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 July and October 2019. 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.

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About the Chronic Pain Research Alliance

NATIONAL MULTI-SITE STUDIES

A MAPP Network case-control study of urologic chronic pelvic pain compared with non-urologic pain conditions.

Afari N, Buchwald D, Clauw D, Hong B, Hou X, Krieger JN, Mullins C, Stephens-Shields AJ, Gasperi M, Williams DA; MAPP Research Network.

Clin J Pain. 2019 Sep 26. doi: 10.1097/AJP.0000000000000769.

OBJECTIVES: Limited research suggests commonalities between urologic chronic pelvic pain syndromes (UCPPS) and other non-urologic chronic overlapping pain conditions (COPCs) including fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome. The goal of this case-control study was to examine similarities and differences between UCPPS and these other COPCs. METHODS: As part of the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research Network, we examined 1,039 individuals with UCPPS (n=424), non-urologic COPCs (n=200), and healthy controls (n=415). Validated standardized measures were used to assess urological symptoms, non-urological pain symptoms, and psychosocial symptoms and traits. RESULTS: Participants with UCPPS had more urologic symptoms than non-urologic COPCs or healthy controls (P<0.001); non-urological COPC group also had significantly worse urological symptoms than healthy controls (P<0.001). Participants with non-urological COPCs reported more widespread pain than those with UCPPS

(P<0.001), yet both groups had similarly increased symptoms of anxiety, depression, negative affect, perceived stress, neuroticism, and lower levels of extraversion than healthy controls (P<0.001). Participants with UCPPS with and without COPCs reported more catastrophizing than those with non-urological COPCs (P<0.001). DISCUSSION: Findings are consistent with the hypothesis of common underlying biopsychosocial mechanisms and can guide the comprehensive assessment and treatment of these conditions regardless of the primary site of pain or diagnosis. Heightened catastrophizing in UCPPS should be examined to inform psychosocial interventions and improve patient care.

PATHOPHYSIOLOGY STUDIES

Brain responses in CFS and TMD to autonomic challenges: An exploratory fMRI study.
Vuong QC, Allison JR, Finkelmeyer A, Newton J, Durham J.
JDR Clin Trans Res. 2019 Aug 28:2380084419872135. doi: 10.1177/2380084419872135.

INTRODUCTION: Dysfunction of the autonomic nervous system (ANS) is seen in chronic fatigue syndrome (CFS) and temporomandibular disorders (TMDs). Both conditions have poorly understood pathophysiology. Several brain structures that play a role in pain and fatigue, such as the insular cortex and basal ganglia, are also implicated in autonomic function. OBJECTIVES: ANS dysfunction may point to common neurophysiologic mechanisms underlying the predominant symptoms for CFS and TMD. No studies to date have investigated the combination of both conditions. Thus, our aim was to test whether patients with CFS with or without TMD show differences in brain responses to autonomic challenges. METHODS: In this exploratory functional imaging study, patients with CFS who screened positive for TMD (n = 26), patients who screened negative for TMD (n = 16), and age-matched control participants (n = 10) performed the Valsalva maneuver while in a 3-T magnetic resonance imaging scanner. This maneuver is known to activate the ANS. RESULTS: For all 3 groups, whole-brain F test showed increased brain activation during the maneuver in the superior and inferior frontal gyri, the left and right putamen and thalamus, and the insular cortex. Furthermore, group contrasts with small-volume correction showed that patients with CFS who screened positive for TMD showed greater activity in the left insular cortex as compared with patients who screened negative and in the left caudate nucleus as compared with controls. CONCLUSION: Our results suggest that increased activity in the cortical and subcortical regions observed during autonomic challenges may be modulated by fatigue and pain. ANS dysfunction may be a contributing factor to these findings, and further work is required to tease apart the complex relationship among CFS, TMD, and autonomic functions. KNOWLEDGE TRANSFER STATEMENT: Brain activity related to activation of the autonomic nervous system in patients with chronic fatigue syndrome who screened positive for painful temporomandibular disorder was greater than in patients who screened negative; activity was seen in brain regions associated with autonomic functions and pain. These findings suggest that autonomic dysfunction may play a role in the pathophysiology of both conditions, explain some of the apparent comorbidity between them, and offer avenues to help with treatment.

MicroRNAs as biomarkers of pain intensity in patients with chronic fatigue syndrome.
Al-Rawaf HA, Alghadir AH, Gabr SA.
Pain Pract. 2019 Jul 8. 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.

Autoantibodies common in patients with gastrointestinal diseases are not found in patients with endometriosis: A cross-sectional study.
Ek M, Roth B, Valentin L, Nordengren J, Ohlsson B.
Eur J Obstet Gynecol Reprod Biol. 2019 Sep;240:370-374. doi: 10.1016/j.ejogrb.2019.05.040.

OBJECTIVES: Gastrointestinal symptoms are common in endometriosis, but the mechanisms behind these symptoms are yet poorly understood. Associations between endometriosis and irritable bowel syndrome (IBS), celiac disease, and various autoimmune diseases have been reported. These diseases express characteristic autoantibodies. The aim of the current study was to investigate autoantibodies against gonadotropin-releasing hormone 1 (GnRH1) and luteinizing hormone (LH) and their receptors, tenascin-C, matrix metalloproteinase-9, deamidated gliadin peptide, and tissue transglutaminase in a cohort of women with endometriosis, compared to controls and women with IBS or enteric dysmotility. STUDY DESIGN: One hundred seventy-two women with laparoscopy-verified endometriosis completed questionnaires regarding socio-demographics, lifestyle habits, medical history, and gastrointestinal symptoms, and sera were analyzed with ELISA for the abovementioned antibodies. Healthy female blood donors (n=100) served as controls, and women with IBS or enteric dysmotility (n=29) were used for comparison. RESULTS: A non-significantly higher prevalence of IgM antibodies directed at tenascin-C (7.6% vs. 2.0%; p=0.06) was the only observed difference in autoantibody levels in endometriosis compared to controls. Antibody presence was not associated with any clinical parameters. Patients with IBS or enteric dysmotility expressed higher levels of IgM antibodies against GnRH1 compared to both patients with endometriosis (p=0.004) and healthy controls (p=0.002), and higher levels of tenascin-C antibodies compared to healthy controls (17.2% vs. 2.0%; p=0.006). CONCLUSIONS: Women with endometriosis do not express higher prevalence of autoantibodies found to be characteristic in other patient groups with gastrointestinal symptoms.

Linaclotide treatment reduces endometriosis-associated vaginal hyperalgesia and mechanical allodynia through viscerovisceral cross-talk.
Ge P, Ren J, Harrington AM, Grundy L, Castro J, Brierley SM, Hannig G.
Pain. 2019 Jul 16. doi: 10.1097/j.pain.0000000000001657.

Endometriosis, an estrogen-dependent chronic inflammatory disease, is the most common cause of chronic pelvic pain. Here, we investigated the effects of linaclotide, a Food and Drug Administration-approved treatment for IBS-C, in a rat model of endometriosis. Eight weeks after endometrium transplantation into the intestinal mesentery, rats developed endometrial lesions as well as vaginal hyperalgesia to

distension and decreased mechanical hind paw withdrawal thresholds. Daily oral administration of linaclotide, a peripherally restricted guanylate cyclase-C (GC-C) agonist peptide acting locally within the gastrointestinal tract, increased pain thresholds to vaginal distension and mechanical hind paw withdrawal thresholds relative to vehicle treatment. Furthermore, using a cross-over design, administering linaclotide to rats previously administered vehicle resulted in increased hind paw withdrawal thresholds, whereas replacing linaclotide with vehicle treatment decreased hind paw withdrawal thresholds. Retrograde tracing of sensory afferent nerves from the ileum, colon, and vagina revealed that central terminals of these afferents lie in close apposition to one another within the dorsal horn of the spinal cord. We also identified dichotomizing dual-labelled ileal/colon innervating afferents as well as colon/vaginal dual-labelled neurons and a rare population of triple traced ileal/colon/vaginal neurons within thoracolumbar DRG. These observations provide potential sources of cross-organ interaction at the level of the DRG and spinal cord. GC-C expression is absent in the vagina and endometrial cysts suggesting that the actions of linaclotide are shared through nerve pathways between these organs. In summary, linaclotide may offer a novel therapeutic option not only for treatment of chronic endometriosis-associated pain, but also for concurrent treatment of comorbid chronic pelvic pain syndromes.

