CUTTING EDGE

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COPCs Research Advances

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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 March and August 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...

About the Chronic Pain Research Alliance

FEATURED ARTICLES

Temporomandibular disorders: Priorities for research and care.
National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services; Board on Health Sciences Policy; Committee on Temporomandibular Disorders: From Research Discoveries to Clinical Treatment
Yost O, Liverman CT, Englgh R, Mackey S, Bond EC, editors.
Washington (DC): National Academies Press (US); 2020 Mar 12.

Temporomandibular disorders (TMDs), are a set of more than 30 health disorders associated with both the temporomandibular joints and the muscles and tissues of the jaw. TMDs have a range of causes and often co-occur with a number of overlapping medical conditions, including headaches, fibromyalgia, back pain and irritable bowel syndrome. TMDs can be transient or long-lasting and may be associated with problems that range from an occasional click of the jaw to severe chronic pain involving the entire orofacial region. Everyday activities, including eating and talking,

are often difficult for people with TMDs, and many of them suffer with severe chronic pain due to this condition. Common social activities that most people take for granted, such as smiling, laughing, and kissing, can become unbearable. This dysfunction and pain, and its associated suffering, take a terrible toll on affected individuals, their families, and their friends. Individuals with TMDs often feel stigmatized and invalidated in their experiences by their family, friends, and, often, the health care community. Misjudgments and a failure to understand the nature and depths of TMDs can have severe consequences - more pain and more suffering - for individuals, their families and our society. Temporomandibular Disorders: Priorities for Research and Care calls on a number of stakeholders - across medicine, dentistry, and other fields - to improve the health and well-being of individuals with a TMD. This report addresses the current state of knowledge regarding TMD research, education and training, safety and efficacy of clinical treatments of TMDs, and burden and costs associated with TMDs. The recommendations of Temporomandibular Disorders focus on the actions that many organizations and agencies should take to improve TMD research and care and improve the overall health and well-being of individuals with a TMD.

ICD-10 codes for the study of chronic overlapping pain conditions in administrative databases.
Schrepf A, Phan V, Clemens JQ, Maixner W, Hanauer D, Williams DA.
J Pain. Jan-Feb 2020;21(1-2):59-70. doi: 10.1016/j.jpain.2019.05.007.

Chronic overlapping pain conditions (COPCs) are a set of painful chronic conditions characterized by high levels of co-occurrence. It has been hypothesized that COPCs co-occur in many cases because of common neurobiological vulnerabilities. In practice, most research on COPCs has focused upon a single index condition with little effort to assess comorbid painful conditions. This likely means that important phenotypic differences within a sample are obscured. The International Classification of Diseases (ICD) coding system contains many diagnostic classifications that may be applied to individual COPCs, but there is currently no agreed upon set of codes for identifying and studying each of the COPCs. Here we seek to address this issue through three related projects 1) we first compile a set of ICD-10 codes from expert panels for ten common COPCs, 2) we then use natural language searches of medical records to validate the presence of COPCs in association with the proposed expert codes, 3) finally, we apply the resulting codes to a large administrative medical database to derive estimates of overlap between the ten conditions as a demonstration project. The codes presented can facilitate administrative database research on COPCs. PERSPECTIVE: This article presents a set of ICD-10 codes that researchers can use to explore the presence and overlap of COPCs in administrative databases. This may serve as a tool for estimating samples for research, exploring comorbidities, and treatments for individual COPCs, and identifying mechanisms associated with their overlap.

Nonopioid pharmacologic treatments for chronic pain [AHRQ Comparative Effectiveness Review].
McDonagh MS, Selph SS, Buckley DI, Holmes RS, Mauer K, Ramirez S, Hsu FC, Dana T, Fu R, Chou R.
Rockville (MD): Agency for Healthcare Research and Quality (US); 2020 Apr. Report No.: 20-EHC010. AHRQ Comparative Effectiveness Reviews.

Objectives: To evaluate the effectiveness and comparative effectiveness of nonopioid pharmacologic agents in patients with specific types of chronic pain, considering effects on pain, function, quality of life, and adverse events. Data sources: Electronic databases (Ovid® MEDLINE®, Embase®, PsycINFO®, CINAHL®, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews) through September 10, 2019, reference lists, data requests, and previous reviews. Review methods: Randomized controlled trials (RCTs) of nonopioid pharmacologic agents in

patients with chronic pain were selected using predefined criteria and dual review. This review focused on seven common chronic pain conditions (neuropathic pain, fibromyalgia, osteoarthritis, inflammatory arthritis, low back pain, chronic headache, sickle cell disease), with effects analyzed at short term (1 to <6 months following treatment completion), intermediate term (≥6 to <12 months), and long term (≥12 months). Magnitude of effects were described as small, moderate, or large using previously defined criteria, and strength of evidence was assessed. Meta-analyses were conducted where data allowed, stratified by duration within each intervention type, using random effects models. We evaluated effect modification through subgroup and sensitivity analyses, including specific drug, dose, study quality, and pain type. Results: We included 185 RCTs in 221 publications and 5 systematic reviews. In the short term, anticonvulsants (pregabalin, gabapentin, and oxcarbazepine for neuropathic pain, pregabalin/gabapentin for fibromyalgia), serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants (duloxetine for neuropathic pain, fibromyalgia, osteoarthritis, and low back pain, milnacipran for fibromyalgia), and nonsteroidal anti-inflammatory drugs (NSAIDs) (for osteoarthritis and inflammatory arthritis) were associated with mostly small improvements (e.g., 5 to 20 points on a 0 to 100 scale) in pain and function. Function was not found to be improved with duloxetine for low back pain or pregabalin/gabapentin for neuropathic pain. Moderate improvement in quality of life was seen with duloxetine in patients with neuropathic pain, and small improvements in patients with osteoarthritis, but evidence was insufficient to draw conclusions for other drugs and conditions. While most comparisons of drugs and doses did not identify differences, diclofenac improved pain and function moderately more than celecoxib. In the intermediate term, limited evidence (1 RCT) showed memantine moderately improved pain, function, and quality of life in patients with fibromyalgia; improvements in pain, but not function, were maintained in the intermediate term with duloxetine and milnacipran for fibromyalgia. Other drugs studied, including acetaminophen (osteoarthritis), capsaicin (neuropathic pain), cannabis (neuropathic pain), amitriptyline (fibromyalgia, neuropathic pain), and cyclobenzaprine (fibromyalgia) had no clear effects. Withdrawal from study due to adverse events was significantly increased with nonopioid drugs, with the greatest increase over placebo seen with cannabis. Large increases in risk of adverse events were seen with pregabalin (blurred vision, cognitive effects, dizziness, peripheral edema, sedation, and weight gain), gabapentin (blurred vision, cognitive effects, sedation, weight gain), and cannabis (nausea, dizziness). Dose reductions reduced the risk of some adverse events with SNRI antidepressants. In the short term small increases in risk of major coronary events and moderate increases in serious gastrointestinal events (both short and long term) were found with NSAIDs. Conclusions: In the short term, small improvements in pain and/or function were seen with SNRI antidepressants for neuropathic pain, fibromyalgia, osteoarthritis, and low back pain; pregabalin/gabapentin for neuropathic pain and fibromyalgia; oxcarbazepine for neuropathic pain; and NSAIDs for osteoarthritis and inflammatory arthritis. Improvement in function was not found with duloxetine for low back pain and pregabalin/gabapentin for neuropathic pain. Intermediate- and long-term outcomes were mostly not assessed. Increased incidence of drug class-specific adverse events led to withdrawal from treatment in some patients, suggesting that careful consideration of patient characteristics is needed in selecting nonopioid drug treatments.

