CUTTING EDGE
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This e-newsletter - published the CPRA to keep the medical-scientific and patient communities abreast of research advances on Chronic Overlapping Pain Conditions (COPCs) - contains abstracts of studies on the epidemiology, pathophysiology and clinical management of COPCs published between October 2019 and March 2020. 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. If you are not already on our mailing list would like to sign up to receive future issues of COPCs Research Advances, click here.

In this Issue...

NATIONAL MULTI-SITE STUDIES

Changes in whole body pain intensity and widespreadness during urologic chronic pelvic pain syndrome flares-Findings from one site of the MAPP study.
Xu T, Lai HH, Pakpahan R, Vetter J, Andriole GL, Bradley C, Naliboff BD, Colditz GA, Sutcliffe S.
Neurourol Urodyn. 2019 Nov;38(8):2333-2350. doi: 10.1002/nau.24150.

OBJECTIVE: To investigate changes in whole body pain during urologic chronic pelvic pain syndrome (UCPPS) flares. MATERIALS AND METHODS: UCPPS participants at one site of the multidisciplinary approach to the study of chronic pelvic pain research network reported their daily flare status and pain levels in 7 pelvic/genital and 42 extrapelvic body areas (scale = 0-10) for 10 days at baseline and during their first flare. Linear mixed models and conditional logistic regression were used to investigate symptom changes during flares. Analyses were stratified by chronic overlapping pain condition (COPC) status. RESULTS: Fifty-five out of 60 participants completed the study, 27 of whom provided information on both nonflare (n=281) and flare (n=208)

days. Pelvic/genital pain intensity (mean change = 3.2 of 10) and widespreadness (mean=1/48) increased significantly during flares for all participants (all P interaction > .1), whereas extrapelvic pain intensity increased significantly only among participants with COPCs (mean=2.09; p interaction < .0001). Pelvic/genital and extrapelvic pain also varied on nonflare days but symptom fluctuations were generally less than/equal to 1 point (80.0%-100% of participants). Increases of greater than/equal to 2 points in pelvic/genital pain intensity (odds ration (OR)=22.0, 95% confidence interval (CI)=4.0-118.6) and greater than/equal to 1 point in the urination-related pain (OR=9.10, 95% CI=1.74-47.7) were independently associated with flare onset for all participants. CONCLUSION: Our observations of extrapelvic pain increases during flares for patients with COPCs and our independent associations between pelvic/genital/urination-related pain intensity and flare onset may provide insight into mechanisms underlying flare development (eg, common biologic pathways between UCPPS phenotypes and flares), flare management (eg, local vs systemic therapies by COPC status), and patient flare definitions.

The Quebec Low Back Pain Study: a protocol for an innovative 2-tier provincial cohort.
Page GM, Lacasse A, Quebec Back Pain Consortium (in alphabetical order), Beaudet N, Choiniere M, Deslauriers S, Diatchenko L, Dupuis L, Gregoire S, Hovey R, Leclair E, Leonard G, Meloto CB, Montagna F, Parent A, Rainville P, Roy JS, Roy M, Ware MA, Wideman TH, Stone LS.
Pain Rep. 2019 Dec 19;5(1):e799. doi: 10.1097/PR9.0000000000000799.

INTRODUCTION: The neurobiological mechanisms underlying recovery from or persistence of low back pain (LBP) remain misunderstood, limiting progress toward effective management. We have developed an innovative two-tier design to study the transition from acute to chronic LBP. The objective of the first tier is to create a provincial web-based infrastructure to recruit and monitor the trajectory of individuals with acute LBP. The objective of the second tier is to fuel hypothesis-driven satellite data collection centers with specialized expertise to study the role of biomechanical, epigenetic, genetic, neuroanatomical, ontological, physiological, psychological, and socioeconomic factors in LBP chronicity. METHODS: This article describes the first tier of the protocol: establishment of the Core Dataset and Cohort. Adults with acute LBP will be recruited through networks, media, and health care settings. A web-based interface will be used to collect self-reported variables at baseline and at 3, 6, 12, and 24 months. Acute LBP will be defined according to the Dionne 2008 consensus. Measurements will include the Canadian minimum data set for chronic LBP research, DN4 for neuropathic pain, comorbidities, EQ-5D-5L for quality of life, and linkage with provincial medico-administrative databases. The primary outcome will be the transition to chronic LBP, as defined by Deyo 2014. Secondary outcomes include health care resource utilization, disability, sick leave, mood, and quality of life. PERSPECTIVE: This study brings together diverse research expertise to investigate the transition from acute to chronic LBP, characterize the progression to recovery or chronicity, and identify patterns associated with that progression.

PATHOPHYSIOLOGY STUDIES

The link between chronic pain and Alzheimer's disease.
Cao S, Fisher DW, Yu T, Dong H.
J Neuroinflammation. 2019 Nov 6;16(1):204. doi: 10.1186/s12974-019-1608-z.

Chronic pain often occurs in the elderly, particularly in the patients with neurodegenerative disorders such as Alzheimer's disease (AD). Although studies indicate that chronic pain correlates with cognitive decline, it is unclear whether chronic pain accelerates AD pathogenesis. In this review, we provide evidence that supports a

link between chronic pain and AD and discuss potential mechanisms underlying this connection based on currently available literature from human and animal studies. Specifically, we describe two intertwined processes, locus coeruleus noradrenergic system dysfunction and neuroinflammation resulting from microglial pro-inflammatory activation in brain areas mediating the affective component of pain and cognition that have been found to influence both chronic pain and AD. These represent a pathological overlap that likely leads chronic pain to accelerate AD pathogenesis. Further, we discuss potential therapeutic interventions targeting noradrenergic dysfunction and microglial activation that may improve patient outcomes for those with chronic pain and AD.

Why do multiple sclerosis and migraine coexist?
Hamamci M, Gocmen AY, Say B, Alpua M, Badem ND, Ergun U, Ertugrul Inan L.
Mult Scler Relat Disord. 2020 Jan 16;40:101946. doi: 10.1016/j.msard.2020.101946.

BACKGROUND: Migraine coexistence, which is high in multiple sclerosis (MS), is reported. To better understand the etiology of the coexistence of MS and migraine and the outcomes of this relationship, the vitamin D, vitamin D-binding protein (VITDBP), vitamin D receptor (VITDR), high-sensitivity C-reactive protein (hs-CRP), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), total antioxidant status (TAS), total oxidant status (TOS), and Oxidative Stress Index (OSI) values were examined in patients with the coexistence of relapsing-remitting multiple sclerosis (RRMS) and migraine. METHODS: This study was conducted between January 1, 2019, and July 25, 2019, at the neurology and biochemistry clinics of two different tertiary hospitals simultaneously. Overall, 50 RRMS patients with migraine, 50 RRMS patients without migraine, and 50 healthy volunteers were included in the study. The participants' vitamin D, VITDBP, VITDR, hs-CRP, SOD, CAT, GSH-Px, TAS, TOS, and OSI values were measured. RESULTS: The vitamin D and VITDR values of the RRMS patients with migraine were lower than those of the RRMS patients without migraine (respectively, $p = 0.014$, $p < 0.001$). There was no significant difference between the RRMS patients with and without migraine in terms of their VITDBP values ($p = 0.570$). The SOD, CAT, GSH-Px, and TAS values of the RRMS patients with migraine were lower than those without migraine (all $p < 0.001$). The hs-CRP and TOS values of the RRMS patients with migraine were higher than those without migraine (all $p<0.001$). CONCLUSION: To the best of our knowledge, this is the first study on this topic to date. Based on the results, our study may shed light on the etiopathogenesis of the coexistence of MS and migraine and new treatments. However, more studies are needed to better understand the etiology of this relationship and its negative effects.

Cross-disorder analysis of endometriosis and its comorbid diseases reveals shared genes and molecular pathways and proposes putative biomarkers of endometriosis.
Vargas E, Aghajanova L, Gemzell-Danielsson K, Altmae S, Esteban FJ.
Reprod Biomed Online. 2020 Feb;40(2):305-318. doi: 10.1016/j.rbmo.2019.11.003.

RESEARCH QUESTION: Women with endometriosis are considered to be at higher risk of several chronic diseases, such as autoimmune disorders, gynaecological cancers, asthma/atopic diseases and cardiovascular and inflammatory bowel diseases. Could the study of endometriosis-associated comorbidities help to identify potential biomarkers and target pathways of endometriosis? DESIGN: A systematic review was performed to identify all possible endometriosis-associated comorbid conditions. Next, this list of disorders was coded into MeSH terms, and the gene expression profiles were downloaded from the Phenopedia database and subsequently analysed following a systems biology approach. RESULTS: The results identified a group of 127 candidate genes that were recurrently expressed in endometriosis and its closest comorbidities and that were defined as 'endometriosis sibling disorders' (ESD). The enrichment analysis showed that these candidate genes are principally involved in immune and drug responses, hormone

metabolism and cell proliferation, which are well-known hallmarks of endometriosis. The expression of ESD genes was then validated on independent sample cohorts (n=2017 samples), in which the involvement of 16 genes (AGTR1, BDNF, C3, CCL2, CD40, CYP17A1, ESR1, IGF1, IGF2, IL10, MMP1, MMP7, MMP9, PGR, SERPINE1 and TIMP2) in endometriosis was confirmed. Several of these genes harbour polymorphisms that associate to either endometriosis or its comorbid conditions. CONCLUSIONS: The study results highlight the molecular processes underlying the aetiopathogenesis of endometriosis and its comorbid conditions, and identify putative endometriosis biomarkers.

Bioinformatics analysis of gene and microRNA targets for fibromyalgia.
Qiu Y, Zhang TJ, Meng LB, Cheng XT, Hua Z.
Clin Exp Rheumatol. 2020 Feb 14. [Epub ahead of print]

OBJECTIVES: Fibromyalgia (FM) is the most common chronic pain disease in middle-aged women. Patients may also complain of migraine, irritable bowel syndrome and depression, which seriously affect their work and life, causing huge economic losses to society. However, the pathogenesis of FM is still controversial and the effect of the current treatment is far from satisfactory. METHODS: Differentially expressed genes (DEGs) and miRNAs (DEMs) were found between FM and normal blood samples. The pathway and process enrichment analysis of the genes were performed. Protein-protein interaction network were constructed. Hub genes were found and analysed in The Comparative Toxicogenomics Database. RESULTS: A total of 102 genes were up-regulated and 46 down-regulated, 206 miRNAs down-regulated, and 15 up-regulated in FM. CD38, GATM, HDC, FOS were found as candidate genes. These genes were significantly associated with musculoskeletal disease, mental disorder, immune system disease. There was partial overlap between metformin therapy-related genes and FM-related genes. CONCLUSIONS: We found DEGs and DEMs in FM patients through bioinformatics analysis, which may be involved in the occurrence and development of FM and serve as potential targets for diagnosis and treatment.