Foot shock stress generates persistent widespread hypersensitivity and anhedonic behavior in an anxiety-prone strain of mice.
Wu PY, Yang X, Wright DE, Christianson JA.
Pain. 2019 Sep 21. doi: 10.1097/j.pain.0000000000001703.

A significant subset of patients with urologic chronic pelvic pain syndrome (UCPPS) suffer from widespread, as well as pelvic, pain and experience mood-related disorders, including anxiety, depression, and panic disorder. Stress is a commonly-reported trigger for symptom onset and exacerbation within these patients. The link between stress and pain is thought to arise, in part, from the hypothalamic-pituitary-adrenal (HPA) axis, which regulates the response to stress and can influence the perception of pain. Previous studies have shown that stress-exposure in anxiety-prone rats can induce both pelvic and widespread hypersensitivity. Here, we exposed female A/J mice, an anxiety-prone inbred murine strain, to 10 days of foot shock stress to determine stress-induced effects on sensitivity, anhedonia, and HPA axis regulation and output in. At 1- and 28-days post-foot shock, A/J mice displayed significantly increased bladder sensitivity and hind paw mechanical allodynia. They also displayed anhedonic behavior, measured as reduced nest building scores and a decrease in sucrose preference during the 10-day foot shock exposure. Serum corticosterone was significantly increased at 1-day post-foot shock and bladder mast cell degranulation rates were similarly high in both sham- and shock-exposed mice. Bladder cytokine and growth factor mRNA levels indicated a persistent shift toward a pro-inflammatory environment following foot shock exposure. Together, these data suggest that chronic stress exposure in an anxiety-prone mouse strain may provide a useful translational model for understanding mechanisms that contribute to widespreadness of pain and increased comorbidity in a subset of UCPPS patients.

Morphological changes in the temporomandibular joints in women with fibromyalgia and myofascial pain: A case series.
Santos CEM, Rodrigues VP, De Oliveira ICV, De Asses DSFR, De Oliveira MM, Conti CF.
Cranio. 2019 Aug 3:1-5. doi: 10.1080/08869634.2019.1650215.

Objective: This study investigated the temporomandibular joint (TMJ) morphological changes in women with fibromyalgia (FM) through clinical and tomographic evaluation. Methods: Ten women diagnosed with myofascial pain who were being treated for FM in a university hospital were included in this study. The data were collected through clinical examination and cone beam computed tomography evaluation of the TMJ in closed and open mouth positions. Results: All patients had crackling in the joint, a habit of grinding teeth during sleep, muscle stiffness, and tinnitus. The tomographic findings revealed a higher frequency of condylar bone wear, reduction of joint space, and posterior positioning of the mandibular condyle. The temporomandibular disorders with the highest

prevalence were osteoarthritis and disc displacement with reduction. Conclusion: The findings suggest that women with FM have a high frequency of TMD related to the displacement of the articular disc, condyle position, and occurrence of osteoarthritis.

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. 2019 Sep 23. 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 catabolized 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 analyzed 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=0.023) and positive correlations between KYN/TRP and pain intensity (r_s =0.59 p=0.013). In FM, KYN/TRP was negatively correlated to anxiety symptoms (r_s =-0.36 p=0.022) and a trend towards significantly lower TRP levels was found compared to controls (p=0.05). 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.

Inflammation is associated with pro-nociceptive brain connections in rheumatoid arthritis patients with concomitant fibromyalgia.
Kaplan CM, Schrepf A, Ichesco E, Larkin T, Harte SE, Harris RE, Murray AD, Waiter GD, Clauw DJ, Basu N.
Arthritis Rheumatol. 2019 Aug 5. doi: 10.1002/art.41069.

OBJECTIVE: Rheumatoid arthritis (RA) patients with comorbid fibromyalgia (FM) manifest alterations in brain connectivity synonymous with central sensitization. Here we consider how peripheral inflammation, the principal nociceptive stimulus in RA, interacts with brain connectivity in RA patients with comorbid FM. METHODS: RA patients with (FM+, n=27) and without (FM-, n=27) comorbid FM completed functional connectivity magnetic resonance imaging. Seed to whole-brain functional connectivity analyses were conducted using left mid/posterior insula and left inferior parietal lobule (IPL) seeds, regions previously linked to FM symptoms and inflammation respectively. The association between functional connectivity and erythrocyte sedimentation rate (ESR) was assessed in each FM group separately, followed by post-hoc analyses to test for interaction effects. Significance was set at a cluster-level family-wise error (FWE) rate of $p < 0.05$. RESULTS: RA patients with and without FM did not differ by age, gender or ESR ($p > 0.2$). In FM+ RA patients, increased insula - left IPL, left IPL - dorsal anterior cingulate and left IPL - medial prefrontal cortex functional connectivity correlated with higher levels of ESR (all $p < 0.05$ FWE). Post-hoc interaction analyses largely confirmed that the relationship between ESR and connectivity changes as FM scores increase. CONCLUSION: Here we provide the first neurobiological evidence that comorbid FM in RA may be linked to peripheral inflammation through pro-nociceptive patterns of brain connectivity. In patients with such 'bottom-up' pain centralization, comorbid symptoms may partially respond to anti-inflammatory treatments.

Machine learning to understand the immune-inflammatory pathways in fibromyalgia.

Andres-Rodriguez L, Borras X, Feliu-Soler A, Perez-Aranda A, Rozadilla-Sacanell A, Arranz B, Montero-Marin J, Garcia-Campayo J, Angarita-Osorio N, Maes M, Luciano JV. Int J Mol Sci. 2019 Aug 29;20(17). pii: E4231. doi: 10.3390/ijms20174231.

Fibromyalgia (FM) is a chronic syndrome characterized by widespread musculoskeletal pain, and physical and emotional symptoms. Although its pathophysiology is largely unknown, immune-inflammatory pathways may be involved. We examined serum interleukin (IL)-6, high sensitivity C-reactive protein (hs-CRP), CXCL-8, and IL-10 in 67 female FM patients and 35 healthy women while adjusting for age, body mass index (BMI), and comorbid disorders. We scored the Fibromyalgia Severity Score, Widespread Pain Index (WPI), Symptom Severity Scale (SSS), Hospital Anxiety (HADS-A), and Depression Scale and the Perceived Stress Scale (PSS-10). Clinical rating scales were significantly higher in FM patients than in controls. After adjusting for covariates, IL-6, IL-10, and CXCL-8 were lower in FM than in HC, whereas hs-CRP did not show any difference. Binary regression analyses showed that the diagnosis FM was associated with lowered IL-10, quality of sleep, aerobic activities, and increased HADS-A and comorbidities. Neural networks showed that WPI was best predicted by quality of sleep, PSS-10, HADS-A, and the cytokines, while SSS was best predicted by PSS-10, HADS-A, and IL-10. Lowered levels of cytokines are associated with FM independently from confounders. Lowered IL-6 and IL-10 signaling may play a role in the pathophysiology of FM.

Delineating conditions and subtypes in chronic pain using neuroimaging.
Holmes SA, Upadhyay J, Borsook D.
Pain Rep. 2019 Aug 7;4(4):e768. doi: 10.1097/PR9.0000000000000768. eCollection 2019 Jul-Aug.

Differentiating subtypes of chronic pain still remains a challenge-both from a subjective and objective point of view. Personalized medicine is the current goal of modern medical care and is limited by the subjective nature of patient self-reporting of symptoms and behavioral evaluation. Physiology-focused techniques such as genome and epigenetic analyses inform the delineation of pain groups; however, except under rare circumstances, they have diluted effects that again, share a common reliance on behavioral evaluation. The application of structural neuroimaging towards distinguishing pain subtypes is a growing field and may inform pain-group classification through the analysis of brain regions showing hypertrophic and atrophic changes in the presence of pain. Analytical techniques such as machine-learning classifiers have the capacity to process large volumes of data and delineate diagnostically relevant information from neuroimaging analysis. The issue of defining a "brain type" is an emerging field aimed at interpreting observed brain changes and delineating their clinical identity/significance. In this review, 2 chronic pain conditions (migraine and irritable bowel syndrome) with similar clinical phenotypes are compared in terms of their structural neuroimaging findings. Independent investigations are compared with findings from application of machine-learning algorithms. Findings are discussed in terms of differentiating patient subgroups using neuroimaging data in patients with chronic pain and how they may be applied towards defining a personalized pain signature that helps segregate patient subgroups (eg, migraine with and without aura, with or without nausea; irritable bowel syndrome vs other functional gastrointestinal disorders).