NATIONAL MULTI-SITE STUDIES

A MAPP Network case-control study of urological chronic pelvic pain compared with nonurological 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. 2020 Jan;36(1):8-15. doi: 10.1097/AJP.0000000000000769.

Objectives: Limited research suggests commonalities between urological chronic pelvic pain syndromes (UCPPS) and other nonurological 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. Materials and methods: As part of the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research (MAPP) Network, we examined 1039 individuals with UCPPS (n=424), nonurological COPCs (n=200), and healthy controls (HCs; n=415). Validated standardized measures were used to assess urological symptoms, nonurological pain symptoms, and psychosocial symptoms and traits. Results: Participants with UCPPS had more urological symptoms than nonurological COPCs or HCs (P<0.001); nonurological COPC group also had significantly worse urological symptoms than HCs (P<0.001). Participants with nonurological 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 HCs (P<0.001). Participants with UCPPS with and without COPCs reported more catastrophizing than those with nonurological 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.

Correlates of 1-year change in quality of life in patients with urologic chronic pelvic pain syndrome: Findings from the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network.

Clemens JQ, Stephens-Shields AJ, Newcomb C, Rodriguez LV, Lai HH, Bradley CS, Naliboff BD, Griffith JW, Taple BJ, Gupta P, Afari N, Harte SE, Strachan E, Guo W, Landis JR.

J Urol. 2020 Apr 15;101097JU0000000000001080. doi: 10.1097/JU.0000000000001080. Online ahead of print.

Purpose: We evaluated and identified baseline factors associated with change in health related quality of life among patients with interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome. Materials and methods: A total of 191 men and 233 women with interstitial cystitis/bladder pain syndrome or chronic prostatitis/chronic pelvic pain syndrome (collectively referred to as urologic chronic pelvic pain syndrome) were followed for 12 months with bimonthly completion of the Short Form 12 to assess general mental and physical health related quality of life, and with biweekly assessment of condition specific health related quality of life using the Genitourinary Pain Index. A functional clustering algorithm was used to classify participants as improved, stable or worsened for each health related quality of life measure. Ordinal logistic regression was used to determine baseline factors associated with change. Results: Physical health related quality of life improved in 22% of the participants, mental health related quality of life improved in 25% and condition specific health related quality of life improved in 47%. Better baseline physical health related quality of life, older age and the presence of nonurological symptoms were associated with lower likelihood of improvement in physical health related quality of life. Better baseline mental health related quality of life, female sex, and greater baseline depression and stress were associated with a lower likelihood of improvement in mental health related quality of life. Better baseline condition specific health related quality of life and more severe baseline urologic chronic pelvic pain syndrome pain symptoms were associated with a lower likelihood of improvement in condition specific health related quality of life. Conclusions: While several nonurologic chronic pelvic pain syndrome factors influenced the trajectory of general health related

quality of life over time, only condition specific baseline health related quality of life and urologic chronic pelvic pain syndrome symptoms were associated with urologic chronic pelvic pain syndrome specific health related quality of life change. Significant differences in how urologic chronic pelvic pain syndrome impacts various aspects of health related quality of life suggest a multidisciplinary approach to assessment and treatment of these patients.

The Multidisciplinary Approach to The Study of Chronic Pelvic Pain (MAPP) Research Network*: Design and implementation of the Symptom Patterns Study (SPS).
Clemens JQ, Kutch JJ, Mayer EA, Naliboff BD, Rodriguez LV, Klumpp DJ, Schaeffer AJ, Kreder KJ, Clauw DJ, Harte SE, Schrepf AD, Williams DA, Andriole GL, Lai HH, Buchwald D, Lucia MS, van Bokhoven A, Mackey S, Moldwin RM, Pontari MA, Stephens-Shields AJ, Mullins C, Landis JR.
Neurourol Urodyn. 2020 Jun 23. doi: 10.1002/nau.24423. Online ahead of print.

Aims: The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network initiated a second observational cohort study-the Symptom Patterns Study (SPS)-to further investigate the underlying pathophysiology of Urologic Chronic Pelvic Pain Syndrome (UCPPS) and to discover factors associated with longitudinal symptom changes and responses to treatments. Methods: This multisite cohort study of males and females with UCPPS features a run-in period of four weekly web-based symptom assessments before a baseline visit, followed by quarterly assessments up to 36 months. Controls were also recruited and assessed at baseline and 6 months. Extensive clinical data assessing urological symptoms, nonurological pain, chronic overlapping pain syndromes, and psychosocial factors were collected. Diverse biospecimens for biomarker and microbiome studies, quantitative sensory testing (QST) data under multiple stimuli, and structural and functional neuroimaging scans were obtained under a standardized protocol. Results: Recruitment was initiated (July 2015) and completed (February 2019) at six discovery sites. A total of 620 males and females with UCPPS and 73 Controls were enrolled, including 83 UCPPS participants who re-enrolled from the first MAPP Network cohort study (2009-2012). Baseline neuroimaging scans, QST measures, and biospecimens were obtained on 578 UCPPS participants. The longitudinal follow-up of the cohort is ongoing. Conclusions: This comprehensive characterization of a large UCPPS cohort with extended follow-up greatly expands upon earlier MAPP Network studies and provides unprecedented opportunities to increase our understanding of UCPPS pathophysiology, factors associated with symptom change, clinically relevant patient phenotypes, and novel targets for future interventions.

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. 2020 Jul;5(3):224-232. 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.

Complex syndromes of chronic pain, fatigue and cognitive impairment linked to autoimmune dysautonomia and small fiber neuropathy.
Shoenfeld Y, Ryabkova VA, Scheibenbogen C, Brinth L, Martinez-Lavin M, Ikeda S, Heidecke H, Watad A, Bragazzi NL, Chapman J, Churilov LP, Amital H.
Clin Immunol. 2020 May;214:108384. doi: 10.1016/j.clim.2020.108384.

Chronic fatigue syndrome, postural orthostatic tachycardia syndrome, complex regional pain syndrome and silicone implant incompatibility syndrome are a subject of debate among clinicians and researchers. Both the pathogenesis and treatment of these disorders require further study. In this paper we summarize the evidence regarding the role of autoimmunity in these four syndromes with respect to immunogenetics, autoimmune co-morbidities, alteration in immune cell subsets, production of autoantibodies and presentation in animal models. These syndromes could be incorporated in a new concept of autoimmune neurosensory dysautonomia with the common denominators of autoantibodies against G-protein coupled receptors and small fiber neuropathy. Sjogren's syndrome, which is a classical autoimmune disease, could serve as a disease model, illustrating the concept. Development of this concept aims to identify an apparently autoimmune subgroup of the disputable disorders, addressed in the review, which may most benefit from the immunotherapy.