Pain condition and sex differences in the descending noradrenergic system following lateral hypothalamic stimulation.
Jeong Y, Wagner MA, Ploutz-Snyder RJ, Holden JE.
IBRO Rep. 2019 Dec 17;8:11-17. doi: 10.1016/j.ibror.2019.12.003.

The lateral hypothalamus (LH) is known to modulate nociception via the descending noradrenergic system in acute nociception, but less is known about its role in neuropathic pain states. In naïve females, LH stimulation produces opposing effects of α-adrenoceptors, with α_2-adrenoceptors mediating antinociception, while pronociceptive α_1-adrenoceptors attenuate the effect. Whether this opposing response is seen in neuropathic conditions or in naïve males is unknown. We used a mixed factorial design to compare male and female rats with chronic constriction injury (CCI) to naïve rats, measured by Total Paw Withdrawal (TPW) responses to a thermal stimulus. Rats received one of three doses of carbachol to stimulate the LH followed by intrathecal injection of either an α_1- or an α_2-adrenoceptor antagonist (WB4101 or yohimbine, resp.) or saline for control. Overall, naïve rats showed a more pronounced opposing alpha-adrenergic response than CCI rats ($p < 0.04$). Naïve male and female rats demonstrated antinociception following α_1-adrenoceptor blockade and hyperalgesia following α_2-adrenoceptor blockade. Male CCI rats also showed dose dependent effects from either WB4101 or yohimbine ($p < 0.05$), while female CCI rats had significant antinociception from WB4101 ($p < 0.05$), but no effect from yohimbine. These results support the idea that peripheral nerve damage differentially alters the descending noradrenergic modulatory system in male and female rats, and notably, that female CCI rats do not show antinociception from descending noradrenergic input. These findings are suggestive that clinical therapies that recruit the descending

noradrenergic system may require a different approach based on patient gender.

Activation of transposable elements in immune cells of fibromyalgia patients.
Ovejero T, Sadones O, Sanchez-Fito T, Almenar-Perez E, Espejo JA, Martin-Martinez E, Nathanson L, Oltra E.
Int J Mol Sci. 2020 Feb 18;21(4). pii: E1366. doi: 10.3390/ijms21041366.

Advancements in nucleic acid sequencing technology combined with an unprecedented availability of metadata have revealed that 45% of the human genome constituted by transposable elements (TEs) is not only transcriptionally active but also physiologically necessary. Dysregulation of TEs, including human retroviral endogenous sequences (HERVs) has been shown to associate with several neurologic and autoimmune diseases, including Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS). However, no study has yet addressed whether abnormal expression of these sequences correlates with fibromyalgia (FM), a disease frequently comorbid with ME/CFS. The work presented here shows, for the first time, that, in fact, HERVs of the H, K and W types are overexpressed in immune cells of FM patients with or without comorbid ME/CFS. Patients with increased HERV expression (N = 14) presented increased levels of interferon (INF-β and INF-γ) but unchanged levels of TNF-α. The findings reported in this study could explain the flu-like symptoms FM patients present with in clinical practice, in the absence of concomitant infections. Future work aimed at identifying specific genomic loci differentially affected in FM and/or ME/CFS is warranted.

Plasma tryptophan and kynurenine in females with temporomandibular disorders and fibromyalgia-An exploratory pilot study.
Barjandi G, Louca Jounger S, Lofgren M, Bileviciute-Ljungar I, Kosek E, Ernberg M.
J Oral Rehabil. 2020 Feb;47(2):150-157. doi: 10.1111/joor.12892.

BACKGROUND: Both temporomandibular disorders myalgia (TMDM) and fibromyalgia (FM) have been linked to central and peripheral changes in serotonin availability. The precursor of serotonin, tryptophan (TRP), is mainly catabolised via another pathway to produce kynurenine (KYN), but whether changes of this pathway are present in TMDM and FM are still unclear. OBJECTIVE: The aim was to explore blood plasma concentrations of TRP and KYN in TMDM and FM in an attempt to identify novel associations for future research. METHODS: Plasma of 113 female participants (17 TMDM, 40 FM and 56 healthy pain-free controls) were analysed for TRP and KYN concentrations. The degradation of TRP via the KYN pathway was indicated by the KYN to TRP ratio (KYN/TRP). Pain intensities were assessed with the Graded Chronic Pain Scale (GCPS) and Visual Analogue Scale (VAS). Psychological symptoms were evaluated using the Hospital Anxiety and Depression Scale (HADS), Patient Health Questionnaire (PHQ-9) and General Anxiety Disorder scale (GAD-7). RESULTS: In TMDM there was a negative correlation between TRP and pain intensity (r_s = -0.55 P = .023) and positive correlations between KYN/TRP and pain intensity (r_s = 0.59 P = .013). In FM, KYN/TRP was negatively correlated with anxiety symptoms (r_s = -0.36 P = .022) and a trend towards significantly lower TRP levels was found compared to controls (P = .05). CONCLUSION: The association between KYN/TRP and pain intensity as well as anxiety ratings in this small exploratory study may indicate that KYN/TRP could be a relevant indicator for symptom severity in TMDM and FM. Further investigations of the KYN pathway in chronic myalgia are warranted.

Altered microbiome composition in individuals with fibromyalgia.
Minerbi A, Gonzalez E, Brereton NJB, Anjarkouchian A, Dewar K, Fitzcharles MA, Chevalier S, Shir Y.
Pain. 2019 Nov;160(11):2589-2602. doi: 10.1097/j.pain.0000000000001640.

Fibromyalgia (FM) is a prevalent syndrome, characterised byy chronic widespread pain, fatigue, and impaired sleep, that is challenging to diagnose and difficult to treat. The microbiomes of 77 women with FM and that of 79 control participants were compared using 16S rRNA gene amplification and whole-genome sequencing. When comparing FM patients with unrelated controls using differential abundance analysis, significant differences were revealed in several bacterial taxa. Variance in the composition of the microbiomes was explained by FM-related variables more than by any other innate or environmental variable and correlated with clinical indices of FM. In line with observed alteration in butyrate-metabolising species, targeted serum metabolite analysis verified differences in the serum levels of butyrate and propionate in FM patients. Using machine-learning algorithms, the microbiome composition alone allowed for the classification of patients and controls (receiver operating characteristic area under the curve 87.8%). To the best of our knowledge, this is the first demonstration of gut microbiome alteration in nonvisceral pain. This observation paves the way for further studies, elucidating the pathophysiology of FM, developing diagnostic aids and possibly allowing for new treatment modalities to be explored.

Feeling down? A systematic review of the gut microbiota in anxiety/depression and irritable bowel syndrome.
Simpson CA, Mu A, Haslam N, Schwartz OS, Simmons JG.
J Affect Disord. 2020 Jan 22;266:429-446. doi: 10.1016/j.jad.2020.01.124.

Background Anxiety/depression and irritable bowel syndrome (IBS) are highly prevalent and burdensome conditions, whose co-occurrence is estimated between 44 and 84%. Shared gut microbiota alterations have been identified in these separate disorders relative to controls; however, studies have not adequately considered their comorbidity. This review set out to identify case-control studies comparing the gut microbiota in anxiety/depression, IBS, and both conditions comorbidly relative to each other and to controls, as well as gut microbiota investigations including measures of both IBS and anxiety/depression. Methods Four databases were systematically searched using comprehensive search terms (OVID Medline, Embase, PsycINFO, and PubMed), following PRISMA guidelines. Results Systematic review identified 17 studies (10 human, 7 animal). Most studies investigated the gut microbiota and anxiety/depression symptoms in IBS cohorts. Participants with IBS and high anxiety/depression symptoms had lower alpha diversity compared to controls and IBS-only cohorts. Machine learning and beta diversity distinguished between IBS participants with and without anxiety/depression by their gut microbiota. Comorbid IBS and anxiety/depression also had higher abundance of Proteobacteria, Prevotella/Prevotellaceae, Bacteroides and lower Lachnospiraceae relative to controls. Limitations A large number of gut microbiota estimation methods and statistical techniques were utilized; therefore, meta-analysis was not possible. Conclusions Well-designed case-control and longitudinal studies are required to disentangle whether the gut microbiota is predicted as a continuum of gastrointestinal and anxiety/depression symptom severity, or whether reported dysbiosis is unique to IBS and anxiety/depression comorbidity. These findings may inform the development of targeted treatment through the gut microbiota for individuals with both anxiety/depression and IBS.

Critical evaluation of animal models of visceral pain for therapeutics development: A focus on irritable bowel syndrome.
Johnson AC, Farmer AD, Ness TJ, Greenwood-Van Meerveld B.
Neurogastroenterol Motil. 2019 Dec 13:e13776. doi: 10.1111/nmo.13776.

The classification of chronic visceral pain is complex, resulting from persistent inflammation, vascular (ischemic) mechanisms, cancer, obstruction or distension, traction or compression, and combined mechanisms, as well as unexplained functional

mechanisms. Despite the prevalence, treatment options for chronic visceral pain are limited. Given this unmet clinical need, the development of novel analgesic agents, with defined targets derived from preclinical studies, is urgently needed. While various animal models have played an important role in our understanding of visceral pain, our knowledge is far from complete. Due to the complexity of visceral pain, this document will focus on chronic abdominal pain, which is the major complaint in patients with disorders of the gut-brain interaction, also referred to as functional gastrointestinal disorders, such as irritable bowel syndrome (IBS). Models for IBS are faced with challenges including a complex clinical phenotype, which is comorbid with other conditions including anxiety, depression, painful bladder syndrome, and chronic pelvic pain. Based upon the multifactorial nature of IBS with complicated interactions between biological, psychological, and sociological variables, no single experimental model recapitulates all the symptoms of IBS. This position paper will contextualize chronic visceral pain using the example of IBS and focus on its pathophysiology while providing a critical review of current animal models that are most relevant, robust, and reliable in which to screen promising therapeutics to alleviate visceral pain and delineate the gaps and challenges with these models. We will also highlight, prioritize, and come to a consensus on the models with the highest face/construct validity.

Association between irritable bowel syndrome and allergic diseases: To make a case for aeroallergen.
Loo EXL, Wang Y, Siah KTH.
Int Arch Allergy Immunol. 2020;181(1):31-42. doi: 10.1159/000503629.

Irritable bowel syndrome (IBS) is a functional gastrointestinal disease and the most common cause of prolonged abdominal pain and bowel disturbances in the developed world. While initially thought to be functional or psychosomatic in nature, IBS is now recognized as a heterogeneous group of conditions. A subset of IBS patients and patients with allergic diseases share some characteristic inflammatory features. In fact, atopic children show an increased likelihood of developing IBS as adults. Given these findings, a subset of IBS may be suffering from allergy-related gut diseases. In this review, we present the allergy-related comorbidities of IBS, including genetic, environmental, and immunologic factors. We discuss studies demonstrating an increased sensitization of IBS patients to aeroallergens compared to food allergens. We then postulate potential pathophysiological mechanisms underlying both IBS and aeroallergens in the gut, followed by potential implications in the screening and treatment of allergies in IBS patients.