Role of brain imaging in disorders of brain-gut interaction: a Rome Working Team Report.
Mayer EA, Labus J, Aziz Q, Tracey I, Kilpatrick L, Elsenbruch S, Schweinhardt P, Van Oudenhove L, Borsook D.
Gut. 2019 Sep;68(9):1701-1715. doi: 10.1136/gutjnl-2019-318308.

Imaging of the living human brain is a powerful tool to probe the interactions between brain, gut and microbiome in health and in disorders of brain-gut interactions, in particular IBS. While altered signals from the viscera contribute to clinical symptoms, the brain integrates these interoceptive signals with emotional, cognitive and memory related inputs in a non-linear fashion to produce symptoms. Tremendous progress has occurred

in the development of new imaging techniques that look at structural, functional and metabolic properties of brain regions and networks. Standardisation in image acquisition and advances in computational approaches has made it possible to study large data sets of imaging studies, identify network properties and integrate them with non-imaging data. These approaches are beginning to generate brain signatures in IBS that share some features with those obtained in other often overlapping chronic pain disorders such as urological pelvic pain syndromes and vulvodynia, suggesting shared mechanisms. Despite this progress, the identification of preclinical vulnerability factors and outcome predictors has been slow. To overcome current obstacles, the creation of consortia and the generation of standardised multisite repositories for brain imaging and metadata from multisite studies are required.

Elucidating the putative link between prefrontal neurotransmission, functional connectivity, and affective symptoms in irritable bowel syndrome.
Icenhour A, Tapper S, Bednarska O, Witt ST, Tisell A, Lundberg P, Elsenbruch S, Walter S.
Sci Rep. 2019 Sep 19;9(1):13590. doi: 10.1038/s41598-019-50024-3.

Altered neural mechanisms are well-acknowledged in irritable bowel syndrome (IBS), a disorder of brain-gut-communication highly comorbid with anxiety and depression. As a key hub in corticolimbic inhibition, medial prefrontal cortex (mPFC) may be involved in disturbed emotion regulation in IBS. However, aberrant mPFC excitatory and inhibitory neurotransmission potentially contributing to psychological symptoms in IBS remains unknown. Using quantitative magnetic resonance spectroscopy (qMRS), we compared mPFC glutamate + glutamine (Glx) and γ-aminobutyric acid (GABA+) concentrations in 64 women with IBS and 32 age-matched healthy women (HCs) and investigated their association with anxiety and depression in correlational and subgroup analyses. Applying functional magnetic resonance imaging (fMRI), we explored whether altered neurotransmission was paralleled by aberrant mPFC resting-state functional connectivity (FC). IBS patients did not differ from HCs with respect to mPFC GABA+ or Glx levels. Anxiety was positively associated with mPFC GABA+ concentrations in IBS, whereas Glx was unrelated to psychological or gastrointestinal symptoms. Subgroup comparisons of patients with high or low anxiety symptom severity and HCs revealed increased GABA+ in patients with high symptom severity, and lower mPFC FC with adjacent anterior cingulate cortex (ACC), a crucial region of emotion modulation. Our findings provide novel evidence that altered prefrontal inhibitory neurotransmission may be linked to anxiety in IBS.

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 Aug 12. 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) has 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 to FM negative CLBP patients. METHODS: 46 participants with CLBP and 22 healthy 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 severe 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.

EPIDEMIOLOGY STUDIES

Prevalence of functional somatic syndromes and bodily distress syndrome in the Danish population: the DanFunD study.
Petersen MW, Schroder A, Jorgensen T, Ornbol E, Dantoft TM, Eliasen M, Carstensen TW, Falgaard Eplov L, Fink P.
Scand J Public Health. 2019 Aug 14:1403494819868592. doi: 10.1177/1403494819868592.

Aims: Little is known about the prevalence and characteristics of functional somatic syndromes (FSS) such as irritable bowel syndrome (IBS), fibromyalgia (FM), chronic fatigue syndrome (CFS), whiplash associated disorders (WAD), multiple chemical sensitivity (MCS), and bodily distress syndrome (BDS) in the general population when they are investigated simultaneously. Method: This cross-sectional study is based on the Danish Study of Functional Disorders (DanFunD) cohort consisting of 9656 adults from the general population. FSS and BDS were identified by questionnaires and characterized by age, sex, vocational training, physical health and comorbidity with physical and psychiatric disease. Results: In total, 16.3% (95% CI: 15.6-17.1) of the participants fulfilled the criteria for at least one FSS, ranging from 1.7% for WAD to 8.6% for CFS, and 16.1% (95% CI: 15.4-16.9) fulfilled the criteria for BDS. Cases had a high risk of poor self-perceived health, limitations in daily activities, and a high psychiatric comorbidity, all increasing with the number of syndromes in each individual. However, the associations differed across the various FSS. Mutual overlaps of IBS, FM and CFS were greater than could be expected by chance. Conclusions: FSS and BDS are prevalent in the adult Danish population, and cases have high risk of poor self-perceived health, limitation in daily activities, and psychiatric comorbidity. These associations were particularly strong for cases with multiple FSS and multi-organ BDS.

Development and course of chronic widespread pain: the role of time and pain characteristics (the HUNT pain study).
Landmark T, Romundstad P, Butler S, Kaasa S, Borchgrevink.
Pain. 2019 Sep;160(9):1976-1981. doi: 10.1097/j.pain.0000000000001585.

Chronic widespread pain (CWP) is common and associated with loss of functioning and health. Subjects with chronic non-widespread pain (CnWP) are at increased risk of developing CWP, but few studies have described the nature of the development over time. We followed a random sample of 3105 participants from the population-based HUNT 3 study with 5 annual measurements of pain over 4 years. Although 29% reported CWP on at least 1 occasion, only 7% reported it consistently on 4 or 5 occasions. The average annual cumulative incidence was 5%, and the recovery rate was 38%. In mutual adjusted analysis, the risk of developing CWP from 1 year to the next was higher in subjects with chronic pain (relative risk [RR] = 2.4; 95% confidence interval [CI]: 1.8-3.4), 2 or more pain regions (RR = 3.3; 95% CI: 2.5-4.4), moderate pain or more (RR = 1.8; 95% CI: 1.5-2.6), and with comorbid chronic disease (RR = 1.6; 95% CI: 1.3-1.9). Developing CWP was associated with a modest concurrent change in self-reported mental and physical health. The risk of developing CWP between the fourth and fifth occasions was 80% lower for subjects without a history of CWP, compared to those with a history of CWP. For subjects without previous CWP, the development was associated with previously reported CnWP, but not with the number of occasions with CnWP, in analyses adjusted for sex, age, and pain severity. A substantial proportion of the new cases of CWP originates from subjects floating below and above the definition for CWP over time and, thus, does not seem to involve major transitions in health.

The association between insomnia, c-reactive protein, and chronic low back pain: cross-sectional analysis of the HUNT study, Norway.

Ho KKN, Simic M, Cvancarova Smastuen M, de Barros Pinheiro M, Ferreira PH, Bakke Johnsen M, Heuch I, Grotle M, Zwart JA, Nilsen KB.
Scand J Pain. 2019 Jul 9. pii: /j/sjpain.ahead-of-print/sjpain-2019-0033/sjpain-2019-0033.xml. doi: 10.1515/sjpain-2019-0033.