Heart rate variability in patients with somatic symptom disorders and functional somatic syndromes: A systematic review and meta-analysis.
Ying-Chih C, Yu-Chen H, Wei-Lieh H.
Neurosci Biobehav Rev. 2020 May;112:336-344. doi: 10.1016/j.neubiorev.2020.02.007.

This research is aimed to systematically review heart rate variability (HRV) findings of functional somatic syndromes (FSSs) and somatic symptom disorders (SSDs), and to compare the HRV values between FSSs/SSDs patients and healthy individuals. We included clinical studies assessing HRV (including baseline HRV and HRV reactivity) in FSSs/SSDs and healthy participants. We searched PubMed, Embase, PsycINFO, MEDLINE, and Web of Science databases from the earliest available date to June 2019. Eighty-five studies comprising 3242 FSSs/SSDs patients and 2321 controls were included in the main meta-analysis; the baseline HRV value was significantly lower compared to healthy individuals (Hedges'g, -0.43; 95 % CI, -0.54 to -0.30; $p < .001$), with the largest effect size in fibromyalgia patients. A significant lower HRV was

also found for total variability (Hedges'g, -0.56; 95 % CI, -0.77 to -0.36) and specific parasympathetic indices (Hedges'g, -0.41, 95 % CI; -0.54 to -0.30). HRV reactivity was significantly lower in FSSs/SSDs patients (Hedges'g, -0.42; 95 % CI, -0.64 to -0.20). Our results support the notion that FSSs/SSDs patients have significantly lower HRV than healthy individuals.

DNA methylation and BDNF expression account for symptoms and widespread hyperalgesia in patients with Chronic Fatigue Syndrome and Fibromyalgia.
Polli A, Ghosh M, Bakusic J, Ickmans K, Monteyne D, Velkeniers B, Bekaert B, Godderis L, Nijs J.
Arthritis Rheumatol. 2020 Jun 20. doi: 10.1002/art.41405. Online ahead of print.

Background: Epigenetics of neurotrophic factors holds the potential to unravel the mechanisms underlying the pathophysiology of complex conditions such as chronic fatigue syndrome (CFS). This study explored the role of brain-derived neurotrophic factor (BDNF) genetics, epigenetics, and protein expression in patients with both CFS and comorbid fibromyalgia (CFS/FM). Methods: A repeated-measures study in 54 participants (28 patients with CFS/FM and 26 matched healthy controls) was conducted. Participants underwent a comprehensive assessment, including questionnaires, sensory testing, and blood withdrawal. BDNF protein level was measured in serum (sBDNF) using ELISA, while polymorphism and DNA methylation were measured in blood, using pyrosequencing technology. To assess temporal stability of the measures, participants underwent the same assessment twice within four days. Results: Repeated-measures mixed linear models were performed for between-group analysis. sBNDF was higher in patients with CFS/FM (F=15.703; mean difference: 3.31 ng/ml, 95% C.I. 1.65 to 4.96; p=.001), whereas BDNF DNA methylation was lower in Exon IX (F=9.312; mean difference -2.38%, C.I. -3.93 to -0.83; p=.003). BDNF DNA methylation was mediated by the Val66Met (rs6265) polymorphism. Lower methylation in the same region predicted higher sBDNF (F=4.910, t= -2.216, p=.029, 95% C.I. = -.712 to -.039) which in turn predicted participants' symptoms (F=14.410, t= 3.796, 95% C.I.= 1.79 to 5.71, p=.001) and widespread hyperalgesia (F=4.147, t= 2.036, 95% C.I.= .01 to .08, p=.044). Discussion: sBDNF is higher in patients with CFS/FM and BDNF methylation in exon IX accounts for regulating protein expression. Altered BDNF might represent a key mechanism explaining CFS/FM pathophysiology.

Peripheral mechanisms contribute to comorbid visceral hypersensitivity induced by preexisting orofacial pain and stress in female rats.
Ji Y, Hu B, Klontz C, Li J, Dessem D, Dorsey SG, Traub RJ.
Neurogastroenterol Motil. 2020 Jul;32(7):e13833. doi: 10.1111/nmo.13833.

Background: Stress exacerbates many chronic pain syndromes including irritable bowel syndrome (IBS). Among these patient populations, many suffer from comorbid or chronic overlapping pain conditions and are predominantly female. Nevertheless, basic studies investigating chronic psychological stress-induced changes in pain sensitivity have been mostly carried out in male rodents. Our laboratory developed a model of comorbid pain hypersensitivity (CPH) (stress in the presence of preexisting orofacial pain inducing chronic visceral pain hypersensitivity that significantly outlasts transient stress-induced pain hypersensitivity (SIH)) facilitating the study of pain associated with IBS. Since CPH and SIH are phenotypically similar until SIH resolves and CPH persists, it is unclear if underlying mechanisms are similar. Methods: In the present study, the visceromotor response (VMR) to colorectal distention was recorded in the SIH and CPH models in intact females and ovariectomized rats plus estradiol replacement (OVx + E2). Over several months, rats were determined to be susceptible or resilient to stress and the role of peripheral corticotrophin-releasing factor (CRF) underlying in the pain hypersensitivity was examined. Key results: Stress alone induced transient (3-4 weeks) visceral hypersensitivity, though some rats were

resilient. Comorbid conditions increased susceptibility to stress prolonging hypersensitivity beyond 13 weeks. Both models had robust peripheral components; hypersensitivity was attenuated by the CRF receptor antagonist astressin and the mast cell stabilizer disodium cromoglycate (DSCG). However, DSCG was less effective in the CPH model compared to the SIH model. Conclusions and inferences: The data indicate many similarities but some differences in mechanisms contributing to comorbid pain conditions compared to transient stress-induced pain.

Down-regulation of spinal 5-HT_{2A} and 5-HT_{2C} receptors contributes to somatic hyperalgesia induced by orofacial inflammation combined with stress.
Xue Y, Wei SQ, Wang PX, Wang WY, Liu EQ, Traub RJ, Cao DY.
Neuroscience. 2020 Aug 1;440:196-209. doi: 10.1016/j.neuroscience.2020.05.044.