MicroRNAs as biomarkers of pain intensity in patients with chronic fatigue syndrome.
Al-Rawaf HA, Alghadir AH, Gabr SA.
Pain Pract. 2019 Nov;19(8):848-860. doi: 10.1111/papr.12817.

BACKGROUND: Numerous experimental models have shown that microRNAs (miRNAs) play an important role in regulating pain processing in clinical pain disorders. In this study, we evaluated a set of miRNAs as diagnostic biomarkers of pain intensity in adolescents with chronic fatigue syndrome (CFS). We then correlated the expression of these miRNAs with the levels of inflammatory markers and pain-related comorbidities in adolescents with CFS and healthy controls (HCs). METHODS: A total of 150 adolescents, 12 to 18 years of age, participated in this study between April 2016 and April 2017. The participants were classified into 2 groups: adolescents with CFS (n = 100) and HCs (n = 50). Reverse-transcription polymerase chain reaction was used to evaluate the expression of miR-558, miR-146a, miR-150, miR-124, and miR-143. Immunoassay analysis was used to assess the levels of immune inflammatory markers interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and cyclooxygenase-2 (COX-2). RESULTS: Adolescents with CFS showed significantly higher pain thresholds than comparable nonfatigued HCs. Ability to enjoy life and relations with others were the parameters least influenced by pain in CFS

patients. Differential expression of miR-558, miR-146a, miR-150, miR-124, and miR-143 was significantly downregulated and notably interfered with pain intensity and frequency in patients with CFS. Also, the expression of these miRNAs was significantly correlated with that of IL-6, TNF-α, and COX-2, which have been shown to mediate pain intensity in patients with CFS. Girls with CFS showed significantly decreased expression levels of these miRNAs compared with the levels of boys with CFS. Girls with CFS also showed increased expression of the inflammatory pain-related markers IL-6, TNF-α, and COX-2 compared with the levels of boys with CFS. CONCLUSIONS: The intensity and consequences of pain were influenced by differential expression of miR-558, miR-146a, miR-150, miR-124, and miR-143, which was directly associated with higher expression of the immune inflammatory-related genes TNFα, IL-6, and COX-2 in adolescents with CFS. Further studies of larger patient cohorts will help clarify the role of miRNAs in the pathogenesis of CFS.

Sex as a biological variable in irritable bowel syndrome.
Gamilleri M.
Neurogastroenterol Motil. 2020 Jan 13:e13802. doi: 10.1111/nmo.13802.

BACKGROUND: The pathophysiology and mechanisms of irritable bowel syndrome (IBS) involve both central and peripheral mechanisms that result in altered perception, as well as changes in bowel functions. These dysfunctions are associated with motor, sensory, immune, barrier, and intraluminal perturbations, including the microbiota, and their products and endogenous molecules with bioactive properties. There is evidence that these mechanisms are altered in both females and males. However, there is also increasing evidence that sex is a biological variable that impacts a number of aspects of the mechanisms, epidemiology, and manifestations of IBS. PURPOSE: The objective of this article is to review the evidence of the differences among genders of the following factors in IBS: the brain-gut axis and sex hormones, epidemiology, diagnostic criteria and prognosis, pain perception, colonic transit, abdominal distension, overlap with urogynecological conditions, psychologic issues, anorexia, fibromyalgia, serotonin, and responsiveness to treatment of IBS. It is important to consider the variations attributable to sex in order to enhance the management of patients with IBS and the research of mechanisms involved in IBS.

Co-occurrence of pain syndromes.
Affaitati G, Costantini R, Tana C, Cipollone F, Giamberardino MA.
J Neural Transm (Vienna). 2019 Nov 29. doi: 10.1007/s00702-019-02107-8.

Many pain conditions in patients tend to co-occur, influencing the clinical expressions of each other in various ways. This paper summarizes the main concurrent pain conditions by analyzing the major interactions observed. In particular, co-occurrence will be examined in: visceral pain (especially ischemic heart disease, irritable bowel syndrome, dysmenorrhea / endometriosis and urinary pain), fibromyalgia, musculoskeletal pain and headache. Two concurrent visceral pains from internal organs sharing at least part of their central sensory projection can give rise to viscero-visceral hyperalgesia, i.e., enhancement of typical pain symptoms from both districts. Visceral pain, headache and musculoskeletal pains (myofascial pain from trigger points, joint pain) can enhance pain and hyperalgesia from fibromyalgia. Myofascial pain from trigger points can perpetuate pain symptoms from visceral pain conditions and trigger migraine attacks when located in the referred pain area from an internal organ or in cervico-facial areas, respectively. The pathophysiology of these pain associations is complex and probably multifactorial; among the possible processes underlying the mutual influence of symptoms recorded in the associations is modulation of central sensitization phenomena by nociceptive inputs from one or the other condition. A strong message in these pain syndrome co-occurrence is that effective treatment of one of the conditions can also improve symptoms from the other, thus suggesting a systematic and thorough evaluation of

the pain patient for a global effective management of his/her suffering.

Neuroimmunology: What role for autoimmunity, neuroinflammation, and small fiber neuropathy in fibromyalgia, chronic fatigue syndrome, and adverse events after human papillomavirus vaccination?
Ryabkova VA, Churilov LP, Shoenfeld Y.
Int J Mol Sci. 2019 Oct 18;20(20). pii: E5164. doi: 10.3390/ijms20205164.

Fibromyalgia is a disorder characterized by chronic widespread pain and non-pain symptoms, such as fatigue, dysautonomia, and cognitive and sleep disturbances. Its pathogenesis and treatment continue to be the subject of debate. We highlight the role of three mechanisms-autoimmunity, neuroinflammation, and small fiber neuropathy-in the pathogenesis of the disease. These mechanisms are shown to be closely interlinked (also on a molecular level), and the review considers the implementation of this relationship in the search for therapeutic options. We also pay attention to chronic fatigue syndrome, which overlaps with fibromyalgia, and propose a concept of "autoimmune hypothalamopathy" for its pathogenesis. Finally, we analyze the molecular mechanisms underlying the neuroinflammatory background in the development of adverse events following HPV vaccination and suggesting neuroinflammation, which could exacerbate the development of symptoms following HPV vaccination (though this is hotly debated), as a model for fibromyalgia pathogenesis.

Painful interactions: Microbial compounds and visceral pain.
van Thiel IAM, Botschuijver S, de Jonge WJ, Seppen J.
Biochim Biophys Acta Mol Basis Dis. 2020 Jan 1;1866(1):165534. doi: 10.1016/j.bbadis.2019.165534.

Visceral pain, characterized by abdominal discomfort, originates from organs in the abdominal cavity and is a characteristic symptom in patients suffering from irritable bowel syndrome, vulvodynia or interstitial cystitis. Most organs in which visceral pain originates are in contact with the external milieu and continuously exposed to microbes. In order to maintain homeostasis and prevent infections, the immune- and nervous system in these organs cooperate to sense and eliminate (harmful) microbes. Recognition of microbial components or products by receptors expressed on cells from the immune and nervous system can activate immune responses but may also cause pain. We review the microbial compounds and their receptors that could be involved in visceral pain development.

A subgroup of chronic low back pain patients with central sensitization.
Aoyagi K, He J, Nicol AL, Clauw DJ, Kluding PM, Jernigan S, Sharma NK.
Clin J Pain. 2019 Nov;35(11):869-879. doi: 10.1097/AJP.0000000000000755.

BACKGROUND: Our knowledge of central sensitization (CS) in chronic low back pain (CLBP) is limited. 2011 fibromyalgia criteria and severity scales (2011 FM survey) have been used to determine FM positive as a surrogate of CS. The major features of CS including widespread hyperalgesia and dysfunction of the descending inhibitory pathways can be identified by pressure pain threshold (PPT) and conditioned pain modulation (CPM) tests. The purpose of the study was to examine neurophysiological characteristics and psychosocial symptoms in a subgroup of FM-positive CLBP compared with FM-negative CLBP patients. METHODS: A total of 46 participants with CLBP and 22 pain-free controls completed outcome measures of the 2011 FM survey, PPT and CPM tests, and psychosocial questionnaires. Differences between FM-positive and FM-negative CLBP participants on these measures and correlations were analyzed. RESULTS: The 2011 FM survey identified 22 (48%) participants with CLBP as FM positive. FM-positive CLBP participants showed lower PPT values of the thumbnail (P=0.011) and lower back (P=0.003), lower CPM values of the thumbnail

(P=0.002), and more sever pain catastrophizing, anxiety, and depression symptoms (P<0.05) than FM-negative CLBP participants. The 2011 FM scores were significantly correlated with the PPT and CPM values of the thumbnail and with psychosocial symptoms (p<0.001). DISCUSSION: Our findings suggest a subgroup of CLBP patients exhibiting with signs and symptoms of CS. Associations between subjective and objective CS measures indicate that the 2011 FM survey can be utilized to identify the presence of CS in CLBP in clinical practice.

Exploring the neural correlates of touch and pain in women with provoked vestibulodynia.
Sutton KS, Yessick LR, Wild CJ, Chamberlain SM, Pukall CF.
Pain. 2019 Dec 10. doi: 10.1097/j.pain.0000000000001778.

Group differences in touch and pain thresholds-and their neural correlates-were studied in women with provoked vestibulodynia (PVD; N = 15), a common subtype of vulvodynia (chronic vulvar pain), and pain-free control women (N = 15). Results from quantitative sensory testing and self-report measures indicated that, as compared with control participants, women with PVD exhibited allodynia (ie, pain in response to a normally nonpainful stimulus) and hyperalgesia (ie, an increased response to a normally painful stimulus) at vulvar and nonvulvar sites. In addition, brain imaging analyses demonstrated reduced difference scores between touch and pain in the S2 area in women with PVD compared with control participants, supporting previous findings of allodynia in women with PVD. There were no significant reductions in difference scores between touch and pain for regions related to cognitive and affective processing of painful stimuli. The results of this study contribute important information to the general pain and vulvodynia literatures in elucidating the specific sensorimotor neural mechanisms that underlie hyperalgesia in a chronic pain population. These results have implications for differentiating neural processing of touch and pain for women with and without PVD. Future research should attempt to examine alterations related to hyperalgesia in commonly comorbid conditions of PVD.

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. 2020 Jan 14;75(2):436-447. 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.

The prevalence of first-onset temporomandibular disorder in low back pain and associated risk factors: A nationwide population-based cohort study with a 15-year follow-up.
Lee KC, Wu YT, Chien WC, Chung CH, Chen LC, Shieh YS.
Medicine (Baltimore). 2020 Jan;99(3):e18686. doi: 10.1097/MD.0000000000018686.