Background and aims: Chronic low back pain (chronic LBP) is the number one cause for years lived with disability among 301 diseases and injuries analyzed by The Global Burden of Disease study 2013. Insomnia is highly prevalent among people with chronic LBP. To explain the sleep-pain relationship, theoretical models propose that insomnia symptoms may be associated with increased basal inflammation, operationalized as c-reactive protein (CRP) and lead to further pain and disrupted sleep. We aimed to determine the associations between insomnia, chronic LBP, and inflammation (operationalized as CRP), whilst controlling for age, body mass index, smoking, physical activity, depression, anxiety and osteoarthritis. Methods: A cross-sectional analysis of the third Nord-Trøndelag Health Study (2006-2008), a rural population survey of 50,666 participants in Norway aged 20-96 years. Insomnia (dichotomous) was defined according to the Diagnostic and Statistical Manual of Mental Disorders 5th Edition, and chronic LBP (dichotomous) as low back pain or stiffness lasting at least 3 months. Data for CRP were obtained from non-fasting serum samples and assessed via latex immunoassay methodology. We excluded participants with the following self-reported chronic somatic diseases: chronic heart failure, chronic obstructive pulmonary disease, rheumatoid arthritis, fibromyalgia or ankylosing spondylosis. Possible associations between presence of insomnia and presence of chronic LBP (dependent), and the level of CRP and presence of chronic LBP (dependent), were assessed using logistic regression models. The possible association between insomnia and CRP (dependent) was assessed using linear regression. Multivariable analyses were conducted adjusting for confounders stated in our aim that achieved a p less than or equal to 0.2 in univariate regressions. We performed stratified analyses for participants with "Normal" (<3 mg/L) "Elevated" (3-10 mg/L) and "Very High" (> 10 mg/L) levels of CRP. Results: In our total included sample (n=30,669, median age 52.6, 54% female), 6.1% had insomnia (n=1,871), 21.4% had chronic LBP (n=6,559), and 2.4% had both (n=719). Twenty four thousand two hundred eighty-eight (79%) participants had "Normal" CRP, 5,275 (17%) had "Elevated" CRP, and 1,136 (4%) had "Very High" CRP. For participants with "Normal" levels of CRP, insomnia was associated with higher levels of CRP (adjusted B=0.04, 95% CI [0.00-0.08], p=0.046), but not for people with "Elevated" or "Very High" levels of CRP. There was an association between CRP and presence of chronic LBP in the total sample (adjusted OR=1.01, [1.00-1.01], p=0.013) and for people with "Normal" CRP (1.05, [1.00-1.10, p=0.034]. Insomnia was associated with the presence of chronic LBP in the total sample (adjusted OR=1.99, 95% CI [1.79-2.21], <0.001) and for people with "Normal", "Elevated" and "Very High". Conclusions: Individuals with insomnia have twice the odds of reporting chronic LBP. Insomnia, CRP and chronic LBP appear to be linked but the role of CRP appears to be limited. Longitudinal studies may help further explore the causal inference between insomnia chronic LBP, and inflammation. Implications: Given the strong relationship between insomnia and chronic LBP, screening and management of comorbid insomnia and chronic LBP should be considered in clinical practice. Further longitudinal studies are required to explore whether the presence of insomnia and increased inflammation affects the development of chronic LBP.

Chronic obstructive pulmonary disease combined with vertebral compression fracture increases the risk of temporomandibular disorder: A population-based cohort study.
Lee KC, Wu YT, Chen LC, Shen CH, Chung CH, Chien WC, Shieh YS.
Medicine (Baltimore). 2019 Sep;98(37):e17162. doi: 10.1097/MD.0000000000017162.

Vertebral compression fracture (VCF) is a common comorbidity of chronic obstructive pulmonary disease (COPD), and the coexistence of COPD and temporomandibular disorder (TMD) has been clinically noted. The present study aimed to investigate whether VCF increases the risk of TMD in patients with COPD. With a follow-up period of 15 years, this retrospective, population-based longitudinal cohort study enrolled sex- and age-matched COPD patients with and without VCF (1:3) who were identified from

Taiwan's National Health Insurance Research Database from 2000 to 2015. Multivariate Cox regression analysis was performed to determine the risk of TMD in COPD patients with and without VCF. The cumulative risk of TMD between groups was estimated using Kaplan-Meier analysis. The risk factors for TMD in patients with COPD were VCF, osteoporosis, and winter season. The COPD with VCF group was more likely to develop TMD (adjusted hazard ratio = 3.011, p< .001) than the COPD without VCF group after adjustment for sex, age, variables, and comorbidities. In the subgroup analysis, the COPD with VCF group had a higher risk of TMD than the COPD without VCF group in almost all stratifications. COPD patients with VCF are at a higher risk of developing TMD. Clinicians taking care of patients with COPD should be aware of the occurrence of TMD as a comorbidity.

The prevalence, comorbidity, management and costs of irritable bowel syndrome.
Hauser W, Marschall U, Layer P, Grobe T.
Dtsch Arztebl Int. 2019 Jul 8;116(27-28):463-470. doi: 10.3238/arztebl.2019.0463.

BACKGROUND: Insufficient data are available on the administrative incidence and prevalence of irritable bowel syndrome (IBS) in Germany, as well as on its comorbidities, diagnostic evaluation, treatment, and costs. METHODS: We analyzed routine data from a statutory health insurance carrier with approximately eight million insurees. IBS was identified from the ICD-10 codes K58.0, K58.9, and F45.32 (outpatient care by a physician, outpatient and inpatient care in a hospital). The cumulative incidence for the year 2017 was determined by the exclusion of insurees who had carried the diagnosis of IBS in any of the preceding 12 years. The frequencies of comorbid diseases and of diagnostic and therapeutic measures were compared with those of persons in age- and sex- matched control groups without IBS. RESULTS: In 2017, the administrative incidence of IBS was 0.36%, and its prevalence was 1.34%. Persons with IBS were often documented as having other gastrointestinal diseases, headache, back pain, and mental disorders. There was evidence for the insufficient use of ultrasound and colonoscopy and for the excessive use of computed tomography and magnetic resonance imaging for diagnostic evaluation. The costs of medical care for insurees with IBS in the year of their initial diagnosis were higher than those of other insurees without the diagnosis of IBD (€ 3770 vs. € 2788) and rose in each of the eight years preceding the initial diagnosis. CONCLUSION: Patients with IBS in Germany are likely not receiving sufficient diagnostic evaluation in conformity with the relevant guidelines. The high prevalence of comorbid mental disorders and other pain syndromes implies that the complaints of patients with IBS need to be more comprehensively evaluated and treated.

Lower socioeconomic status is associated with an increased prevalence of comorbid anxiety and depression among patients with irritable bowel syndrome: results from a multicenter cohort.
Silvernale C, Kuo B, Staller K.
Scand J Gastroenterol. 2019 Sep;54(9):1070-1074. doi: 10.1080/00365521.2019.1665095.

Background/Aims: Anxiety and depression are common comorbid psychiatric disorders in IBS patients, but the population-level determinants influencing these comorbidities in IBS patients are poorly understood. We sought to determine whether there was an association between comorbid affective disorders and socioeconomic status among irritable bowel syndrome (IBS) patients. Methods: We assembled a retrospective cohort of 1074 IBS patients with comorbid Generalized Anxiety Disorder (GAD) and/or Major Depressive Disorder (MDD) seen at two tertiary referral centers between 2007 and 2015. IBS patients with comorbid GAD and/or MDD were matched 3:1 by age, sex, and race to controls with IBS and no history of comorbid GAD and/or MDD. Socioeconomic status was approximated by patient zip codes. Results: IBS patients in the lowest socioeconomic group were more likely to be diagnosed with GAD and/or MDD compared to controls (OR = 1.38, *p* = .0004). The median average per capita income for comorbid GAD/MDD IBS patient cohort was also significantly lower than the control IBS patient cohort ($39,880.50 vs. $41,277.00, p=.02). Conclusions: Among IBS patients, the presence of comorbid Generalized Anxiety Disorder and/or Major Depressive

Disorder is associated with lower socioeconomic status and lower average per capita income. These findings speak to a biopsychosocial model of illness, which should be considered by clinicians in the care of IBS patients.

Higher prevalence of irritable bowel syndrome and greater gastrointestinal symptoms in obsessive-compulsive disorder.
Turna J, Grosman Kaplan K, Patterson B, Bercik P, Anglin R, Soreni N, Van Ameringen M.
J Psychiatr Res. 2019 Nov;118:1-6. doi: 10.1016/j.jpsychires.2019.08.004.