Patients suffering with functional somatic pain syndromes such as temporomandibular disorders (TMD) and fibromyalgia syndrome (FMS) have some similar symptoms, but the underlying cause is still unclear. The purpose of this study was to investigate whether 5-HT_{2A} and 5-HT_{2C} receptors in the spinal cord contribute to somatic hyperalgesia induced by orofacial inflammation combined with different modes of stress. Ovariectomized rats were injected subcutaneously with estradiol and bilateral masseter muscles were injected with complete Freund's adjuvant followed by stress. Somatic sensitivity was assessed with thermal and mechanical stimulation. The anxiety- and depression-like behaviors were measured by immobility time, sucrose preference, elevated plus maze and open field tests. The expression of 5-HT_{2A} and 5-HT_{2C} receptors in the spinal cord was examined by Western blot. Orofacial inflammation combined with 11 day forced swim stress (FSS) induced persistent mechanical allodynia for 15 days and thermal hyperalgesia for 2 days. The mechanical and thermal hyperalgesia lasted for 43 days and 30 days respectively following orofacial inflammation combined with 11 day heterotypic stress. Orofacial inflammation combined with stress induced anxiety- and depression-like behaviors. The expression of 5-HT_{2A} and 5-HT_{2C} receptors significantly decreased in the orofacial inflammation combined with stress groups. Intrathecal injection of 5-HT_{2A} or 5-HT_{2C} receptor agonist reversed somatic hyperalgesia. The results suggest that down-regulation of 5-HT_{2A} and 5-HT_{2C} receptors in the spinal cord contributes to somatic hyperalgesia induced by orofacial inflammation combined with stress, indicating that 5-HT_{2A} and 5-HT_{2C} receptors may be potential targets in the treatment of TMD comorbid with FMS.

The metabolomics of chronic pain conditions: A systematic review.
Aroke EN, Powell-Roach KL.
Biol Res Nurs. 2020 Jul 15;1099800420941105. doi: 10.1177/1099800420941105.

Background: Chronic pain is a significant public health problem in the United States, affecting approximately 100 million people. Yet there is a lack of robust biomarkers for clinical use in chronic pain conditions. Downstream effects of environmental, genomic, and proteomic variations in individuals with chronic pain conditions can be identified and quantified using a metabolomic approach. Aim/design: The purpose of this systematic review was to examine the literature for reports of potential metabolomic signatures associated with chronic pain conditions. Methods: We searched relevant electronic databases for published studies that used various metabolomic approaches to investigate chronic pain conditions among subjects of all ages. Results: Our search identified a total of 586 articles, 18 of which are included in this review. The reviewed studies used metabolomics to investigate fibromyalgia (n = 5), osteoarthritis (n = 4), migraine (n = 3), musculoskeletal pain (n = 2), and other chronic pain conditions (n = 1/condition). Results show that several known and newly identified metabolites differ in individuals with chronic pain conditions compared to those without these conditions. These include amino acids (e.g., glutamine, serine, and phenylalanine) and

intermediate products (e.g., succinate, citrate, acetylcarnitine, and N-acetylornithine) of pathways that metabolize various macromolecules. Conclusion: Though more high-quality research is needed, this review provides insights into potential biomarkers for future metabolomics studies in people with chronic pain conditions.

Dysmenorrhea subtypes exhibit differential quantitative sensory assessment profiles.
Hellman KM, Roth GE, Dillane KE, Garrison EF, Oladosu FA, Clauw DJ, Tu FF.
Pain. 2020 Jun;161(6):1227-1236. doi: 10.1097/j.pain.0000000000001826.

Women who develop bladder pain syndrome (BPS), irritable bowel syndrome, or dyspareunia frequently have an antecedent history of dysmenorrhea. Despite the high prevalence of menstrual pain, its role in chronic pelvic pain emergence remains understudied. We systematically characterized bladder, body, and vaginal mechanical sensitivity with quantitative sensory testing in women with dysmenorrhea (DYS, n = 147), healthy controls (HCs) (n = 37), and women with BPS (n = 25). Previously, we have shown that a noninvasive, bladder-filling task identified a subset of women with both dysmenorrhea and silent bladder pain hypersensitivity, and we repeated this to subtype dysmenorrhea sufferers in this study (DYSB; n = 49). DYS, DYSB, and BPS participants had lower vaginal mechanical thresholds and reported more pain to a cold stimulus during a conditioned pain modulation task and greater pelvic examination after-pain than HCs (P's < 0.05). DYSB participants also had reduced body mechanical thresholds and less conditioned pain modulation compared to HCs and DYS participants (P's < 0.05). Comparing quantitative sensory testing results among the DYS and HC groups only, provoked bladder pain was the only significant predictor of self-reported menstrual pain (r = 0.26), bladder pain (r = 0.57), dyspareunia (r = 0.39), and bowel pain (r = 0.45). Our findings of widespread sensory sensitivity in women with dysmenorrhea and provoked bladder pain, much like that observed in chronic pain, suggest a need to study the trajectory of altered mechanisms of pain processing in preclinical silent visceral pain phenotypes to understand which features convey inexorable vs modifiable risk.

Shared molecular genetic mechanisms underlie endometriosis and migraine comorbidity.
Adewuyi EO, Sapkota Y, International Endogene Consortium (IEC), 23andMe Research Team, International Headache Genetics Consortium (IHGC), Auta A, Yoshihara K, Nyegaard M, Griffiths LR, Montgomery GW, Chasman DI, Nyholt DR.
Genes (Basel). 2020 Feb 29;11(3):268. doi: 10.3390/genes11030268.

Observational epidemiological studies indicate that endometriosis and migraine co-occur within individuals more than expected by chance. However, the aetiology and biological mechanisms underlying their comorbidity remain unknown. Here we examined the relationship between endometriosis and migraine using genome-wide association study (GWAS) data. Single nucleotide polymorphism (SNP) effect concordance analysis found a significant concordance of SNP risk effects across endometriosis and migraine GWAS. Linkage disequilibrium score regression analysis found a positive and highly significant genetic correlation (r_G = 0.38, P = 2.30 × 10^{-25}) between endometriosis and migraine. A meta-analysis of endometriosis and migraine GWAS data did not reveal novel genome-wide significant SNPs, and Mendelian randomisation analysis found no evidence for a causal relationship between the two traits. However, gene-based analyses identified two novel loci for migraine. Also, we found significant enrichment of genes nominally associated (P_{gene} < 0.05) with both traits ($P_{binomial\text{-}test}$ = 9.83 × 10^{-6}). Combining gene-based p-values across endometriosis and migraine, three genes, two (*TRIM32 and SLC35G6)* of which are at novel loci, were genome-wide significant. Genes having P_{gene} < 0.1 for both endometriosis and migraine ($P_{binomial\text{-}test}$ = 1.85 ×$10^{-\circ 3}$) were significantly enriched for

biological pathways, including interleukin-1 receptor binding, focal adhesion-PI3K-Akt-mTOR-signaling, MAPK and TNF-α signalling. Our findings further confirm the comorbidity of endometriosis and migraine and indicate a non-causal relationship between the two traits, with shared genetically-controlled biological mechanisms underlying the co-occurrence of the two disorders.

Exploring the neural correlates of touch and pain in women with provoked vestibulodynia.
Sutton KS, Yessick LR, Wild CJ, Chamberlain SM, Pukall CF.
Pain. 2020 May;161(5):926-937. 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.

