norms about men's and women's experience and expression of pain, their identity, lifestyle, and coping style. Gender bias in pain treatment was identified, as part of the patient-provider encounter and the professional's treatment decisions. It was discussed how gendered norms are consolidated by hegemonic masculinity and andronormativity. CONCLUSIONS: Awareness about gendered norms is important, both in research and clinical practice, in order to counteract gender bias in health care and to support health-care professionals in providing more equitable care that is more capable to meet the need of all patients, men and women.

Influence of morphine and naloxone on pain modulation in rheumatoid arthritis, chronic fatigue syndrome/fibromyalgia, and controls: A double-blind, randomized, placebo-controlled, cross-over study.
Hermans L, Nijs J, Calders P, De Clerck L, Moorkens G, Hans G, Grosemans S, Roman De Mettelinge T, Tuynman J, Meeus M.
Pain Pract. 2018 Apr;18(4):418-430. doi: 10.1111/papr.12613.

BACKGROUND: Impaired pain inhibitory and enhanced pain facilitatory mechanisms are repeatedly reported in patients with central sensitization pain. However, the exact effects of frequently prescribed opioids on central pain modulation are still unknown. METHODS: A randomized, double-blind, placebo-controlled cross-over trial was carried out. Ten chronic fatigue syndrome (CFS) / fibromyalgia (FM) patients, 11 rheumatoid arthritis (RA) patients and 20 controls were randomly allocated to the experimental (10 mg morphine or 0.2 mg/mL Naloxone) and placebo (2 mL Aqua) group. Pressure pain thresholds (PPTs) and temporal summation at the Trapezius and Quadriceps were assessed by algometry. Conditioned pain modulation (CPM) efficacy and deep tissue pain pressure were assessed by adding ischemic occlusion at the opposite upper arm. RESULTS: Deep tissue pain pressure was lower and temporal summation higher in CFS/FM (P = 0.002 respectively P = 0.010) and RA patients (P = 0.011 respectively P = 0.047) compared to controls at baseline. Morphine had only a positive effect on PPTs in both patient groups (P time = 0.034). Accordingly, PPTs increased after placebo (P time = 0.015), and no effects on the other pain parameters were objectified. There were no significant effects of naloxone nor nocebo on PPT, deep tissue pain, temporal summation or CPM in the control group. CONCLUSIONS: This study revealed anti-hyperalgesia effects of morphine in CFS/FM and RA patients. Nevertheless, these effects were comparable to placebo. Besides, neither morphine nor naloxone influenced deep tissue pain, temporal summation or CPM. Therefore, these results suggest that the opioid system is not dominant in (enhanced) bottom-up sensitization (temporal summation) or (impaired) endogenous pain inhibition (CPM) in patients with CFS/FM or RA.

Clinical criteria of central sensitization in chronic pelvic and perineal pain (Convergences PP Criteria): Elaboration of a clinical evaluation tool based on formal expert consensus.
Levesque A, Riant T, Ploteau S, Rigaud J, Labat JJ, for Convergencess PP Network.
Pain Med. 2018 Mar 7. doi: 10.1093/pm/pny030.

BACKGROUND: The evaluation of chronic pelvic and perineal pain (CPP) is often complex. The patient's description of the pain often appears to be disproportionate to the limited findings on physical examination and/or complementary investigations. The concept of central sensitization may allow

better understanding and management of patients with CPP. OBJECTIVE: The aim of this study was to elaborate a clinical evaluation tool designed to simply identify sensitization in pelvic pain. METHODS: A list of 63 items was submitted to 22 international CPP experts according to the Delphi method. RESULTS: Ten clinical criteria were adopted for the creation of a clinical evaluation tool: 1) pain influenced by bladder filling and/or urination, 2) pain influenced by rectal distension and/or defecation, 3) pain during sexual activity, 4) perineal and/or vulvar pain in response to normally nonpainful stimulation, 5) pelvic trigger points (e.g., in the piriformis, obturator internus, and/or levator ani muscles), 6) pain after urination, 7) pain after defecation, 8) pain after sexual activity, 9) variable (fluctuating) pain intensity and/or variable pain distribution, 10) migraine or tension headaches and/or fibromyalgia and/or chronic fatigue syndrome and/or post-traumatic stress disorder and/or restless legs syndrome and/or temporomandibular joint dysfunction and/or multiple chemical sensitivity. CONCLUSIONS: This process resulted in the elaboration of a clinical evaluation tool designed to identify and appropriately manage patients with CPP comprising a sensitization component.

Temporomandibular disorders in adolescents with headache.
Sojka A, Zarowski M, Steinborn B, Hedzelek W, Wisniewska-Spychala B, Dorocka-Bobkowska B.
Adv Clin Exp Med. 2018 Feb;27(2):193-199. doi: 10.17219/acem/64945.