BACKGROUND: Anxiety and mood symptoms often co-occur with gastrointestinal problems, such as irritable bowel syndrome (IBS). The extent to which these relate to Obsessive-Compulsive Disorder (OCD) is unclear, despite anxiety being a prominent symptom of this disorder. The purpose of this analysis was to examine gastrointestinal symptoms in unmedicated, non-depressed adult OCD patients compared to age- and sex-matched community controls. METHODS: Twenty-one OCD patients and 22 controls were recruited from the community (Hamilton, ON, Canada) and enrolled in this cross-sectional study. In addition to a standardized psychiatric assessment, participants completed clinician- and self-rated psychiatric and gastrointestinal symptom severity measures. Presence of IBS was assessed using Rome III criteria. RESULTS: Gastrointestinal symptom severity (GSRS total; OCD=8.67 +/- 6.72 vs. controls = 2.32 +/- 2.12) and prevalence of IBS (OCD = 47.6%; Controls = 4.5% was higher in OCD patients than in controls. A comparison of OCD patients based on IBS status revealed greater depressive symptom severity (total MADRS: 12.60 +/- 1.89 vs 6.91 +/- 2.77), $p < 0.001$) among those with IBS. CONCLUSIONS: High prevalence and severity of gastrointestinal symptoms may be an important clinical consideration when treating OCD patients. More specifically, assessment of IBS and gastrointestinal symptoms may be useful when considering pharmacotherapeutic treatments options for patients. Given the high comorbidity noted with IBS, a disorder of the "gut-brain axis", results may suggest a shared pathophysiological mechanism between psychiatric and gastrointestinal disorders which should be explored in future research.

Risks of interstitial cystitis among patients with systemic lupus erythematosus: A population-based cohort study.
Wen JY, Lo TS, Chuang YC, Ho CH, Long CY, Law KS, Tong YC, Wu MP.
Int J Urol. 2019 Sep;26(9):897-902. doi: 10.1111/iju.14065.

OBJECTIVE: To investigate whether the risk of interstitial cystitis increases among the patients with systemic lupus erythematosus. METHODS: This was a nationwide population-based cohort study. Data were obtained from the National Health Insurance Research Database in Taiwan. Women aged >18 years newly diagnosed as systemic lupus erythematosus during 2001-2008 were identified as the control group. The comparison included individuals randomly selected from the National Health Insurance Research Database in the year of 2000, by matching one systemic lupus erythematosus participant with eight non-systemic lupus erythematosus participants with sex and age. These participants were followed up until being diagnosed as interstitial cystitis, or the end of 2011. Women diagnosed with lupus cystitis were excluded from this study. RESULTS: This study included 7240 women with systemic lupus erythematosus and 57 920 women without systemic lupus erythematosus as controls. The incidence rate of interstitial cystitis was significantly higher in the systemic lupus erythematosus group, with an incidence rate ratio of 2.26 (95% confidence interval 1.57-3.27, $P < 0.0001$). After adjustment, the risk increased by 2.45-fold (adjusted hazard ratio 2.45, 95% confidence interval 1.57-3.27, $p<.05$). Age as a factor increases incidence rate ratios among all age groups, 2.12-, 3.32- and 4.65-fold. Age ≥45 years had an increased adjusted hazard ratio (2.07, 95% confidence interval 1.37-3.13, $p < 0.05$). Comorbidities, for example, hypertension, diabetes mellitus, dyslipidemia and renal disease, were insignificant. CONCLUSIONS: This is the first population-based cohort study showing a higher incidence of interstitial cystitis among patients with systemic lupus erythematosus. These findings support the concordance of interstitial cystitis with autoimmune diseases, and the temporal relationship to develop interstitial cystitis in patients with systemic lupus

erythematosus.

Relationship of migraine and tension-type headache with hypothyroidism: A literature review.
Spanou I, Bougea A, Liakakis G, Rizonaki K, Anagnostou E, Duntas L, Kararizou E.
Headache. 2019 Sep;59(8):1174-1186. doi: 10.1111/head.13600.

BACKGROUND: Migraine, tension-type headache, and hypothyroidism constitute very common medical conditions. Headache is one of the most common symptoms of hypothyroidism, occurring in approximately one-third of the patients. To date, data about the relationship between migraine and tension-type headache and thyroid dysfunction, and in particular hypothyroidism have been contradictory, while the underlying pathophysiological basis explaining this association is still unclear. OBJECTIVE: In this review, we investigated the association between primary headaches and hypothyroidism, with the aim of shedding light on its pathophysiological basis. METHODS: We conducted a systematic search in the MEDLINE database using both subject headings and keywords for headache, migraine, tension-type headache, thyroid hormones, and hypothyroidism, and we also examined manually the reference lists of all articles that met the inclusion criteria. Included studies were related to headache and thyroid disease comorbidity, with emphasis on hypothyroidism (ideally demonstrated by hormonal measurements), and with the term headache including migraine, tension-type headache including migraine, tension-type headache, and headache attributed to hypothyroidism (HAH) based on the International Classification of Headache Disorders IIIb. Quality of studies was assessed by the Newcastle-Ottawa scale. RESULTS: Of a total of 640 identified articles, 9 studies were included. Overall, there was vast heterogeneity across the included studies concerning population, study design and outcomes. Two studies investigated the HAH, with emphasis on the clinical characteristics of headache (time of onset, localization, quality, intensity, and response to hormonal replacement treatment). Five studies investigated comorbidity between migraine and thyroid disorders, especially hypothyroidism, and in the majority of them a positive association was demonstrated. One study found that headache, and particularly migraine, may increase the risk of developing hypothyroidism. Finally, only 1 study on chronic tension-type headache found coexistence of migraine and hypoactivity of the hypothalamus-pituitary-thyroid axis. The strengths and limitations of these studies are analyzed and possible pathophysiological mechanisms are suggested. CONCLUSIONS: The existing data are considered inadequate to answer with certainty the relationship between headaches and thyroid disorders. According to our analysis, it seems that suggestions for a possible bidirectional association between headaches and especially migraine and hypothyroidism could exist. It hence lays the foundation for further research into the aforementioned association and its pathogenesis via large prospective multicenter studies.

National trends in inpatient endometriosis admissions: Patients, procedures and outcomes, 2006-2015.
Estes SJ, Soliman AM, Epstein AJ, Bond JC, Gordon K, Missmer SA.
PLoS One. 2019 Sep 19;14(9):e0222889. doi: 10.1371/journal.pone.0222889. eCollection 2019.

INTRODUCTION: Despite guidance towards minimally invasive, outpatient procedures for endometriosis, many patients nonetheless receive inpatient care. Our objective was to assess trends in patient and hospital characteristics, surgical complications and hospital charges for women with an endometriosis-related inpatient admission in the United States. METHODS: We conducted a pooled cross-sectional analysis of Healthcare Cost and Utilization Project Nationwide Inpatient Sample data. Visits were stratified into three time-period-defined cohorts (2006-2007, 2010-2011, and 2014 through the first three quarters of 2015). Visits were included if the patient was aged 18-49 years and the primary diagnosis code was for endometriosis (International Classification of Diseases, 9th Revision code 617.xx). We evaluated counts of inpatient admissions and rates of patient and hospital characteristics. RESULTS: The number of inpatient admissions with a primary diagnosis code for endometriosis decreased by

72.8% from 2006 to 2015. At the same time, among those admitted for inpatient care for endometriosis, the proportions who had Medicaid insurance and multiple documented comorbidities increased. From 2006 to 2015, mean total hospital charges increased by 75% to $39,662 in 2015 US dollars, although average length of stay increased by <1 day. CONCLUSIONS: The number of inpatient admissions with a primary diagnosis of endometriosis decreased over the past decade, while surgical complications and associated hospital charges increased. The share of patients with multiple comorbidities increased and an increasing proportion of inpatient endometriosis admissions were covered by Medicaid and occurred at urban teaching hospitals. These findings suggest a demographic shift in patients receiving inpatient care for endometriosis towards more complex, vulnerable patients.

The association of vulvar pain and urological urgency and frequency: findings from a community-based case-control study.
Sun Y, Harlow BL.
Int Urogynecol J. 2019 Aug 2. doi: 10.1007/s00192-019-04052-2.