Determining the association between fibromyalgia, the gut microbiome and its biomarkers: A systematic review.
Erdrich S, Hawrelak JA, Myers SP, Harnett JE.
BMC Musculoskelet Disord. 2020 Mar 20;21(1):181. doi: 10.1186/s12891-020-03201-9.

Background: The association between fibromyalgia and irritable bowel syndrome is well-established. Alterations in the composition and diversity of the gut microbiome in irritable bowel syndrome have been reported, however, this association is poorly understood in fibromyalgia. Our aim was to summarise the research reporting on the gastrointestinal microbiome and its biomarkers in people with fibromyalgia. Methods: A systematic review of published original research reporting on the gastrointestinal microbiota and its biomarkers in adults with a diagnosis of fibromyalgia was undertaken. Results: From 4771 studies, 11 met our inclusion criteria and were separated into four main groups: papers reporting Helicobacter pylori; other gut bacterial markers; metabolomics and other biomarkers, which included intestinal permeability and small intestinal bacterial overgrowth. Conclusion: The results suggest there is a paucity of quality research in this area, with indications that the gut microbiota may play a role in fibromyalgia within the emerging field of the gut-musculoskeletal axis. Further investigations into the relationship between the gut microbiota, gut dysfunction and fibromyalgia are warranted.

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 Apr 1;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.

Gut-brain axis and migraine headache: A comprehensive review.
Arzani M, Jahromi SR, Ghorbani Z, Vahabizad F, Martelletti P, Ghaemi A, Sacco S, Togha M, School of Advanced Studies of the European Federation (EHF-SAS).
J Headache Pain. 2020 Feb 13; 21(1):15.doi: 10.1186/s10194-020-1078-9.

The terminology "gut-brain axis "points out a bidirectional relationship between the GI system and the central nervous system (CNS). To date, several researches have shown that migraine is associated with some gastrointestinal (GI) disorders such as Helicobacter pylori (HP) infection, irritable bowel syndrome (IBS), and celiac disease (CD). The present review article aims to discuss the direct and indirect evidence suggesting relationships between migraine and the gut-brain axis. However, the mechanisms explaining how the gut and the brain may interact in patients with migraine are not entirely clear. Studies suggest that this interaction seems to be influenced by multiple factors such as inflammatory mediators (IL-1β, IL-6, IL-8, and TNF-α), gut microbiota profile, neuropeptides and serotonin pathway, stress hormones and nutritional substances. Neuropeptides including CGRP, SP, VIP, NPY are thought to have antimicrobial impact on a variety of the gut bacterial strains and thus speculated to be involved in the bidirectional relationship between the gut and the brain. According to the current knowledge, migraine headache in patients harboring HP might be improved following the bacteria eradication. Migraineurs with long headache history and high headache frequency have a higher chance of being diagnosed with IBS. IBS and migraine share some similarities and can alter gut microflora composition and thereby may affect the gut-brain axis and inflammatory status. Migraine has been also associated with CD and the condition should be searched particularly in patients with migraine with occipital and parieto-occipital calcification at brain neuroimaging. In those patients, gluten-free diet can also be effective in reducing migraine frequency. It has also been proposed that migraine may be improved by dietary approaches with beneficial effects on gut microbiota and gut-brain axis including appropriate consumption of fiber per day, adhering to a low glycemic index diet, supplementation with vitamin D, omega-3 and probiotics as well as weight loss dietary plans for overweight and obese patients.

Targeting the gut microbiota for the treatment of irritable bowel syndrome.
Herndon CC, Wang Y, Lu C.
Kaohsiung J Med Sci. 2020 Mar;36(3):160-170. doi: 10.1002/kjm2.12154.

Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder that affects an estimated 11% of people across the world. IBS patients are one of the largest subgroups seen in gastroenterology clinics, exhibit a lesser quality of life, and take greater use of the healthcare system. The exact etiology of IBS remains uncertain. Alterations in the gut microbiome may characterize a potential mechanism in the pathogenesis of IBS. This hypothesis is paralleled by rodent models in which manipulation of the gut microbiota leads to disturbed physiological functions along the brain-gut axis. Recent research in IBS treatments has redirected its focus towards gut microbiome based therapeutics. In this review, we discuss potential roles of enteric bacteria in the pathogenesis of IBS and its comorbidities. We then explore the manipulation of the enteric microbiota by prebiotics, probiotics, antibiotics, dietary changes, and fecal microbiota transfer. We also discuss the positive and negative effects of these therapeutics on IBS symptoms.

From IBS to ME - The dysbiotic march hypothesis.
Berstad A, Hauso O, Berstad K, Berstad JER.
Med Hypotheses. 2020 Feb 26;140:109648. doi: 10.1016/j.mehy.2020.109648.

Irritable bowel syndrome (IBS) is often associated with other unexplained complaints like chronic fatigue syndrome (CFS), fibromyalgia and myalgic encephalopathy (ME). The pathogenesis of the relationship is unknown. Intestinal dysbiosis may be a common abnormality, but based on 1100 consecutive IBS patients examined over a nine years period, we hypothesize that the development of the disease, often from IBS to ME, actually manifests a "dysbiotic march". In analogy with "the atopic march" in allergic diseases, we suggest "a dysbiotic march" in IBS; initiated by extensive use of antibiotics during childhood, often before school age. Various abdominal complaints including IBS may develop soon thereafter, while systemic symptom like CFS, fibromyalgia and ME may appear years later.

Convergent syndromic atrophy of pain and emotional systems in patients with irritable bowel syndrome and depressive symptoms.
Li J, Yuan B, Li G, Lu X, Guo Y, Yang Y, Liang M, Ding J, Zhou Q.
Neurosci Lett. 2020 Apr 1;723:134865. doi: 10.1016/j.neulet.2020.134865.

Irritable bowel syndrome (IBS) is a brain-gut disorder that is often accompanied by psychiatric comorbidities, particularly depression. However, the neuroanatomical substrates of IBS with depressive symptoms (DEP-IBS) and how depressive symptoms and brain morphology modulate IBS symptoms remain unknown. In this study, structural MRI data were processed using a voxel-based morphometry technique and one-way analysis of covariance (ANCOVA) and post-hoc t-tests were performed to compare gray matter volume (GMV) among 28 patients with DEP-IBS, 21 patients with IBS who lacked depressive symptoms (nDEP-IBS), and 36 healthy controls (HC). Correlation and mediation analyses were performed to evaluate the relationship between differing GMV in DEP-IBS and clinical variables. We found that GMV in the bilateral prefrontal, insular, and dorsal striatal areas, as well as the left temporal pole, were significantly lower in the DEP-IBS group than in the HC group. Moreover, compared with the nDEP-IBS group, the DEP-IBS group exhibited decreased GMV in the bilateral medial, dorsolateral prefrontal, and orbitofrontal cortices, bilateral dorsal striatum, and left insular cortices. Correlation analysis revealed that GMV in these atrophic brain areas of the DEP-IBS group was negatively correlated with depression, gastrointestinal symptoms, and disease duration. Our results further revealed that depressive symptoms served as a mediator between gastrointestinal symptoms and GMV in the left insula, right medial prefrontal cortex,

and right middle frontal gyrus, while gastrointestinal symptoms served as a mediator between depression and GMV in these regions. Our results suggest convergent syndromic atrophy in the pain and emotional systems of patients with DEP-IBS.