BACKGROUND: Headache is a common complaint in all age groups and is a frequent cause of medical consultations and hospitalization. OBJECTIVES: The aim of this study was to evaluate the prevalence of bite and non-bite parafunctions as well as the signs and symptoms of temporomandibular disorder (TMD) in adolescents presenting with primary headaches. MATERIAL AND METHODS: Parents of adolescents presented with headaches to the Department of Developmental Neurology within a 12-month period were asked to complete a questionnaire developed by the authors of this study. Of the 1000 patients evaluated, 19 females and 21 males, aged 13 to 17 years, met the inclusion criterion - a confirmed clinical diagnosis of migraine or a tension headache according to the International Classification of Headache Disorders, 2nd edition. The diagnostic algorithm of the study group consisted of a full medical history, an assessment of the occurrence of bite habits and a physical examination based on the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD). RESULTS: Bite and non-bite parafunctions were found in 36 of the study group patients. A significant difference ($p = 0.0003$) between the number of bite parafunctions and non-bite parafunctions was found in females but not in males. However, bite parafunctions were more frequent in boys compared to girls ($p = 0.01$). CONCLUSIONS: Our findings suggest that it may be useful for pediatricians and neurologists to include TMD dysfunctions as a part of a standard examination of adolescents presenting with persistent headaches.

A systematic review of outcome measures utilised to assess self-management in clinical trials in patients with chronic pain.
Banerjee A, Hendrick P, Bhattacharjee P, Blake H.
Patient Educ Couns. 2018 May;101(5):767-778. doi: 10.1016/j.pec.2017.12.002.

OBJECTIVES: The aim of this review was to identify, appraise and synthesise the outcome measures used to assess self-management in patients with chronic pain. METHODS: Medline, Embase, CINAHL, PsycINFO, the Cochrane Library and Google Scholar were searched to identify quantitative measures used within randomised or non-randomised clinical trials to assess self-management in adults (≥18 years) with chronic pain. RESULTS: 25 RCTs published between 1998 and 2016 were included in this review. Studies included patients with chronic pain, hip/knee osteoarthritis, rheumatoid arthritis, chronic low back pain, fibromyalgia and chronic fatigue syndrome. Included studies utilised 14 different measures assessing a variety of constructs including self-efficacy (n=19), coping (n=4), empowerment (n=2). pain attitude and management (n=3), self-care (n=1), role behaviour (n=1) and multiple constructs of self-management (n=1). The Chronic Pain Coping Inventory (CPCI) and Health Education Impact Questionnaire (heiQ) cover different self-management related constructs across the physical, mental and social health domains. CONCLUSION: The review identified 14 measures used as proxy measure to assess self-management in patients with chronic pain. These measures have good content and construct validity, and internal consistency. However additional research is required to develop their reliability, responsiveness and interpretability. PRACTICE IMPLICATIONS: Multi-constructs measures (CPCI, heiQ) are suitable for assessing self-management.

A systematic review of probiotic interventions for gastrointestinal symptoms and irritable bowel syndrome in chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME).
Corbitt M, Campagnolo N, Staines D, Marshall-Gradisnik S.
Probiotics Antimicrob Proteins. 2018 Feb 20. doi: 10.1007/s12602-018-9397-8.

Gastrointestinal (GI) symptoms and irritable bowel (IB) symptoms have been associated with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). The aim of this study was to conduct a systematic review of these symptoms in CFS/ME, along with any evidence for probiotics as treatment. Pubmed, Scopus, Medline (EBSCOHost) and EMBASE databases were searched to source relevant studies for CFS/ME. The review included any studies examining GI symptoms, irritable bowel syndrome(IBS) and/or probiotic use. Studies were required to report criteria for CFS/ME and study design, intervention and outcome measures. Quality assessment was also completed to summarise the level of evidence available. A total of 3381 publications were returned using our search terms. Twenty-five studies were included in the review. Randomised control trials were the predominant study type (n=24). Most of the studies identified examined the effect of probiotic supplementation on the improvement of IB symptoms in IBS patients, or IB symptoms in CFS/ME patients, as well as some other significant secondary outcomes (e.g. quality of life, other gastrointestinal symptoms, psychological symptoms). The level of evidence identified for the use of probiotics in IBS was excellent in quality; however, the evidence available for the use of probiotic interventions in CFS/ME was poor and limited. There is currently insufficient evidence for the use of probiotics in CFS/ME patients, despite probiotic interventions being useful in IBS. The studies pertaining to probiotic interventions in CFS/ME patients were limited and of poor quality overall. Standardisation of protocols and methodology in these studies is required.

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). These 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.

Your support is vital to the CPRA's existence. Please donate today! One-hundred percent of your tax-deductible gift will be used to further CPRA's mission and will specifically support initiatives to: i) promote a rigorous, standardized and collaborative scientific research effort on COPCs; ii) translate research findings into educational initiatives for clinicians and patients; and iii) advance industry efforts to research and develop safe and effective therapies for COPCs.