INTRODUCTION AND HYPOTHESIS: Vulvodynia is chronic debilitating burning vulvar pain or pain on contact. Although women who suffer from vulvodynia are more likely than others to experience co-morbid interstitial cystitis (IC) and urinary tract infections (UTIs), few studies have explored whether women with vulvodynia experience adverse urinary symptoms (lower urinary tract symptoms [LUTS]) in the absence of urological pain. METHODS: Two hundred and eleven participants with and 226 participants without clinically confirmed vulvodynia completed the Pelvic Pain and Urgency / Frequency (PUF) questionnaire and were scored using all questions, and then a subset of questions relating only to their current frequency and bother of urination during day and night, and the frequency, severity and bother of urgency after voiding. Total, symptom, and bother scores were compared in women with and without vulvodynia, and regression models estimated adjusted odds ratios and 95% confidence intervals for the various LUTS symptoms. RESULTS: As expected, 40% of women with vulvodynia met the criteria for IC (PUF > 12) compared with 2% without vulvodynia. fter excluding questions related to bladder or vulvovaginal pain, women with vulvodynia, compared with those without, were skewed toward higher PUF scores, including being 2.4 times more likely to report usually or always bothered by night-time voiding (95% CI 1.22-4.74), and 18 times more likely to report moderate/severe urgency after urination (95% CI 5.48-64.12). CONCLUSIONS: Women with vulvodynia are substantially more likely to report voiding dysfunction and symptoms of urgency than women with no history of vulvar pain. These findings are independent of comorbid interstitial cystitis or history of UTIs.

Vulvodynia and chronic pelvic pain in a gynecologic outpatient clinic.
Trutnovsky G, Plieseis C, Bjelic-Radisic V, BertholinyGalvez MC, Tamussino K, Ulrich D.
J Psychosom Obstet Gynaecol. 2019 Sep;40(3):243-247. doi: 10.1080/0167482X.2018.1477753.

Introduction: Vulvodynia and chronic pelvic pain are common but underdiagnosed chronic gynecologic pain syndromes. Insufficient knowledge regarding prevalence, typical pain patterns and associated factors contribute to delayed diagnosis. The present study explored the symptoms and characteristics of women presenting with vulvodynia and/or chronic pelvic pain to a gynecologic outpatient clinic. Materials and methods: Electronic charts of women diagnosed with vulvodynia and/or chronic pelvic pain between January 2010 and December 2015 were reviewed. Type of pain, duration of symptoms, previous medical assessments and therapies, comorbidities and patient characteristics were analyzed with descriptive statistics. Results: One hundred and twenty-seven women (mean age 36, range 18-75 years) met the diagnostic criteria for chronic gynecologic pain syndromes. Sixty-five women were diagnosed with CPP only, 42 with vulvodynia and 20 with both conditions. Endometriosis was suspected or diagnosed in 36 (54%) women with CPP. History of pain ranged from 3 months to 20 years. Comorbidities were common, with 40% of women being diagnosed with depression or other mood disorders, 15% with urological pain and 9% with gastrointestinal conditions. Conclusions: There is a need for increased awareness

regarding vulvodynia and CPP among health care providers. A comprehensive history is important for adequate diagnosis.

Fibromyalgia-like syndrome associated with Parkinson's disease-A cohort study.
Abuhasira R, Zlotnik Y, Horev A, Ifergane G.
J Clin Med. 2019 Jul 28;8(8). pii: E1118. doi: 10.3390/jcm8081118.

Parkinson's disease (PD) and fibromyalgia (FM) are two relatively common disorders that are considered distinct diagnoses. The aim of this study was to investigate the epidemiological characteristics of patients with both PD and FM, as well as their comorbidities and medication use. We performed a population-based retrospective cohort study in Israel from 2000 to 2015. We identified patients with PD according to a refined medication tracer algorithm and patients with FM according to their medical records. Using the algorithm, we identified 2606 patients diagnosed with PD, 60 of them (2.3%) were also diagnosed with FM. Most of the patients were females (88.3%) and the mean age of FM diagnosis was 63.95 ± 12.27 years. These patients had a higher prevalence of depression, anxiety, and dementia. Of the patients diagnosed with PD + FM, 46 (76.7%) were diagnosed with FM after the diagnosis of PD. Patients with PD + FM used analgesics of distinct kinds in higher rates, as well as more anti-PD medications. We suggest that patients with PD + FM represent a distinct subgroup with a fibromyalgia-like syndrome associated with Parkinson's disease (FLISPAD). Their PD is more treatment resistant, and they take more medications, both analgesics and anti-PD.

Association of bruxism and anxiety symptoms among military firefighters with frequent episodic tension type headache and temporomandibular disorders.
Wagner BA, Moreira Filho PF, Bernardo VG.
Arq Neuropsiguiatr. 2019 Jul 29;77(7):478-484. doi: 10.1590/0004-282X20190069.

OBJECTIVE: To assess the presence of bruxism and anxiety among military firefighters with frequent episodic tension-type headache and painful temporomandibular disorders (TMDs). METHODS: The sample consisted of 162 individuals aged 18 to 55 years divided into four groups. Headache was diagnosed in accordance with the International Classification of Headache Disorders-III. The Research Diagnostic Criteria for Temporomandibular Disorders questionnaire was used to classify TMDs and awake bruxism; sleep bruxism was diagnosed in accordance with the International Classification of Sleep Disorders-3; and anxiety was classified using the Beck Anxiety Inventory. In statistical models, a significance level of 95% was used. The chi-square test was used to assess anxiety. RESULTS: Associations were found among frequent episodic tension-type headache, painful TMDs, awake bruxism and anxiety ($p < 0.0005$). Sleep bruxism was not a risk factor ($p = 0.119$) except when associated with awake bruxism ($p = 0.011$). CONCLUSION: Anxiety and awake bruxism were independent risk factors for developing frequent episodic tension-type headache associated with painful TMDs; only awake bruxism was a risk factor for frequent episodic tension-type headache with non-painful TMDs.

Nature and specificity of altered cognitive functioning in IBS.
Wong KM, Mak ADP, Yuen SY, Leung ONW, Ma DY, Chan Y, Cheong PK, Lui R, Wong SH, Wu JC.
Neurogastroenterol Motil. 2019 Aug 7:e13696. doi: 10.1111/nmo.13696.

BACKGROUND: It is unknown whether cognitive dysfunction found in patients with irritable bowel syndrome (IBS) was attributable to the different subtypes, ongoing pathophysiological processes, trait characteristics, or psychiatric comorbidity. METHODS: Forty Rome-III patients with IBS (20 diarrhea-predominant [IBS-D] and 20 constipation-predominant [IBS-C]) and 40 age-, sex-, education-matched healthy controls were systematically recruited and compared on their cognitive function with continuous performance test (CPT), Wisconsin Card Sorting Test (WCST) and emotional Stroop test. Beck Anxiety Inventory (BAI), Beck Depression Inventory-II (BDI-II), Patient Health Questionnaire-15 (PHQ-15) and a structured bowel symptom

questionnaire were performed to measure anxiety, depressive, somatization, and bowel symptoms, respectively. Psychiatric diagnoses were ascertained with SCID-I (Structured Clinical Interview for DSM-IV Axis I Disorders). KEY RESULTS: Patients with IBS showed significantly increased standard deviation of reaction time (SDRT) (P = .003) on CPT, increased failure to maintain set (FMS) (P=.002), and percentage of perseverative errors (P = .003) on WCST. SDRT did not correlate with illness chronicity or bowel symptoms. FMS correlated with bowel symptom severity. In logistic regression models controlled for BAI, BDI-II, and PHQ-15, SDRT (AOR = 1.08, P = .025), but not FMS (P = .25) or percentage of perseverative errors (P = .24), significantly differentiated IBS from controls. Cognitive function was not significantly different between IBS-C and IBS-D (P > .05), or between pure IBS (n = 22) and IBS with generalized anxiety disorder (GAD) (n = 17) (P > .05). CONCLUSIONS & INFERENCES: Patients with IBS showed attentional and executive function impairment irrespective of subtypes but otherwise heterogeneous in terms of its state-trait correlations and overlap with anxiety comorbidity.

Uncovering demographic, clinical, triggering factors similarities between migraine and irritable bowel syndrome: A prospective study.
Hajj A, Mourad D, Ghossob M, Hallit S, Geagea A, Abboud H, El Mouallem H, Saniour P, El Hachem N, Rabbaa Khabbaz L.
J Nerv Ment Dis. 2019 Sep 9. doi: 10.1097/NMD.0000000000001033.