The coexistence of low back pain (LBP) and temporomandibular disorder (TMD) has often been noted clinically. However, studies of the association between these two conditions involving a large population with longitudinal evidences are lacking. Therefore, the study aimed to investigate the association between LBP and TMD in a nationwide-matched cohort population with a 15-year follow-up. Data of 65,121 patients newly diagnosed with LBP were analyzed, along with those of 195,363 (1:3) sex- and age-matched controls. Multivariate Cox regression analysis was used to determine TMD risk between the LBP and non-LBP groups. Kaplan-Meier method was used for determining the cumulative risk of first-onset TMD between groups, with a 15-year follow-up. The LBP group was more likely to develop first-onset TMD (adjusted hazards ratio (HR)=1.561, p<.001), after adjusting for demographic variables and comorbidities. The risk factors for TMD were LBP, young age, higher insured premium, and osteoporosis. In the subgroup analysis, the LBP group had a higher risk of TMD than the non-LBP group in all stratifications. LBP is the risk factor contributing to the development of first-onset TMD. Therefore, clinicians should be reminded to manage LBP disorders concurrently when treating TMD.

Does adolescent self-reported TMD pain persist into early adulthood? A longitudinal study.
Nilsson IM, List T.
Acta Odontol Scand. 2020 Feb 19:1-7. doi: 10.1080/00016357.2020.1730000.

Objective: To follow up 2209 individuals in a longitudinal study and assess self-reported TMD pain, painful and non-painful comorbid conditions, and pain-related disability. Materials and methods: During 2012-2014, questionnaires were sent to 2209 eligible individuals who had been screened for TMD pain each year during 2000-2003. The two screening questions were (1) Do you have pain in the temple, face, jaw joint, or jaws once a week or more often? and (2) Do you have pain when you open your mouth wide or chew once a week or more often? If the patient answered 'yes' to one or both of the questions, TMD pain was recorded. Non-respondents received reminders; telephone interviews were offered a randomised group. The questionnaire queried TMD pain, and painful and non-painful comorbid conditions. Results: The overall response rate was 36.5%. Individuals were placed into one of four pain groups defined by their pain experience at baseline and at the follow-up: no TMD pain (69.0%), new TMD pain (13.0%), previous TMD pain (9.9%), and persistent TMD pain (8.1%). Based on the self-report surveys, significantly more responders with TMD pain at follow-up had had pain as adolescents than not. Of adolescents with TMD pain, 45.1% had pain at follow-up as young adults, while 15.8% had pain at follow-up without a previous history of TMD pain. Individuals with persistent TMD pain had high frequencies of comorbid pains (p<.001), 45.2% reported moderate-severe depression scores (p<.001), and 13.0% had moderate pain-related disability (GCPS). Conclusions: Based on self-report surveys, TMD pain in adolescence appears to triple the risk of TMD pain in young adulthood, and persistent pain increased comorbid pain and psychosocial distress.

Rome IV functional gastrointestinal disorders and health impairment in subjects with hypermobility spectrum disorders or hypermobile ehlers-danlos syndrome.
Lam CY, Palsson OS, Whitehead WE, Sperber AD, Tornblom H, Simren M, Aziz I.
Clin Gastroenterol Hepatol. 2020 Feb 25. pii: S1542-3565(20)30204-4. doi:

10.1016/j.cgh.2020.02.034.

BACKGROUND & AIMS: Individuals with hypermobility spectrum disorder or hypermobile Ehlers-Danlos Syndrome (HSD/hEDS) are increasingly encountered by gastroenterologists and pose complex clinical challenges. Uncontrolled studies have found functional gastrointestinal disorders (FGIDs) to be common in patients with HSD/hEDS. Some patients have somatic symptoms (medically unexplained symptoms) that might affect FGIDs. We performed a case-control study to determine the prevalence of and factors associated with Rome IV FGIDs in subjects with HSD/hEDS compared with age- and sex- matched population-based controls. METHODS: An online general health survey was completed by 603 individuals with HSD/hEDS in October 2018 (cases) and 603 matched individuals from the population of the United Kingdom (controls) in 2015. The mean participant age was 39 yrs, and 96% were women. The survey included questions about Rome IV FGIDs, non-GI and non-musculoskeletal somatic symptoms (maximum number, 10), quality of life, medical history and healthcare use. The prevalence of FGIDs was compared between cases and controls, with subsequent logistic regression models - adjusting for the number of somatic symptoms - used to determine the associations for FGIDs in HSD/hEDS compared with controls. RESULTS: Nearly all subjects (98%) with HSD/hEDS fulfilled symptom-based criteria for 1 or more Rome IV FGIDs, compared with 47% of controls (P<.0001). The gastrointestinal regions most commonly affected by FGIDs in individuals with HSD/hEDS and control subjects were the bowel (90% vs 40% of controls), gastroduodenal (70% vs 13% of controls), esophageal (56% vs 6% of controls), and anorectal (53% vs 9% of controls); P<.0001. A higher proportion of subjects with HSD/hEDS had FGIDs in 2 or more regions (84% vs 15% of controls; P<.0001). Subjects with HSD/hEDS also reported a significantly higher number of non-GI and non-musculoskeletal somatic symptoms (7.1 vs 3.3 in controls), lower quality of life, and greater healthcare use, including abdominal surgeries and medication use (for example, 84% used analgesics compared with 29% of controls). Almost 40% of subjects with HSD/hEDS reported a diagnosis of chronic fatigue syndrome and/or fibromyalgia. Following adjustments for somatic symptoms, the association for FGIDs in subjects with HSD/hEDS was reduced by as much as 4-fold and in some instances was eliminated. CONCLUSIONS: In a large case-control study of persons with HSD/hEDS, almost all of the cases met criteria for Rome IV FGIDs, incurred considerable health impairment, and had high healthcare use. Patients with HSD/hEDS frequently have somatic symptoms that should be treated to reduce the high burden of gastrointestinal illness in this population.

Concomitant medical conditions and total cost of care in patients with migraine: a real-world claims analysis.
Polson M, Williams TD, Speicher LC, Mwamburi M, Staats PS, Tenaglia AT.
Am J Manag Care. 2020 Feb;26(1 Suppl):S3-S7. doi: 10.37765/ajmc.2020.42543.

This study evaluates the impact of concomitant medical conditions on patients with and without migraine, assessing healthcare utilization, and total cost of care. Medical and pharmacy claims from multiple health plans, both nationally and internationally, were examined to evaluate overall real-world trends in commercially insured patients diagnosed with migraine. A total of 53,608 patients with diagnosis codes for migraine met the study criteria and were matched 1:1 with controls (81.8% female; mean age, 42 years; mean Charlson Comorbidity Index score, 0.34). During the 3-year measurement period, mean medical costs per patient in the migraine cohort were about 1.7 times that of the control group ($22,429 vs $13,166). Unique encounters and cost per patient by medical service type for the migraine cohort compared with the control group were as follows: emergency department, 4.13 ($4000) versus 2.94 ($2639); hospital inpatient, 3.15 ($17,748) versus 2.67 ($16,010); hospital outpatient, 5.14 ($365) versus 4.85 ($396); physician office, 36.78 ($6803) versus 21.39 ($4069); laboratory, 10.12 ($1433) versus 7.71 ($1057); radiology, 7.64 ($2609) versus 5.94

($1733). Mean pharmacy costs per patient were approximately 1.8 times higher in the migraine cohort compared with the control cohort ($8441 vs $4588, respectively; P <.0001). These results suggest that patients with migraine have more comorbidities compared with those without migraine. These patients also utilize healthcare resources at a significantly higher rate compared with similar patients without a migraine diagnosis. An unmet need exists for new treatment modalities in this patient population. More effective interventions and proper management may lead to improved patient outcomes and healthcare costs for patients with migraine.

Baseline self-report 'central mechanisms' trait predicts persistent knee pain in the Knee Pain in the Community (KPIC) cohort.
Akin-Akinyosoye K, Sarmanova A, Fernandes GS, Frowd N, Swaithes L, Stocks J, Valdes A, McWilliams DF, Zhang W, Doherty M, Ferguson E, Walsh DA.
Osteoarthritis Cartilage. 2020 Feb;28(2):173-181. doi: 10.1016/j.joca.2019.11.004.

OBJECTIVES: We investigated whether baseline scores for a self-report trait linked to central mechanisms predict 1-year pain outcomes in the Knee Pain in the Community cohort. METHOD: 1471 participants reported knee pain at baseline and responded to a 1-year follow-up questionnaire, of whom 204 underwent pressure pain detection thresholds (PPTs) and radiographic assessment at baseline. Logistic and linear regression models estimated the relative risks (RRs) and associations (β) between self-report traits, PPTs and pain outcomes. Discriminative performance for each predictor was compared using receiver-operator characteristics (ROC) curves. RESULTS: Baseline Central Mechanisms trait scores predicted pain persistence (Relative Risk, RR = 2.10, P = 0.001) and persistent pain severity (β = 0.47, P < 0.001), even after adjustment for age, sex, BMI, radiographic scores and symptom duration. Baseline joint-line PPTs also associated with pain persistence (RR range = 0.65 to 0.68, P < 0.02), but only in univariate models. Lower baseline medial joint-line PPT was associated with persistent pain severity (β = -0.29, P = 0.013) in a fully adjusted model. The Central Mechanisms trait model showed good discrimination of pain persistence cases from resolved pain cases (Area Under the Curve, AUC = 0.70). The discrimination power of other predictors (PPTs (AUC range = 0.51 to 0.59), radiographic OA (AUC = 0.62), age, sex and BMI (AUC range = 0.51 to 0.64), improved significantly (P < 0.05) when the central mechanisms trait was included in each logistic regression model (AUC range = 0.69 to 0.74). CONCLUSION: A simple summary self-report Central Mechanisms trait score may indicate a contribution of central mechanisms to poor knee pain prognosis.

Migraine progression in subgroups of migraine based on comorbidities: Results of the CaMEO Study.
Lipton RB, Fanning KM, Buse DC, Martin VT, Hohaia LB, Adams AM, Reed ML, Goadsby PJ.
Neurology. 2019 Dec 10;93(24):e2224-e2236. doi: 10.1212/WNL.0000000000008589.