Experimentally induced spinal nociceptive sensitization increases with migraine frequency: a single-blind controlled study.
De Icco R, Perrotta A, Grillo V, Cosentino G, Sances G, Sandrini G, Tassorelli C.
Pain. 2020 Feb;161(2):429-438. doi: 10.1097/j.pain.0000000000001726.

The nitric-oxide donor nitroglycerin (NTG) administration induces a facilitation of nociceptive pathways in episodic migraine. This study aims to test the hypothesis that induced spinal sensitization could be more pronounced in patients affected by high-frequency migraine (HF-MIG) with respect to low-frequency migraine (LF-MIG). We enrolled 28 patients with LF-MIG (1-5 migraine days/month), 19 patients with HF-MIG (6-14 migraine days/month), and 21 healthy controls (HCs). Spinal sensitization was evaluated with the neurophysiological recording of the temporal summation threshold (TST) of the nociceptive withdrawal reflex at the lower limb. Temporal summation threshold was recorded at baseline and 30, 60, and 120 minutes after NTG administration (0.9 mg sublingual). Spinal sensitization was detected in LF-MIG at 60 ($P = 0.010$) and 120 minutes ($P = 0.001$) and in HF-MIG at 30 ($P = 0.008$), 60 ($P = 0.001$), and 120 minutes ($P = 0.001$) after NTG administration. Temporal summation threshold did not change in HC ($P = 0.899$). Moreover, TST reduction was more pronounced in HF-MIG with respect to LF-MIG ($P = 0.002$). The percentage of patients who developed a migraine-like headache after NTG was comparable in the 2 migraine groups (LF-MIG: 53.6%, HF-MIG: 52.6%, $P = 0.284$), whereas no subjects in the HC group developed a delayed-specific headache. Notably, the latency of headache onset was significantly shorter in the HF-MIG group when compared with the LF-MIG group ($P = 0.015$). Our data demonstrate a direct relationship between migraine frequency and both neurophysiological and clinical parameters, to suggest an increasing derangement of the nociceptive system control as the disease progresses, probably as a result of the interaction of genetic and environmental factors.

Sex as a biological variable in irritable bowel syndrome.
Camilleri 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.

Sex-dependent mechanisms of chronic pain: A focus on microglia and P2X4R.
Halievski K, Ghazisaeidi S, Salter MW.
J Pharmacol Exp Ther. 2020 Feb 29;jpet.120.265017. doi: 10.1124/jpet.120.265017. Online ahead of print.

For over two decades, purinergic signaling in microglia has persisted in the spotlight as a major pathomechanism of chronic pain. Of the many purinoreceptors, the P2X4R of the ionotropic family has a well-described causal role underlying chronic neuropathic pain. This review will first briefly examine microglial P2X4R signaling in the spinal cord as it relates to chronic pain through a historical lens, followed by a more in-depth examination of recent work, which has revealed major sex differences. We also discuss the generalizability of sex differences in microglial and P2X4R signaling in other pain conditions, as well as in non-spinal regions. Finally, we speculate on remaining gaps in the literature as well as what can be done to address them with the ultimate goal of using our collective knowledge to treat chronic pain effectively and in both sexes. SIGNIFICANCE STATEMENT: Effective treatments are lacking for chronic pain sufferers, and this may be explained by the vast sex differences underlying chronic pain mechanisms. In this Minireview, we focus on the roles of microglia and P2X4R in chronic pain, with specific attention to the circumstances under which these pathomechanisms differ between males and females. By delineating the ways in which pain occurs differently between the sexes, we can start developing successful therapies for all.

EPIDEMIOLOGY STUDIES

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 XY, Xie YX, Zhang XX, Huang JX, Liu Y, Cheng MJ, Liu N, Wang PX.
Aging Clin Exp Res. 2020 Jul;32(7):1327-1334. 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 (β = - 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.

Overlap between irritable bowel syndrome diagnosis and endometriosis in adolescents.
DiVasta AD, Zimmerman LA, Vitonis AF, Fadayomi AB, Missmer SA.
Clin Gastroenterol Hepatol. 2020 Mar 14;S1542-3565(20)30324-4.

Background & aims: Gastroenterologic symptoms often are reported by adults with endometriosis, leading to unnecessary diagnostic tests or complicated treatment. We investigated associations between endometriosis and irritable bowel syndrome (IBS) in adolescents and whether concurrent pain disorders affect these. Methods: We collected data from within The Women's Health Study: Adolescence to Adulthood, which is a US longitudinal study of premenopausal females with and without endometriosis. Our study cohort included participants younger than 21 years enrolled from 2012 to 2018. Participants completed an extensive health questionnaire. Those with IBS based on a self-reported diagnosis or meeting Rome IV diagnostic criteria were considered cases and those without IBS were controls. Subjects without concurrent gastrointestinal disorders or missing pain data (n = 323) were included in the analyses. We calculated adjusted odds ratios using unconditional logistic regression. Results: More adolescents with endometriosis (54 of 224; 24%) had comorbid IBS compared with adolescents without endometriosis (7 of 99; 7.1%). The odds of IBS was 5.26-fold higher among participants with endometriosis than without (95% CI, 2.13-13.0). In girls with severe acyclic pelvic pain, the odds of IBS was 35.7-fold higher in girls without endometriosis (95% CI, 4.67-272.6) and 12-fold higher in girls with endometriosis (95% CI, 4.2-36.3), compared with no/mild pain. For participants with endometriosis, each 1-point increase in acyclic pain severity increased the odds of IBS by 31% (adjusted odds ratio, 1.31; 95% CI, 1.18-1.47). Conclusions: In an analysis of data from a longitudinal study of girls and women with and without endometriosis, we found significant associations between endometriosis and IBS, and a linear relationship between acyclic pelvic pain severity and the odds of IBS. Increased provider awareness and screening for IBS and endometriosis will improve patient outcomes and increase our understanding of these complex disorders.

Comorbidities of patients with functional somatic syndromes before, during and after first diagnosis: A population-based study using bavarian routine data.
Donnachie E, Schneider A, Enck P.
Sci Rep. 2020 Jun 17;10(1):9810. doi: 10.1038/s41598-020-66685-4.

Functional somatic syndromes (FSS) are characterised by the presence of one or multiple chronic symptoms that cannot be attributed to a known somatic disease. They are thought to arise though a complex interaction of biological and psychosocial factors, but it is unclear whether they share a common aetiology. One hypothesis supported by recent studies is that the FSS are postinfectious disorders, as is widely recognised for a subset of patients with irritable bowel syndrome. Our study used claims data submitted by office-based physicians to compare groups of patients with different FSS in the five years before and after the point of first diagnosis. Even five years prior to diagnosis, FSS patients consulted more frequently for a range of psychological and somatic conditions than did controls. Following diagnosis, consultation rates increased further and remained persistently high. Five years after diagnosis, between 34% (somatization disorder) and 66% (fibromyalgia) of patients were still being treated for the condition. Both prior gastrointestinal and upper-respiratory infection were associated with an increased risk of developing an FSS. We therefore recommend that patients at risk should be identified at an early stage and the underlying psychosocial and somatic issues addressed to prevent progression of the condition.