The objective was to uncover demographical and clinical factors associated with migraine and irritable bowel syndrome (IBS) in a group of patients experiencing both painful disorders and to identify their triggering factors. A prospective study was performed between January 2016 and June 2017. Clinical characteristics and potential generating factors for both pathologies were then assessed using validated questionnaires. Our study showed that the percentage of patients diagnosed with migraine and having IBS was 34.3%. Compared with patients with migraine alone, patients having both diseases were identified with higher prevalence of concomitant chronic/psychiatric diseases, lower frequency of migraine attacks, and lower prevalence of throbbing/distressing/enervating pain and concentration difficulties than patients with migraine alone. Moreover, patients in this subgroup had moderate abdominal pain intensity, and constipation was the predominant stool type. Finally, some dietary and environmental factors seem to be significantly important triggering factors of migraine/IBS pain.

Migraine: Epidemiology, burden, and comorbidity.
Burch RC, Buse DC, Lipton RB.
Neurol Clin. 2019 Nov;37(4):631-649. doi: 10.1016/j.ncl.2019.06.001.

Migraine affects an estimated 12% of the population. Global estimates are higher. Chronic migraine (CM) affects 1% to 2% of the global population. Approximately 2.5% of persons with episodic migraine progress to CM. Several risk factors are associated with the progression to CM. There is significant short-term variability in migraine frequency independent of treatment. Migraine is associated with cardiovascular disease, psychiatric disease, and sleep disorders. It is the second most disabling condition worldwide. CM is associated with higher headache-related disability/impact, medical and psychiatric comorbidities, health care resource use, direct and indirect costs, lower socioeconomic status, and health-related quality of life.

Treatment patterns and predictors of costs among patients with migraine: evidence from the United States medical expenditure panel survey.
Ford JH, Ye W, Nichols RM, Foster SA, Nelson DR.
J Med Econ. 2019 Sep;22(9):849-858. doi: 10.1080/13696998.2019.1607358.

Aim: Within a treated migraine population, to evaluate if the sub-group meeting criteria for high disease-specific total costs is significantly different to the sub-group with medium and/or low-costs, and to identify the associated risk factors. Methods: Data from the Household Component of Medical Expenditure Panel Survey (MEPS-HC, 2008-2012), a

nationally representative survey of non-institutionalized civilians in the US, were analyzed. Key inclusion criteria were migraine diagnosis (ICD-9 code: 346.XX) and prescribed treatment for migraine. Patients were categorized into high (>top 10th percentile), low (<bottom 10th percentile), and medium (between high and low) cost sub-groups per migraine-specific total costs. Logistic regression models were applied to identify predictors of high vs medium and medium vs low-costs. Preventive eligibility, defined as (i) past/current use of migraine preventives or (ii) overuse of acute medications, was compared to non-preventive eligibility. Results: Within the treated migraine cohort (n=1,735), the mean age was 39 years, 80% were female, and the majority were in the medium-cost sub-group (n=1,360) (low-cost n=195). Significant predictors of high vs medium-costs were low SF-12 Physical Composite Scores (OR=0.95, 95% CI =0.92-0.97), low SF-6D health utility index scores (OR=0.019; 95% CI = 0.002-0.193), preventive eligibility-i (OR=0.019; 95% CI=0.002-0.193), and preventive-eligibility-ii (OR=3.10; 95% CI=1.62-5.91). Statistically significant ($p<0.05$) predictors of medium vs low-costs included anxiety, Fleishman score, preventive-eligible-i, and preventive-eligible-ii. Conclusions: Among patients treated for migraine, distinct characteristics, including patient-functioning measures and comorbidities, are predictive of high vs medium-costs, and medium vs low-costs. Preventive eligibility is a predictor of being in the higher cost sub-groups; however, preventive treatments that improve functioning and reduce acute medication use have the potential to reduce migraine-specific costs. Limitations: The results are limited to a population that is diagnosed and treated for migraine. Over-the-counter medication use, and migraine headache frequency and severity were not captured.

The relation of physical comorbidity and multimorbidity to fibromyalgia, widespread pain and fibromyalgia-related variables.
Wolfe F, Ablin J, Guymer EK, Littlejohn GO, Rasker JJ.
J Rheumatol. 2019 Aug 1. pii: jrheum.190149. doi: 10.3899/jrheum.190149.

OBJECTIVE: To investigate the relation of physical (non-psychological) comorbidity and multimorbidity to quantitative measures of fibromyalgia and musculoskeletal pain. METHODS: We studied 12, 215 patients in a research databank with quantitative measures of fibromyalgia related variables (FMV) that included binary determinations of fibromyalgia and widespread pain, and constituent variables of fibromyalgia diagnosis that included the widespread pain index (WPI), symptom severity score (SSS) and the polysymptomatic distress scale (PSD). We assessed 10 self-reported comorbid conditions, and covariates that included age, sex, body mass index, hypertension, smoking history and total household income. We used nearest neighbor matching and regression adjustment treatment effects models to measure the effect of comorbidities on FMV. RESULTS: We found a positive association between FMV and the probability of having each comorbid condition. Patients with one or more comorbidities had PSD, WPI and SSS increases of 3.0 (95% CI 2.7-3.3), 1.8 (95% CI 1.6-2.0) and 1.2 (95% CI 1.1-1.3) units, and an increase in FM prevalence from 20.4% to 32.6%. As the number of comorbid conditions present increased from 1 to 4 or more, PSD, WPI, SSS and fibromyalgia percent increased stepwise. For patients with ≥4 conditions, the predicted prevalence of fibromyalgia was 55.2%. CONCLUSION: Fibromyalgia and FMV are associated with increase in the number of comorbidities, and the association can be measured quantitatively. However, the association with widespread pain and fibromyalgia may be an effect of man-made definitions of widespread pain and fibromyalgia, as comorbidity increases are also present with sub-syndromal levels of widespread pain and fibromyalgia.

Gender differences in pain risk in old age: Magnitude and contributors.
Garcia-Esquinas E, Rodriguez-Sanchez I, Ortola R, Lopez-Garcia E, Caballero FF, Rodriguez-Manas L, Banegas JR, Rodriguez-Artalejo F.
May Clin Proc. 2019 Sep;94(9):1707-1717. doi: 10.1016/j.mayocp.2019.03.034.

OBJECTIVES: To identify the factors associated with the excess risk of pain observed among older women compared with men. PATIENTS AND METHODS: We used information from a cohort of 851 women and men age 63 years and older who were free

of pain during 2012 and were followed up to December 31, 2015. Sociodemographic variables, health behaviors, psychosocial factors, morbidity, and functional limitations were assessed in 2012 during home visits. Incident pain in 2015 was classified according to its frequency, intensity, and number of localizations into lowest, middle, and highest categories. RESULTS: During a mean follow-up of 2.8 years, the incidence of middle and highest pain was 12.5% and 22.6% in women and 12.4% and 12.6% in men, respectively. The age-adjusted relative risk ratios and 95% CIs of middle and highest pain in women versus men were 1.20 (0.79-1.83) and 2.03 (1.40-2.94), respectively. In a mediation analysis, a higher frequency in women than men of osteomuscular disease, impaired mobility, and impaired agility accounted, respectively, for 31.1%, 46.6%, and 32.0% of the excess risk of highest pain in women compared with men. Other relevant mediators were psychological distress (25.2%), depression (8.7%), poor sleep quality (10.7%), and lower recreational physical activity (12.6%). CONCLUSION: A greater frequency of some chronic diseases, worse functional status, psychological distress, and lower physical activity can mediate the excess risk of pain in older women compared with men.

The mediating effect of pain on the association between multimorbidity and disability and impaired physical performance among community-dwelling older adults in southern China.
Peng X, Bao X, Xie Y, Zhang X, Huang J, Liu Y, Cheng M, Liu N, Wang P.
Aging Clin Exp Res. 2019 Sep 14. doi: 10.1007/s40520-019-01324-1.