OBJECTIVE: To test the hypothesis that statistically defined subgroups of migraine (based on constellations of comorbidities and concomitant conditions; henceforth comorbidities), previously identified using Chronic Migraine Epidemiology and Outcomes (CaMEO) Study data, differ in prognosis, as measured by rates of progression from episodic migraine (EM) to chronic migraine (CM). METHODS: The onset of CM was assessed up to 4 times over 12 months in individuals with EM and ≥1 comorbidity at baseline, based on constellations of comorbidities (comorbidity classes). The "fewest comorbidities" class served as reference. Individuals completing ≥1 follow-up survey from the web-based CaMEO Study were included. Covariates included sociodemographic variables and headache characteristics. Sex, income, cutaneous allodynia, and medication overuse were modeled as binary variables; age, body mass index, headache-body mass index, headache-related disability (Migraine Disability Assessment [MIDAS]), and Migraine Symptom Severity Scale as continuous

variables. CM onset was assessed using discrete time analysis. RESULTS: In the final sociodemographic model, all comorbidity classes had significantly elevated hazard ratios (HRs) for risk of progression to CM from EM, relative to fewest comorbidities. HRs for CM onset ranged from 5.34 (95% confidence interval [CI] 3.89-7.33; $p \leq 0.001$) for most comorbidities to 1.53 (95% CI 1.17-2.01; $p < 0.05$) for the respiratory class. After adjusting for headache covariates independently, each comorbidity class significantly predicted CM onset, although HRs were attenuated. CONCLUSIONS: Subgroups of migraine identified by comorbidity classes at cross-section predicted progression from EM (with 1 or more comorbidity at baseline) to CM. The relationship of comorbidity group to CM onset remained after adjusting for indicators of migraine severity, such as MIDAS.

Influence of the number and severity of comorbidities in the course of acute non-specific low back pain in older adults: longitudinal results from the Back Complaints in the Elders (BACE-Brazil).
Leopoldino AAO, Megale RZ, Diz JBM, Moreira BS, Lustosa LP, Pereira LSM, Ferreira ML.
Age Ageing. 2019 Dec 1;49(1):96-101. doi: 10.1093/ageing/afz134.

BACKGROUND: The presence of comorbidities is quite common in older adults. However, the effects of comorbidities on the course of acute low back pain (LBP) are not fully understood. OBJECTIVE: To investigate the effects of the number and severity of comorbidities on the severity of pain and disability 3 months from baseline in people with an acute episode of non-specific LBP. METHODS: Data from the Back Complaints in the Elders study, a cohort that enrolled 602 community-dwelling older adults with acute LBP at baseline, were used in these analyses. Comorbidities, pain intensity and disability were assessed using the Self-Administered Comorbidities Questionnaire (SCQ), the Numeric Rating Scale (NRS) and the Roland-Morris Disability Questionnaire (RMDQ), respectively. Age, sex, marital status, education, income and body mass index were covariates. RESULTS: The mean age of participants was 67.6 +/- 7.0 years. Both pain and disability scores decreased from 7.2 (95% confidence interval [95% CI] 7.0-7.4) to 5.8 (95% CI 5.5-6.1) in NRS and from 13.5 (95% CI 13.0-14.1) to 12.0 (95% CI 11.4-12.7) in RMDQ 3 months from baseline. The linear regression analysis showed a significant association between SCQ scores at baseline and pain (coefficient=0.16, 95% CI 0.08-0.24;p<0.001) or disability (coefficient=0.29, 95% CI 0.16-0.41; p<0.001) scores at the 3-month follow-up, after adjusting for confounders. Participants with highest SCQ scores were less likely to report improvement of at least 30% in pain (OR: 0.41, 95% CI 0.22-0.79;p+0.008) and disability (OR:0.42, 95% CI 0.28-0.85;p=0.015). CONCLUSION: The presence and severity of comorbidities were independently associated with the prognosis of acute non-specific LBP in older adults.

Gender-stratified prevalence of psychiatric and pain diagnoses in a primary care patient sample with fibromyalgia.
Wan B, Gebauer S, Salas J, Jacobs CK, Breeden M, Scherrer JF.
Pain Med. 2019 Nov 1;20(11):2129-2133. doi: 10.1093/pm/pnz084.

OBJECTIVE: Comorbid psychiatric and pain-related conditions are common in patients with fibromyalgia. Most studies in this area have used data from patients in specialty care and may not represent the characteristics of fibromyalgia in primary care patients. We sought to fill gaps in the literature by determining if the association between psychiatric diagnoses, conditions associated with chronic pain, and fibromyalgia differed by gender in a primary care patient population. DESIGN: Retrospective cohort. SETTING AND SUBJECTS: Medical record data obtained from 38,976 patients, 18 years of age or older with a primary care encounter between July 1, 2008, to June 30, 2016. METHODS: International Classification of Diseases-9 codes were used to define fibromyalgia, psychiatric diagnoses, and conditions

associated with chronic pain. Unadjusted associations between patient demographics, comorbid conditions, and fibromyalgia were computed using binary logistic regression for the entire cohort and separately by gender. RESULTS: Overall, 4.6% of the sample had a fibromyalgia diagnosis, of whom 76.1% were women. Comorbid conditions were more prevalent among patients with vs without fibromyalgia. Depression and arthritis were more strongly related to fibromyalgia among women (odds ratio [OR]=2.80, 95% confidence interval [CI]=2.50-3.13; and OR=5.19, 95% CI=4.62-5.84) compared with men (OR=2.16, 95% CI=1.71-2.71; and (OR=3.91, 95% CI=3.22-4.75). The relationship of fibromyalgia and other diagnoses did not significantly differ by gender. CONCLUSIONS: Except for depression and arthritis, the burden of comorbid conditions in patients with fibromyalgia is similar in women and men treated in primary care. Fibromyalgia comorbidities in primary care are similar to those found in specialty care.

Migraine in relation with endometriosis phenotypes: Results from a French case-control study.
Maitrot-Mantelet L, Hugon-Rodin J, Vatel M, Marcellin L, Santulli P, Chapron C, Plu-Blureau G.
Cephalalgia. 2019 Dec 6:333102419893965. doi: 10.1177/0333102419893965.

BACKGROUND: Studies have shown a significant association between migraine and endometriosis, but no study has explored the relationship between migraine and endometriosis phenotypes: Superficial peritoneal endometriosis, ovarian endometrioma, and deep infiltrating endometriosis. METHODS: We conducted a case-control study using data collected from 314 women aged 18 to 42 years who had undergone surgery for benign gynecological conditions between January 2013 and December 2015. All women completed a self-administered headache questionnaire according to the IHS classification. Cases (n=182) are women with histologically proven endometriosis and controls are women (n=132) without endometriosis. Occurrence of migraine was studied according to endometriosis phenotypes. RESULTS: Migraine prevalence in cases was significantly higher compared with controls (35.2% vs. 17.4%, p=0.003). The risk of endometriosis was significantly higher in migrainous women (OR=2.62; 95% CI=1.43-4.79). When we take into account endometriosis phenotypes, the risk of ovarian endometrioma and deep infiltrating endometriosis were significant (OR=2.78; 95% CI=1.11-6.98 and OR=2.51; 95% CI=1.25-5.07, respectively). In women with endometriosis, the intensity of chronic non-cyclical pelvic pain was significantly greater for those with migraine (visual analogic scale (VAS)=3.6 +/- 2.9) compared with the women without headache (VAS=2.3 +/- 2.8, p=0.0065). CONCLUSION: Our study shows a significant association between migraine and endometriosis. In clinical practice, women of reproductive age who suffer from migraine should be screened for endometriosis criteria in order to optimise the medical and therapeutic care of this condition.

Bodily changes and sensory sensitivity in complex regional pain syndrome and fibromyalgia.
Ten Brink AF, Peters L, Kompouli PI, Jordan A, McCabe CS, Goebel A, Bultitude JH.
Pain. 2020 Feb 10. doi: 10.1097/j.pain.0000000000001830.

Complex regional pain syndrome (CRPS) and fibromyalgia are chronic pain conditions of unexplained origins. In addition to symptoms in the diagnostic criteria, patients can report changes to vision and other sensations or bodily functions. It is unclear whether these are greater than would be expected due to normal ageing, living with chronic pain generally, or common co-morbidities of chronic pain such as depression or anxiety. We administered an on-line survey evaluating the frequencies and types of self-reported somatic symptoms, bodily changes, and sensory sensitivity in respondents with CRPS (n=390), fibromyalgia (n=425), and both CRPS

and fibromyalgia ('CRPS+fibromyalgia'; n=88) compared to respondents with other chronic pain conditions (n=331) and pain-free controls (n=441). The survey assessed somatic symptoms (Patient Health Questionnaire-15), bodily changes, pain/discomfort/distress triggers, and pain intensifiers. We conducted ANCOVA's with age, sex, Patient Health Questionnaire-9 (measuring depression), Generalized Anxiety Disorder-7, pain duration in years, hours of pain per day, and number of pain-related medical diagnoses as covariates. After controlling for covariates, respondents with CRPS and/or fibromyalgia reported more somatic symptoms, changes in movement and biological responses, pain/discomfort/distress triggers, and pain intensifiers than pain(-free) control groups. Fibromyalgia specifically related to changes in vision and hearing; urinary/intestinal function; and drinking and eating. CRPS changes related to changes in hair, skin, and nails; and infection and healing. The CRPS+fibromyalgia group presented with features of both disorders with minimal additional stressors or symptoms over and above these. Our findings suggest CRPS and fibromyalgia share underlying pathophysiologies, although specific mechanisms might be different.

Social factors, disability and depressive symptoms in adults with chronic pain.
Sole E, Racine M, Tome-Pires C, Galan S, Jensen MP, Miro J.
Clin J Pain. 2020 Feb 7. doi: 10.1097/AJP.0000000000000815.

OBJECTIVES: The primary aim of this study was to better understand the role that social factors (i.e., social support, satisfaction in participation with social roles, social isolation, and self-perceived ability to perform social roles and activities) play in pain-related interference and depressive symptoms in adults with chronic pain. Moreover, this study also examined if sex exerts a moderating role in these associations. METHODS: In this cross-sectional-study, three hundred and sixty-four adults with chronic pain participated: 133 were university students and 231 were individuals from the community. University students completed a paper-and-pencil survey and individuals from the community responded to a web-based survey. Both surveys included the same questions assessing socio-demographic, pain characteristics, pain-related interference, depressive symptoms and social factors. RESULTS: Only satisfaction in participation in social usual roles and self-perceived ability for participating in such social roles contributed independently, significantly and negatively to the prediction of pain interference, whereas all four social factors made independent and significant contributions to the prediction of depressive symptoms. Satisfaction with participation in usual social roles, self-perceived social ability and social support were negatively related to depressive symptoms, whereas social isolation was positively related. The results also indicated that sex moderated the associations between social factors and depressive symptoms, but not between social factors and pain interference. DISCUSSION: The study provides important new findings regarding the associations between social factors and physical and psychological function of individuals with chronic pain, supporting biopsychosocial models.

The impact of the presence of fibromyalgia on fatigue in patients with psoriatic arthritis: comparison with controls.
Ulus Y, Akyol Y, Bilgici A, Kuru O.
Adv Rheumatol. 2019 Dec 31;60(1):1. doi: 10.1186/s42358-019-0104-6.