Predictors of new onsets of irritable bowel syndrome, chronic fatigue syndrome and fibromyalgia: the lifelines study.
Monden R, Rosmalen JGM, Wardenaar KJ, Creed F.
Psychol Med. 2020 Jun 17;1-9. doi: 10.1017/S0033291720001774.

Background: It has been claimed that functional somatic syndromes share a common etiology. This prospective population-based study assessed whether the same

variables predict new onsets of irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS) and fibromyalgia (FM). Methods: The study included 152 180 adults in the Dutch Lifelines study who reported the presence/absence of relevant syndromes at baseline and follow-up. They were screened at baseline for physical and psychological disorders, socio-demographic, psycho-social and behavioral variables. At follow-up (mean 2.4 years) new onsets of each syndrome were identified by self-report. We performed separate analyses for the three syndromes including participants free of the relevant syndrome or its key symptom at baseline. LASSO logistic regressions were applied to identify which of the 102 baseline variables predicted new onsets of each syndrome. Results: There were 1595 (1.2%), 296 (0.2%) and 692 (0.5%) new onsets of IBS, CFS, and FM, respectively. LASSO logistic regression selected 26, 7 and 19 predictors for IBS, CFS and FM, respectively. Four predictors were shared by all three syndromes, four predicted IBS and FM and two predicted IBS and CFS but 28 predictors were specific to a single syndrome. CFS was more distinct from IBS and FM, which predicted each other. Conclusions: Syndrome-specific predictors were more common than shared ones and these predictors might form a better starting point to unravel the heterogeneous etiologies of these syndromes than the current approach based on symptom patterns. The close relationship between IBS and FM is striking and requires further research.

Prevalence and impact of comorbid widespread pain in adults with chronic low back pain: A registry-based study.
Licciardone JC, Pandya V.
J Am Board Fam Med. Jul-Aug 2020;33(4):541-548.

Introduction: Widespread pain (WP) is emerging as a key comorbid condition in patients with chronic low back pain (CLBP). This study measured the prevalence of comorbid WP in adults with CLBP, WP predictors, and impact on patients.
Methods: Patients with CLBP were recruited from the Pain Registry for Epidemiologic, Clinical, and Interventional Studies and Innovation from 2016 through 2019. They were followed over 12 months to measure annual WP period prevalence rates using an item from the minimum dataset recommended by the National Institutes of Health Task Force on Research Standards for Chronic Low Back Pain. Patients were classified as not having WP, having nonpersistent WP, or having persistent WP. Pain intensity, back-related disability, and quality of life were measured using a numerical rating scale, the Roland-Morris Disability Questionnaire, and the PROMIS-29 instrument, respectively. Results: A total of 358 patients were studied, including 56 (16%) without WP, 272 (76%) with nonpersistent WP, and 30 (8%) with persistent WP. There were no significant differences among the WP groups with regard to age, sex, or CLBP duration. However, being non-White and having moderate or high levels of pain catastrophizing remained significant predictors of nonpersistent or persistent WP after adjusting for potential confounders. Patients reported greater pain intensity and back-related disability and poorer quality of life over 12 months with increasing levels of WP persistence ($P < .001$ for each measure). Conclusion: Greater efforts are needed in primary care to help close these gaps in pain intensity, back-related disability, and quality-of-life outcomes associated with WP.

Metabolic syndrome, depression, and fibromyalgia syndrome prevalence in patients with irritable bowel syndrome: A case-control study.
Bayrak M.
Medicine (Baltimore). 2020 Jun 5;99(23):e20577. doi: 10.1097/MD.0000000000020577.

Although both metabolic syndrome (MetS) and irritable bowel syndrome (IBS) have been linked with altered gut microbiota, only a few studies investigated the association between them. Hence, we aimed to evaluate the prevalence of MetS along with depression and fibromyalgia syndrome (FMS) in IBS patients. This was a case-control

study in which 3808 consecutive patients who attended outpatient clinics of Erzurum Regional Training and Research Hospital between May 2019 and August 2019 were evaluated in terms of IBS with Rome-IV criteria. Out of 486 patients who were diagnosed as IBS, 176 patients were excluded for various reasons. Control subjects were randomly selected from IBS-negative subjects. MetS was diagnosed based on International Diabetes Federation criteria. Depression, anxiety disorder, and FMS were assessed via Hamilton Depression Scale, Beck Anxiety Inventory, and American College of Rheumatology criteria, respectively. Blood samples were obtained to measure biochemical parameters. Study group included 310 IBS patients, and control group included 304 subjects. The prevalence of the MetS was significantly higher among IBS patients compared with controls (36.8% vs 21.7%, respectively, P = .006). The rate of obesity was 18.1% among IBS subjects, and 10.2% in the controls. The prevalence of fibromyalgia (30% vs 3%, respectively, P < .001), anxiety-disorder (39.7% vs 10.2%, P < .001) and depression (8.1% vs 4.9%, P < .001) were significantly higher in IBS group than controls. Metabolic syndrome and obesity were significantly more frequent in IBS patients compared with controls. FMS, anxiety disorder, and depression were also more common among IBS patients.

Non-bladder centric interstitial cystitis/bladder pain syndrome phenotype is significantly associated with co-occurring endometriosis.
Overholt TL, Evans RJ, Lessey BA, Matthews CA, Hines KN, Badlani G, Walker SJ.
Can J Urol. 2020 Jun;27(3):10257-10262.

Introduction: Interstitial cystitis/bladder pain syndrome (IC/BPS) and endometriosis are coexistent diagnoses in 48%-65% of women with chronic pelvic pain (CPP), suggesting that dual screening may be warranted. To further investigate the clinical relationship and risk factors between these two conditions, we performed a retrospective review of our large IC/BPS patient data registry. Materials and methods: We evaluated IC/BPS patients who were prospectively enrolled into our registry who completed validated questionnaires and underwent therapeutic hydrodistension, during which anesthetic bladder capacity (BC) and Hunner's lesion (HL) status were recorded. Demographic / medical history were reviewed. IC/BPS patients with co-occurring endometriosis diagnosis versus those without were compared using descriptive statistics as well as multivariate regression analyses to determine predictors of co-occurring disease.
Results: Of 431 IC/BPS participants, 82 (19%) were also diagnosed with endometriosis. These women were significantly younger, had increased prevalence of non-low BC (> 400 cc), and decreased prevalence of HL ($p < 0.05$). Patients with co-occurring endometriosis also had increased prevalence of irritable bowel syndrome (IBS), CPP, fibromyalgia, and vulvodynia ($p < 0.05$). On multivariate analysis, non-low BC (OR 4.53, CI 1.004-20.42, $p = 0.049$), CPP (OR 1.84, CI 1.04-3.24, $p = 0.04$), and fibromyalgia (OR 1.80, CI 1.03-3.14, $p < 0.04$) were significantly associated with a diagnosis of endometriosis. Conclusions: Patients with IC/BPS and co-occurring endometriosis were significantly more likely to carry a non-bladder centric IC/BPS phenotype as well as several comorbid, systemic pain diagnoses. This study characterizes features of a target IC/BPS phenotype that could potentially benefit from endometriosis and systemic pain syndrome screening.