AIM: To investigate the association between multimorbidity and disability and impaired physical performance, and to further evaluate the mediating effect of physical pain in this association. METHODS: 1321 community-dwelling older adults, who were over 60 years old in southern China, were regarded as participants in this cross-sectional study. Subjects completed a multi-instrument questionnaire including essential characteristics and physical function assessments. Physical function was assessed by activities of daily living (ADL), instrumental activities of daily living (IADL), index of mobility scale (NAGI), index of basic physical activities scale (RB), and short physical performance battery (SPPB). Multimorbidity was defined as the simultaneous presence of two or more chronic conditions. Multivariable regression and mediation analyses were conducted and gender differences were explored. RESULTS: The prevalence of multimorbidity was 44.6% in our study. In gender stratification analysis, multimorbidity was significantly associated with ADL disability (OR=2.16), IADL disability (OR=1.97), NAGI disability (OR=2.84), RB disability (OR=2.65) and lower SPPB score (beta = -0.83) in women. The rate of pain increased with the number of chronic diseases and the multimorbidity patients with higher pain prevalence. Moreover, the presence of pain was also significantly associated with disability and impaired physical performance. Mediation analysis illustrated that pain was accounted for 16.5% to 22.1% of the adverse effects of multimorbidity on disability and impaired physical performance in women. CONCLUSIONS: Multimorbidity was significantly associated with disability and impaired physical performance, and pain might be a mediating factor for adverse effects of multimorbidity on disability and impaired physical performance in women.

CLINICAL STUDIES

Cervical muscle tenderness in temporomandibular disorders and its associations with diagnosis, disease-related outcomes, and comorbid pain conditions.
Almoznino G, Zini A, Zakuto A, Zlutky H, Bekker S, Shay B, Haviv Y, Sharav Y, Benoliel R.
J Oral Facial Pain Headache. 2019 Aug 27. doi: 10.11607/ofph.2374.

AIMS: To analyze cervical tenderness scores (CTS) in patients with various temporomandibular disorders (TMD) and in controls and to examine associations of CTS with demographic and clinical parameters. METHODS: This case-control study included 192 TMD patients and 99 controls diagnosed based on a questionnaire and a clinical examination following the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) guidelines. CTS, adapted from the widely used total tenderness

score, was the mean sum of the palpation scores from the suboccipital, sternocleidomastoid, and trapezius muscles. Depending on the variables, data were analyzed using Pearson chi-square, analysis of variance, t test, Bonferroni post hoc adjustment, and/or multivariate linear regression analyses. RESULTS: CTS was higher in TMD compared to controls (P < .001). Across TMD subgroups, CTS was notable only in those with a myogenous TMD diagnosis, but not in arthrogenous TMD (P = .014). CTS was positively associated with: female sex (P = .03), whiplash history, higher verbal pain scores, comorbid headaches, body pain, increased pain on mouth opening, and higher masticatory muscles tenderness scores (MTS) (P < .001 for all). Sex (P < .001), MTS (p < .001), comorbid headache (p=.042), and pain on opening (mild: p=.031; moderate: p=.022) retained significant associations with CTS in the multivariate analysis, and these main effects were influenced by interactions with whiplash history and comorbid body pain. CONCLUSION: CTS differentiated between TMD patients and controls and between TMD diagnoses. Specific patient and pain characteristics associated with poor outcome in terms of CTS included effects of interactions between myogenous TMD, female sex, whiplash history, comorbid body pain and headaches, and pain on opening. It can therefore be concluded that routine clinical examination of TMD patients should include assessment of the cervical region.

Effects of occlusal splint therapy in patients with migraine or tension-type headache and comorbid temporomandibular disorder: A randomized controlled trial.
Saha FJ, Pulla A, Ostermann T, Miller T, Dobos G, Cramer H.
Medicine (Baltimore). 2019 Aug;98(33):e16805. doi: 10.1097/MD.0000000000016805.

BACKGROUND: Migraine and tension-type headache often occur comorbid with temporomandibular disorder; occlusal splint therapy is the most common treatment for temporomandibular disorder. The aim of this study was to assess the effects of occlusal splint therapy on headache symptoms in patients with migraine and/or tension-type headache comorbid with temporomandibular disorder. METHODS: Sixty adult patients with migraine and/or tension-type headache and comorbid temporomandibular disorder were randomly assigned to individualized occlusal splint therapy applied during day- and nighttime plus usual care (n=30) or usual care alone (n=30). Primary outcome was the change in current pain intensity on a 100mm visual analogue scale from week 1 to week 12. Secondary outcomes included changes in headache days and headache hours assessed by headache diaries over a 2-week period, health-related quality of life (SF-36), and adverse events from week 1 to week 12 and (in the occlusal splint plus usual care group only) to week 24. RESULTS: No group differences in changes in pain intensity from week 1 to week 12 were found. The number needed to treat was 3.8. Physical quality of life reduced stronger in the usual care group than in the occlusal splint plus usual care group. In the occlusal splint plus usual care group, headache intensity significantly decreased and physical quality of life significantly increased from week 1 to week 12 and to week 24 (all p<.001). No adverse events were reported. CONCLUSIONS: A day- and night-time occlusal splint therapy in addition to usual care was not superior to usual care alone in patients with chronic headache and comorbid TMD. Four patients need to be treated to induce a minimal clinically relevant improvement in one patient. The small sample size and lack of power limit these findings.

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). 2019 Aug 14. pii: kez303. 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.

Effects of diet based on IgG elimination combined with probiotics on migraine plus irritable bowel syndrome.
Xie Y, Zhou G, Xu Y, He B, Wang Y, Ma R, Chang Y, He D, Xu C, Xiao Z.
Pain Res Manag. 2019 Aug 21;2019:7890461. doi: 10.1155/2019/7890461. eCollection 2019.

Several research studies have revealed that migraine has a solid link with gastrointestinal diseases especially irritable bowel syndrome (IBS). This study was carried out to investigate therapeutic potential of diet based on IgG elimination combined with probiotics on migraine plus irritable bowel syndrome. A total of 60 patients diagnosed with migraine plus IBS were recruited for the study. IgG antibodies against 266 food varieties were detected by ELISA. Then, the subjects were randomized into three groups for treatment of IgG elimination diet or probiotics or diet combined with probiotics. Migraine symptom, gut function score, medication use, and serum serotonin level were measured at baseline, 7 weeks, and 14 weeks. Improvement of migraine and gut symptom was achieved at a certain time point. Reduced use of over-the-counter- (OTC-) analgesics was seen in all groups. However, use of triptans did not show significant difference. An increased serum serotonin level was seen in subjects treated with elimination diet and elimination diet combined with probiotics. IgG elimination diet combined with probiotics may be beneficial to migraine plus IBS. It may provide new insight by understanding the intricate relationship between migraine and gastrointestinal diseases.

"Understand your illness and your needs": Assessment-informed patient education for people with multiple functional somatic syndromes.
Frolund Pedersen H, Holsting A, Frostholm L, Rask C, Jensen JS, Hoeg MD, Schroder A.
Patient Educ Couns. 2019 Sep;102(9):1662-1671. doi: 10.1016/j.pec.2019.04.016.

OBJECTIVES: Patients suffering from multiple functional somatic syndromes (FSS) such as fibromyalgia, chronic fatigue syndrome, or irritable bowel syndrome, often lack both a clear diagnosis and tangible illness explanations, which is a barrier for treatment engagement. We tested a short-term intervention taking the unifying concept of Bodily Distress Syndrome (BDS) as a point of departure. The intervention consisted of a clinical assessment, group-based patient education, and one follow-up consultation. METHODS: 174 patients were included and received questionnaires at baseline, after clinical assessment, after patient education, and median 19 weeks after baseline. Data were analyzed using random effects models and simple t-tests. Qualitative data were thematically analyzed. RESULTS: We found small reductions in symptom levels, considerable reductions in illness worry, and improvement of illness perceptions and illness-related behaviors. Overall, patients evaluated the intervention positively and expressed high expectations for further treatment. Qualitative results mainly supported these findings. CONCLUSION: Targeting illness perceptions through patient education is crucial to obtain patient engagement in self-help management or further treatment. This may lead to improved outcomes. PRACTICAL IMPLICATIONS: Physicians in primary and secondary care should strive to give patients with multiple FSS a clear understanding that their various FSS diagnoses are related and provide tangible illness

explanations.

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.