BACKGROUND: Coexisting fibromyalgia (FM) to psoriatic arthritis (PsA) has been identified and it has been associated with more severe symptoms, impaired function, and greater disability. It was aimed to explore the effect of the presence of FM on fatigue in patients with PsA comparing with controls. METHODS: Fifty patients with PsA and 34 sex-age matched controls were enrolled. In patients;pain was assessed by Visual Analogue Scale, disease activity by DAS-28, enthesitis by The Leeds Enthesitis Index. Fatigue level of all participants was evaluated by Multidimensional

Assessment of Fatigue. In all participants, FM was determined according to 2010 American College of Rheumatology criteria. RESULTS: Seventeen patients with PsA (34%) and 4 controls (11.8%) were diagnosed with FM and all of them were women. There was significant difference between the patients and controls in terms of presence of FM ($p<0.05$). Patients' fatigue scores were significantly higher than controls' ($p=0.001$). There were significant differences between the PsA patients with and without FM with regard to gender, enthesitis, DAS-28 and pain scores ($p<0.05$); fatigue scores ($p<0.001$). The significant effect of the presence of FM on fatigue was found by univariate analysis of variance in patients ($p<0.001$). CONCLUSION: It was observed that FM presence and fatigue were more common in PsA patients than controls and comorbid FM had significant effect on fatigue in these patients. Physicians should be aware of the possibility of concomitant FM in patients with PsA.

A systematic review and meta-analysis of the associations between endometriosis and irritable bowel syndrome.
Saidi K, Sharma S, Ohlsson B.
Eur J Obstet Gynecol Reprod Biol. 2020 Mar;246:99-105. doi: 10.1016/j.ejogrb.2020.01.031.

Endometriosis and Irritable Bowel Syndrome (IBS) are common conditions among young women of reproductive age. The etiologies to the diseases are uncertain, but multifactorial pathophysiology has been proposed for each of them. Many studies have examined the two conditions separately, but the literature on the associations between endometriosis and IBS is sparse. However, there is an increasing amount of research on how endometriosis patients are likely to also have a diagnosis of IBS. Furthermore, endometriosis shares several features with IBS, such as low-grade inflammation and visceral hypersensitivity. This systematic review summarized published original articles in English that have compared associations between endometriosis and IBS. The inclusion criteria for articles in the review were: i) endometriosis was diagnosed by surgical methods, ii) gastrointestinal symptoms were examined in a structured manner and iii) IBS was diagnosed by Rome criteria. From the initial 254 publications identified on PubMed, Web of Science and EMBASE, 13 fulfilled the criteria and could finally be included in the summary. The findings from the review showed that women diagnosed with endometriosis seem to have a twofold or threefold risk to also fulfill the criteria for IBS. The summary risk estimate of the four studies included in the meta-analysis was 2.39 (95 % confidence interval: 1.83-3.11). In women initially diagnosed with IBS, some studies reported a threefold risk of having an endometriosis diagnosis. Despite the strong associations reported between the two conditions, this review also revealed a gap in adjusting for factors that may have affected the expression of gastrointestinal symptoms, e.g., phases of the menstrual cycle, medication and psychological aspects, which may have interpretation of the reviewed articles' results. The conclusion of this review is that there is a coexistence of gastrointestinal symptoms fulfilling the Rome criteria in patients with endometriosis, but it is uncertain whether there is a true comorbidity between endometriosis and IBS, or whether the gastrointestinal symptomatology in endometriosis depends on medication. Additionally, the adequacy of the Rome criteria to differentiate IBS from the shared symptomatology of other diseases with visceral hypersensitivity must be further evaluated.

Irritable bowel, chronic widespread pain, chronic fatigue and related syndromes are prevalent and highly overlapping in the general population: DanFunD.
Petersen MW, Schroder A, Jorgensen T, Ornbol E, Meinertz Dantoft T, Eliasen M, Benros ME, Fink P.
Sci Rep. 2020 Feb 24;10(1):3273. doi: 10.1038/s41598-020-60318-6.

Prevalence of functional somatic syndromes (FSS) in the general population varies with observed overlap between syndromes. However, studies including a range of

FSS are sparse. We investigated prevalence and characteristics of various FSS and the unifying diagnostic construct bodily distress syndrome (BDS), and identified mutual overlap of the FSS and their overlap with BDS. We included a stratified subsample of 1590 adults from a randomly selected Danish general population sample (n=7493). Telephonic diagnostic interviews performed by three trained physicians were used to identify individuals with FSS and BDS. Prevalence of overall FSS was 9.3%; 3.8% for irritable bowel, 2.2% for chronic widespread pain, 6.1% for chronic fatigue, 1.5% for whiplash associated disorders, and 0.9% for multiple chemical sensitivity. Prevalence of BDS was 10.7% where 2.0% had the multi-organ type. FSS were highly overlapping with low likelihood of having a "pure" type. Diagnostic agreement of FSS and BDS was 92.0%. Multi-syndromatic FSS and multi-organ BDS were associated with female sex, poor health, physical limitations, and comorbidity. FSS are highly prevalent and overlapping, and multi-syndromatic cases are most affected. BDS captured the majority of FSS and may improve clinical management, making the distinction between multi- and mono-syndromatic patients easier.

Gender differences in the prevalence and characteristics of pain in Spain: Report from a population-based study.
Jimenez-Trujillo I, Lopez-de-Andres A, Del Barrio JL, Hernandez-Barrera V, Valero-de-Bernabe M, Jimenez-Garcia R.
Pain Med. 2019 Dec 1;20(12):2349-2359. doi: 10.1093/pm/pnz004.

OBJECTIVE: To assess the prevalence and characteristics of chronic neck pain, chronic low back pain, and migraine or frequent headaches among Spanish adults in 2014 according to gender, to identify predictors for each of these types of pains, and to compare the prevalence with those found in 2009.DESIGN: Cross-sectional study. SETTING: Spain. METHODS: We used data collected from the 2014 European Health Interview Survey (n=22,842). Sociodemographic features, self-rated health status, lifestyle habits, comorbid conditions, pain characteristics, and self-reported use of medications were analyzed. RESULTS: The prevalence of all types of pain was significantly higher among women than men. For chronic neck pain, the figures were 25.68% vs 12.54%, for chronic low back pain, 27.03% vs 18.83%, and for migraine or frequent headaches, 15.93% vs 6.74%, in women and men, respectively. Predictors of these types of pain included female gender, advanced age, poor self-rated health, psychological distress, comorbidities, and obesity. The prevalence of neck pain and low back pain increased from 2009 to 2014 for both sexes, and the prevalence of migraine or frequent headaches remained stable over time. CONCLUSIONS: The prevalence and intensity of all the forms of chronicpain were higher among women. Women experiencing pain used prescribed medications for pain, anxiety, and/or depression and sleeping pills more than men. The prevalence of chronic neck and low back has increased in the last five years in Spain, and the prevalence of migraine or frequent headaches has remained stable.

Does disordered sleep moderate the relationship between pain, disability and downstream health care utilization in patients with low back pain?: A longitudinal cohort from the US Military Health System.
Rhon DI, O'Hagan E, Mysliwiec V, Lentz TA.
Spine (Phila Pa 1976). 2019 Nov 1;44(21):1481-1491. doi: 10.1097/BRS.0000000000003114.

STUDY DESIGN: Prospective cohort. OBJECTIVE: The purpose of this study was to evaluate the influence of disordered sleep on the relationship between pain and health care utilization (HCU) and pain-related disability and HCU in individuals with low back pain (LBP). SUMMARY OF BACKGROUND DATA: Disordered sleep and pain influence LBP outcomes, but their relationship with health care seeking after an episode of LBP has not been investigated and could help identify who is at risk for long-term medical care. METHODS: This study included patients with LBP

participating in a self-management class at a large US military hospital between March 1, 2010 and December 4, 2012. Pain intensity, disability (Oswestry Disability Index), and sleepiness (Epworth Sleepiness Scale) were captured at baseline. Medical visits for a sleep disorder in the 12 months before the class and LBP-related healthcare utilization for the 12 months following the class were abstracted from the Military Health System Data Repository. Separate multivariate analyses evaluating pain intensity and disability as predictors of HCU were developed, with sleepiness and the presence of a sleep disorder as potential moderators. Analyses were adjusted for age, sex, history of back pain, and mental health comorbidities. RESULTS: A total of 757 consecutive participants were included, with 195 (26.8%) diagnosed with a subsequent sleep disorder. Sleepiness was not a significant predictor of HCU. The main effects of disability, pain intensity, and presence of a sleep disorder were significant across all analyses, with higher disability, pain intensity, and presence of a sleep disorder associated with higher predicted visits and costs for LBP. The presence of a sleep disorder was not a significant moderator in any model. CONCLUSION: Higher pain intensity and disability predicted higher pain-related HCU in the year following a LBP self-management class. The presence of a sleep disorder diagnosis, as recorded in medical records, had a significant independent effect on LBP-related health care visits and costs beyond the influences of pain intensity, disability, and other key demographic and health-related characteristics, but did not moderate these relationships.

Do socio-demographic characteristics and/or health status explain the magnitude of differences between patient and general public utility values? A chronic low back pain patients case study.
van Dongen JM, van Hooff ML, Finch AP, van Tulder MW, Bosmans JE, Ostelo RWJG, de Kleuver M.
Health Qual Life Outcomes. 2019 Nov 6;17(1):166. doi: 10.1186/s12955-019-1240-8.

BACKGROUND: Utility values can be obtained from different respondent groups, including patients and members of the general public. Evidence suggests that patient values are typically higher than general public values. This study explores whether the magnitude of disagreement between both values can be explained by socio-demographic characteristics and/or health status. METHODS: Data of 5037 chronic low back pain patients were used. Self-reported EQ-VAS was employed as a proxy of patients' preference for their own health state. General public values for the patients' EQ-5D-3L health states were obtained using the Dutch VAS-based tariff. The difference between patient and general public values was assessed using a paired t-test. Subsequently, this difference was used as a dependent variable and regressed upon dummy variables of socio-demographic and health status characteristics. Coefficients represented age, gender, education level, social support, back pain intensity, leg pain intensity, functional status, comorbidities, catastrophizing, and treatment expectations. RESULTS: Patient values were higher than general public values (0.069; 95%CI:0.063-0.076). The magnitude of disagreement between both values was associated with age, gender, education level, social support, functional status, and comorbidities, but not with back pain intensity, leg pain intensity, catastrophizing, and treatment expectations. CONCLUSIONS: Patients were found to value their own health status higher than members of the general public. The magnitude of disagreement between both values was found to differ by various socio-demographic and/or health status characteristics. This suggest that patient characteristics account for a relevant fraction of the identified disagreements between patient and general public values, and that mechanisms thought to be responsible for these disagreements, such as adaptation and response shift, have a differential impact across patient sub-groups.

CLINICAL STUDIES

Exploring natural clusters of chronic migraine phenotypes: A cross-sectional clinical study.
Woldeamanuel YW, Sanjanwala BM, Peretz AM, Cowan RP.
Sci Rep. 2020 Feb 18;10(1):2804. doi: 10.1038/s41598-020-59738-1.

Heterogeneity in chronic migraine (CM) presents significant challenge for diagnosis, management, and clinical trials. To explore naturally occurring clusters of CM, we utilized data reduction methods on migraine-related clinical dataset. Hierarchical agglomerative clustering and principal component analyses (PCA) were conducted to identify natural clusters in 100 CM patients using 14 migraine-related clinical variables. Three major clusters were identified. Cluster I (29 patients) - the severely impacted patient featured highest levels of depression and migraine-related disability. Cluster II (28 patients) - the minimally impacted patient exhibited highest levels of self-efficacy and exercise. Cluster III (43 patients) - the moderately impacted patient showed features ranging between Cluster I and II. The first 5 principal components (PC) of the PCA explained 65% of variability. The first PC (eigenvalue 4.2) showed one major pattern of clinical features positively loaded by migraine-related disability, depression, poor sleep quality, somatic symptoms, post-traumatic stress disorder, being overweight and negatively loaded by pain self-efficacy and exercise levels. CM patients can be classified into three naturally-occurring clusters. Patients with high self-efficacy and exercise levels had lower migraine-related disability, depression, sleep quality, and somatic symptoms. These results may ultimately inform different management strategies.

Persistent dentoalveolar pain disorder: A putative intraoral chronic overlapping pain condition.
Herrero Babiloni A, Nixdorf DR, Moana-Filho EJ.
Oral Dis. 2019 Dec 4. doi: 10.1111/odi.13248.

Chronic overlapping pain conditions (COPCs) are conditions that share several clinical characteristics and symptomatology, are usually considered idiopathic in nature, and are frequently comorbid. Currently, there are no established inclusion criteria to determine which conditions should be included under this umbrella term despite different systems proposed. Persistent dentoalveolar pain disorder (PDAP), also referred to as atypical odontalgia and thought to be a component of persistent idiopathic facial pain, is a chronic pain condition that manifests as a persistent tooth pain or pain over a dentoalveolar site formerly occupied by a tooth in the absence of detectable pathology during clinical or radiological examination. PDAP is considered idiopathic in nature, and its pathophysiological mechanisms are not fully understood. Our objective was to investigate whether PDAP fits the conceptual paradigm of COPC given its characteristics and commonalities with other COPC, based on published literature identified through a scoping review. We found that PDAP fits 16 out of 18 common characteristics among COPCs, and based on this finding, we discuss the implications of PDAP being considered a COPC.

Clinical profile of comorbid dysmenorrhea and bladder sensitivity: a cross-sectional analysis.
Tu FF, Datta A, Atashroo D, Senapati S, Roth G, Clauw DJ, Hellman KM.
Am J Obstet Gynecol. 2019 Dec 20. pii: S0002-9378(19)32767-X. doi: 10.1016/j.ajog.2019.12.010.

BACKGROUND: Antecedents of chronic pelvic pain are not well characterized, but pelvic organ visceral sensitivity is a hallmark of these disorders. Recent studies have identified that some dysmenorrhea sufferers are much more likely to exhibit comorbid bladder hypersensitivity. Presumably, these otherwise healthy women may be at

higher risk of developing full-blown chronic bladder pain later in life. To encourage early identification of patients harboring potential future risk of chronic pain, we describe the clinical profile of women matching this putative pain-risk phenotype. OBJECTIVE(S): The objectives of the study were to characterize demographic, menstrual, pelvic examination, and psychosocial profiles of young women with comorbid dysmenorrhea and bladder hypersensitivity, defined using a standardized experimental visceral provocation test, contrasted with healthy controls, pure dysmenorrhea sufferers, and women with existing bladder pain syndrome. STUDY DESIGN: This prospective cohort study acquired data on participants with moderate to severe dysmenorrhea (n = 212), healthy controls (n = 44), and bladder pain syndrome (n = 27). A subgroup of dysmenorrhea patients was found on screening with noninvasive oral water challenge to report significantly higher bladder pain during experimentally monitored spontaneous bladder filling (>15 out of 100 on visual analogue scale, based on prior validation studies) and separately defined as a group with dysmenorrhea plus bladder pain. Medical/menstrual history and pain history were evaluated with questionnaires. Psychosocial profile and impact were measured with validated self-reported health status Patient Reported Outcomes Measurement Information System short forms and a Brief Symptom Inventory for somatic sensitivity. Pelvic anatomy and sensory sensitivity were examined via a standardized physical examination and a tampon provocation test. RESULTS: In our largely young, single, nulliparous cohort (24 ± 1 years old), approximately a quarter (46 out of 212) of dysmenorrhea sufferers tested positive for the dysmenorrhea plus bladder pain phenotype. Dysmenorrhea-only sufferers were more likely to be African American (24%) than healthy controls (5%, post hoc χ^2, P = .007). Pelvic examination findings did not differ in the nonchronic pain groups, except for tampon test sensitivity, which was worse in dysmenorrhea plus bladder pain and dysmenorrhea sufferers vs healthy controls (2.6 ± 0.3 and 1.7 ± 0.2 vs 0.7 ± 0.2, P < .05). Consistent with heightened pelvic sensitivity, participants with dysmenorrhea plus bladder pain also had more nonmenstrual pain, dysuria, dyschezia, and dyspareunia (P's < .05). Participants with dysmenorrhea plus bladder pain had Patient Reported Outcomes Measurement Information System Global Physical T-scores of 47.7 ± 0.9, lower than in women with dysmenorrhea only (52.3 ± 0.5), and healthy controls 56.1 ± 0.7 (P < .001). Similarly, they had lower Patient Reported Outcomes Measurement Information System Global Mental T-score than healthy controls (47.8 ± 1.1 vs 52.8 ± 1.2, P = .017). Similar specific impairments were observed on Patient Reported Outcomes Measurement Information System scales for anxiety, depression, and sleep in participants with dysmenorrhea plus bladder pain vs healthy controls. CONCLUSION: Women with dysmenorrhea who are unaware they also have bladder sensitivity exhibit broad somatic sensitivity and elevated psychological distress, suggesting combined preclinical visceral sensitivity may be a precursor to chronic pelvic pain. Defining such precursor states is essential to conceptualize and test preventative interventions for chronic pelvic pain emergence. Dysmenorrhea plus bladder pain is also associated with higher self-reported pelvic pain unrelated to menses, suggesting central nervous system changes are present in this potential precursor state.

Irritable bowel syndrome-like disorders in endometriosis: Prevalence of nickel sensitivity and effects of a low-nickel diet. An open-label pilot study.
Borghini R, Porpora MG, Casale R, Marino M, Palmieri E, Greco N, Donato G, Picarelli A.
Nutrients. 2020 Jan 28;12(2). pii: E341. doi: 10.3390/nu12020341.

Alimentary nickel (Ni) may result in allergic contact mucositis (ACM), whose prevalence is >30% and may present with IBS-like and extra-intestinal symptoms. These symptoms are also frequent in endometriosis, and Ni allergic contact dermatitis has already been observed in endometriosis. Therefore, intestinal and extra-intestinal symptoms in endometriosis may depend on a Ni ACM, and a low-Ni diet could improve

symptoms. We studied the prevalence of Ni ACM in endometriosis and focused on the effects of a low-Ni diet on gastrointestinal, extra-intestinal, and gynecological symptoms. We recruited 84 women with endometriosis, symptomatic for gastrointestinal disorders. Thirty-one out of 84 patients completed the study. They underwent Ni oral mucosa patch test (omPT), questionnaire for intestinal/extra-intestinal/gynecological symptoms, and a low-Ni diet. Clinical evaluation was performed at baseline (T0) and after three months (T1). Twenty-eight out 31 (90.3%) patients showed Ni omPT positive results, with Ni ACM diagnosis, whereas three out of 31 (9.7%) patients showed negative Ni omPT. After three months of low-Ni diet, all gastrointestinal, extra-intestinal and gynecological symptoms showed a statistically significant reduction. Ni ACM has a high prevalence in endometriosis and a low-Ni diet may be recommended in this condition to reduce gastrointestinal, extra-intestinal and gynecological symptoms.

The effect of comorbid medical and psychiatric diagnoses on chronic fatigue syndrome.
Natelson BH, Lin JS, Lange G, Khan S, Stegner A, Unger ER.
Ann Med. 2019 Nov - Dec;51(7-8):371-378. doi: 10.1080/07853890.2019.1683601.

Objective: To determine if presence of co-existing medically unexplained syndromes or psychiatric diagnoses affect symptom frequency, severity or activity impairment in Chronic Fatigue Syndrome. Patients: Sequential Chronic Fatigue Syndrome patients presenting in one clinical practice. Design: Participants underwent a psychiatric diagnostic interview and were evaluated for fibromyalgia, irritable bowel syndrome and/or multiple chemical sensitivity. Main Measures: Structured Clinical Interview [SCID] for DSM-IV; SF-36, Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Short Form; Patient Health Questionnaire-8; Multidimensional Fatigue Inventory (MFI-20), CDC Symptom Inventory Results: Current and lifetime psychiatric diagnosis was common (68%) increasing mental fatigue/health but no other illness variables and not with diagnosis of other medically unexplained syndromes. 81% of patients had at least one of these conditions with about a third having all three co-existing syndromes. Psychiatric diagnosis was not associated with their diagnosis. Increasing the number of these unexplained conditions was associated with increasing impairment in physical function, pain and rates of being unable to work. Conclusions: Patients with Chronic Fatigue Syndrome should be evaluated for current psychiatric conditions because of their impact on patient quality of life, but they do not act as a symptom multiplier for the illness. Other co-existing medically unexplained syndromes are more common than psychiatric co-morbidities in patients presenting for evaluation of medically unexplained fatigue and are also more associated with increased disability and the number and severity of symptoms. Key messages: When physicians see patients with medically unexplained fatigue, they often infer that this illness is due to an underlying psychiatric problem. This paper shows that the presence of co-existing psychiatric diagnoses does not impact on any aspect of the phenomenology of medically unexplained fatigue also known as chronic fatigue syndrome. Therefore, psychiatric status is not an important causal contributor to CFS. In contrast, the presence of other medically unexplained syndromes (irritable bowel syndrome; fibromyalgia and/or multiple chemical sensitivity) do impact on the illness such that the more of these that co-exist the more health-related burdens the patient has.

The Fibromyalgia Bladder Index in 100 consecutive women with fibromyalgia.
Hamed N, Rida MA, Uthman I, El Taha L, Assad M, Mikhael E, Bazi T.
Int Urogynecol J. 2020 Jan 9. doi: 10.1007/s00192-019-04199-y.

INTRODUCTION AND HYPOTHESIS: The Fibromyalgia Bladder Index (FBI) is a validated instrument to quantify bothersome bladder symptoms specifically in women with fibromyalgia syndrome (FMS). The FBI includes two sub-scales: one addressing urinary urgency and bladder pain (UP), the other addressing urinary frequency and

nocturia (FN). The objectives of this study are to evaluate the FBI in a cohort of patients with FMS, to correlate it with certain characteristics in this cohort, and to compare it with controls. METHODS: We performed a case-control study of 100 women with FMS and 155 controls. Demographic data, comorbidities, and other characteristics were registered. Comparison between FBI scores of participants with and without FMS, as well as correlation of FBI scores with the characteristics of FMS patients, were undertaken using independent two-sample t test for continuous outcomes and Pearson's Chi-squared test for categorical outcomes. RESULTS: The mean UP subscale score of the FBI was significantly higher in the FMS group (10.29 ± 5.61) compared with the controls (1.65 ± 2.65; (p = 0.001). The mean FN subscale score was significantly higher in the FMS group (9.93 ± 5.37) compared with the controls (2.95 ± 3.27; p = 0.001). FMS patients diagnosed >3 years ago had a higher UP subscale score and a higher FN subscale score compared with FMS patients diagnosed <3 years ago (p = 0.020 and p = 0.024 respectively). Menopause and parity significantly increased the FBI scores. Smoking and a history of depression did not significantly affect any of the FBI subscale scores in the FMS group. CONCLUSION: Women with FMS suffer from bothersome bladder symptoms that can be readily identified and quantified.

Top down or bottom up? An observational investigation of improvement in fibromyalgia symptoms following hip and knee replacement.
Schrepf A, Moser S, Harte SE, Basu N, Kaplan C, Kolarik E, Tsodikov A, Brummett CM, Clauw DJ.
Rheumatology (Oxford). 2020 Mar 1;59(3):594-602. doi: 10.1093/rheumatology/kez303.

OBJECTIVES: Many patients with osteoarthritis have comorbid symptoms of FM, but it is unknown how these symptoms respond to surgical procedures that address nociceptive input in the periphery, such as total joint replacement. Here we explore differences in clinical characteristics between patients whose FM symptoms do and do not improve following total hip or knee replacement. METHODS: Participants were 150 patients undergoing knee or hip replacement who had a minimum FM survey score of 4 or greater prior to surgery. The top tertile of patients experiencing the most improvement in FM symptoms at month 6 were categorized as 'Improve' (n = 48) while the bottom two tertiles were categorized as 'Worsen/Same' (n = 102). Baseline symptom characteristics were compared between groups, as well as improvement in overall pain severity, surgical pain severity and physical function at 6 months. RESULTS: The Worsen/Same group had higher levels of fatigue, depression and surgical site pain at baseline (all P < 0.05). Additionally, they improved less on overall pain severity and physical functioning 6 months after surgery (both P < 0.05). CONCLUSION: Most patients derive significant benefit in improvement of comorbid FM symptoms following total joint replacement, but a substantial proportion do not. Understanding the neurobiological basis for these different trajectories may help inform clinical judgment and improve patient care.

Association between pain phenotype and disease activity in rheumatoid arthritis patients: a non-interventional, longitudinal cohort study.
Ten Klooster PM, de Graaf N, Vonkeman HE.
Arthritis Res Ther. 2019 Nov 29;21(1):257. doi: 10.1186/s13075-019-2042-4.

BACKGROUND: In well-controlled rheumatoid arthritis (RA) without significant joint damage, a substantial proportion of patients complain of persistent pain. Previous studies have identified different pain phenotypes in RA, in which non-nociceptive pain phenotypes are associated with higher concurrent disease activity scores. In this longitudinal study, we explored associations between pain phenotypes and long-term disease activity outcome in RA patients. Secondly, we explored whether pain phenotype is associated with comorbid conditions. METHODS: One

hundred eighty established RA patients were classified with a nociceptive (61%) or a non-nociceptive (39%) pain phenotype, based on their responses to the painDETECT-questionnaire. Two years of clinical follow-up data on disease activity outcomes were collected. Information on comorbid diseases was derived from electronic patient files. RESULTS: Patients with a non-nociceptive pain phenotype showed higher mean disease activity scores (DAS28, 2.57; 95% CI, 2.37-2.77 vs. 2.11; 95% CI, 1.94-2.27;p<0.001) and a twofold lower chance of achieving sustained DAS28 remission (OR=0.49;95% CI, 0.26-0.92;p+0.020). Only the tender joint count and patient global health significantly differed between the pain phenotype groups. Patients with a non-nociceptive pain phenotype had more often been diagnosed with concurrent fibromyalgia (9.9% vs. 0.9%;p=0.007) and other pain-associated comorbid diseases (52.1% vs. 35.8%; p=0.030) compared with patients with a nociceptive pain phenotype. CONCLUSION: This longitudinal study showed consistently worse long-term disease activity outcomes in RA patients with a non-nociceptive pain phenotype which appeared to be mainly due to differences in the subjective components of the disease activity score.

Chronic pain and sleep disturbances: A pragmatic review of their relationships, comorbidities, and treatments.
Husak AJ, Bair MJ.
Pain Med. 2020 Jan 7. pii: pnz343. doi: 10.1093/pm/pnz343.

OBJECTIVE: The objective of this review is to answer three questions: 1) How are chronic pain severity and pain duration affected in patients with chronic pain and sleep disturbances that occur simultaneously? 2) What are common comorbidities and pain-related symptoms seen in patients with chronic pain and sleep disturbances? and 3) What are potentially effective pharmacological and nonpharmacological treatment options for both conditions? METHODS: Ovid Medline and PubMed were searched. Search terms included sleep wake disorder, chronic pain, fibromyalgia, treatment outcome, psychotherapy, complementary therapies, and therapeutics. Studies that assessed outcomes between individuals with chronic pain and those with concurrent chronic pain and sleep disturbances were included. Randomized controlled clinical trials of treatments for both conditions were included. RESULTS: Sixteen studies indicated that patients with both chronic pain and sleep disturbances have greater pain severity, longer duration of pain, greater disability, and are less physically active than those without sleep disturbances. Patients with both conditions are more likely to have concurrent depression, catastrophizing, anxiety, and suicidal ideation. Thirty-three randomized controlled trials assessed treatment for both chronic pain and sleep disturbances. Pregabalin was the most frequently studied medication, showing improvement in pain and sleep symptoms. Cognitive behavioral therapy for insomnia showed long-term improvement in sleep for patients with chronic pain. CONCLUSIONS: Individuals with chronic pain and sleep disturbances have greater symptom severity, longer duration of symptoms, more disability, and additional comorbidities. Pharmacological and nonpharmacological treatments may be useful in the treatment of concurrent chronic pain and sleep disturbances, but further study is needed.

Clinical and morphological effects of hyperbaric oxygen therapy in patients with interstitial cystitis associated with fibromyalgia.
Bosco G, Ostardo E, Rizzato A, Garetto G, Paganini M, Melloni G, Giron G, Pietrosanti L, Martinelli I, Camporesi E.
BMC Urol. 2019 Nov 5;19(1):108. doi: 10.1186/s12894-019-0545-6.

BACKGROUND: Interstitial Cystitis (IC) is a debilitating disorder of the bladder, with a multifactorial and poorly understood origin dealing with microcirculation repeated damages. Also Fibromyalgia (FM) is a persistent disorder whose etiology is not completely explained, and its theorized alteration of pain processing can compromise

the quality of life. Both these conditions have a high incidence of conventional therapeutic failure, but recent literature suggests a significant beneficial response to Hyperbaric Oxygen Therapy (HBOT). With this study, this study we evaluated the effects of HBOT on quality of life, symptoms, urodynamic parameters, and cystoscopic examination of patients suffering from both IC and FM. METHODS: We structured an observational clinical trial design with repeated measures (questionnaires, urodynamic test, and cystoscopy) conducted before and 6 months after a therapeutic protocol with hyperbaric oxygen for the treatment of patients suffering from both IC and FM. Patients were exposed to breathing 100% oxygen at 2 atm absolute (ATA) in a multiplace pressure chamber for 90 min using an oro-nasal mask. Patients undertook a cycle of 20 sessions for 5 days per week, and a second cycle of 20 session after 1 week of suspension. RESULTS: Twelve patients completed the protocol. Changes after HBOT were not significant, except for hydrodistension tolerance (mean pre-treatment: 409.2 ml; mean post-treatment: 489.2 ml; $p<0.05$). A regression of petechiae and Hunner's ulcers was also noted 6 months after the completion of HBOT. CONCLUSIONS: Our study showed no improvement of symptoms, quality of life, and urodynamic parameters, except for hydrodistension, and a slight improvement in cystoscopic pattern. However, to date, we could not demonstrate the significance of overall results to justify the use of HBOT alone in patients with IC and FM. This observation suggests that additional studies are needed to better understand if HBOT could treat this subset of patients.

The factors driving self-efficacy in intractable chronic pain patients: a retrospective study.
Tsuji H, Tetsunaga T, Tetsunaga T, Nishida K, Misawa H, Ozaki T.
J Orthop Surg Res. 2019 Dec 30;14(1):473. doi: 10.1186/s13018-019-1535-9.

BACKGROUND: The fear-avoidance model is a theoretical paradigm for explaining acute and chronic pain. In this model, pain catastrophizing plays an important role. On the other hand, self-efficacy influences whether patients view their pain optimistically, ultimately preventing the conversion of pain into intractable pain. The aim of the present study was to evaluate the factors that influence self-efficacy in patients with chronic pain. METHODS: Study participants included 147 outpatients (35 men, 112 women) with intractable chronic pain who visited our hospital between September 2014 and July 2015. Their mean age was 71.0 (range 32-92) years. Pain sites were as follows: low back, 97 patients; knee, 71 patients; shoulder, 34 patients; and hip, 15 patients. All patients were assessed using the following measures: Numeric Rating Scale (NRS), Pain Catastrophizing Scale (PCS), Hospital Anxiety and Depression Scale (HADS), Pain Disability Assessment Scale (PDAS), and Pain Self-Efficacy Questionnaire (PSEQ). All participants were further divided into two groups based on median PSEQ scores (group L: PSEQ of 35 points or less, n=74; group H: PSEQ greater than 35 points, n=73). The factors that influenced self-efficacy in these patients were analyzed using univariate and multiple linear regression analyses. RESULTS: Significant differences were observed in gender; pain duration; and NRS, PDAS, HADS, and PCS scores between group L and group H. Multiple linear regression analysis revealed that self-efficacy was correlated with PDAS score, HADS depression score, and pain duration. CONCLUSIONS: Patients with longer pain duration indicated greater self-efficacy and patients with higher pain disability and depression exhibited lower self-efficacy.

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 consider a contribution 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; iii) and advance industry efforts to research and development of safe and effective therapies for COPCs.

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