Comorbid conditions associated with painful temporomandibular disorders in adolescents from Brazil, Canada and France: A cross-sectional study.
Khan K, Muller-Bolla M, Teixeira Jr. OA, Gornitsky M, Guimaraes AS, Velly AM.
J Oral Rehabil. 2020 Apr;47(4):417-424. doi: 10.1111/joor.12923.

Background: Painful temporomandibular disorder (TMD) is common among adolescents. Presence of painful comorbidities may worsen painful TMD and impact treatment effectiveness. Objective: The aim of this study was to assess the association between painful TMD and comorbidities. Methodology: In this cross-

sectional study, adolescents were recruited in Montreal (Canada), Nice (France) and Arceburgo (Brazil). Reliable instruments were used to assess painful TMD and comorbidities. Multivariable logistic and linear regression analyses were conducted to assess the study aims. Results: The prevalence of self-reported painful TMD was estimated at 31.6%; Arceburgo (31.6%), Montreal (23.4%) and Nice (31.8%). Painful TMD was more common among girls than boys (OR = 1.96). Painful TMD was associated with a higher number of comorbidities (OR = 1.77); Arceburgo (OR = 1.81), Montreal (OR = 1.80) and Nice (OR = 1.72). A stronger association was found between painful TMD and headaches (OR = 4.09) and a weaker one with stomach pain (OR = 1.40). Allergies were also related to painful TMD (OR = 1.43). Conclusion: Painful TMD was associated with comorbidities. Headaches were consistently associated with painful TMD. Other associations were modified by sex and/or covariates related to the cities where participants were recruited.

Widespread pain and central sensitization in adolescents with signs of painful temporomandibular disorders.
Campi LB, Visscher CM, Ongaro PCJ, Vinicius do Vale Braido G, Fernandes G, Goncalves DAG.
J Oral Facial Pain Headache. Winter 2020;34(1):83-91. doi: 10.11607/ofph.2288.

Aims: To investigate the associations between signs of painful temporomandibular disorders (TMD) and number of tender points (TPs) and fibromyalgia in adolescents, as well as the relationship between TPs and pressure-pain threshold (PPT) in individuals presenting with local, regional, or widespread pain as a way to investigate the presence of central sensitization (CS). Methods: The sample consisted of 690 Brazilian adolescents with and without signs of painful TMD, aged 12 to 14 years old. Painful TMD was classified according to the Research Diagnostic Criteria for TMD (RDC/TMD) Axis I. The criteria established by Yunus were applied to assess juvenile fibromyalgia and TPs. Mann-Whitney and chi-square tests were applied to test the associations between signs of painful TMD and demographic variables. Regression models were used to estimate the association between signs of painful TMD and number of TPs and to determine which additional predictive variables were associated with TPs. Regression analyses were performed to test the associations between PPT values and number of TPs. Fisher test was used to estimate the association between signs of painful TMD and FM. Results: Significant associations between signs of painful TMD and the number of TPs ($P < .001$), as well as between TPs and the PPT values for local, regional, and widespread pain ($P < .001$), were found. No association between signs of painful TMD and fibromyalgia was found ($P = .158$). Conclusion: Individuals with signs of painful TMD presented with more TPs compared to pain-free adolescents. Moreover, the higher the number of TPs, the lower the PPT. This finding suggests that adolescents with signs of painful TMD are at increased risk of presenting with CS.

Comorbid and co-occurring conditions in migraine and associated risk of increasing headache pain intensity and headache frequency: results of the migraine in America symptoms and treatment (MAST) study.
Buse DC, Reed ML, Fanning KM, Bostic R, Dodick DW, Schwedt TJ, Munjal S, Singh P, Lipton RB.
J Headache Pain. 2020 Mar 2;21(1):23. doi: 10.1186/s10194-020-1084-y.

Background: Migraine has many presumed comorbidities which have rarely been compared between samples with and without migraine. Examining the association between headache pain intensity and monthly headache day (MHD) frequency with migraine comorbidities is novel and adds to our understanding of migraine comorbidity. Methods: The MAST Study is a prospective, web-based survey that identified US population samples of persons with migraine (using modified International Classification of Headache Disorders-3 beta criteria) and without

migraine. Eligible migraine participants averaged ≥1 MHDs over the prior 3 months. Comorbidities "confirmed by a healthcare professional diagnosis" were endorsed by respondents from a list of 21 common cardiovascular, neurologic, psychiatric, sleep, respiratory, dermatologic, pain and medical comorbidities. Multivariable binary logistic regression calculated odds ratios (OR) and 95% confidence intervals for each condition between the two groups adjusting for sociodemographics. Modeling within the migraine cohort assessed rates of conditions as a function of headache pain intensity, MHD frequency, and their combination. Results: Analyses included 15,133 people with migraine (73.0% women, 77.7% White, mean age 43 years) and 77,453 controls (46.4% women, 76.8% White, mean age 52 years). People with migraine were significantly (P < 0.001) more likely to report insomnia (OR 3.79 [3.6, 4.0]), depression (OR 3.18 [3.0, 3.3]), anxiety (OR 3.18 [3.0 3.3]), gastric ulcers/GI bleeding (OR 3.11 [2.8, 3.5]), angina (OR 2.64 [2.4, 3.0]) and epilepsy (OR 2.33 [2.0, 2.8]), among other conditions. Increasing headache pain intensity was associated with comorbidities related to inflammation (psoriasis, allergy), psychiatric disorders (depression, anxiety) and sleep conditions (insomnia). Increasing MHD frequency was associated with increased risk for nearly all conditions and most prominent among those with comorbid gastric ulcers/GI bleeding, diabetes, anxiety, depression, insomnia, asthma and allergies/hay fever. Conclusions: In regression models controlled for sociodemographic variables, all conditions studied were reported more often by those with migraine. Whether entered into the models separately or together, headache pain intensity and MHD frequency were associated with increased risk for many conditions. Future work is required to understand the causal sequence of relationships (direct causality, reverse causality, shared underlying predisposition), the potential confounding role of healthcare professional consultation and treatment, and potential detection bias.

Vulvar pain: The revealing scenario of leading comorbidities in 1183 cases.
Graziottin A, Murina F, Gambini D, Taraborrelli S, Gardella B, Campo M, VuNet Study Group.
Eur J Obstet Gynecol Reprod Biol. 2020 May 30;252:50-55.

Objectives: This study set out to investigate the epidemiological characteristics and comorbidities of chronic vulvar pain. Secondary goals were to identify the preferred approaches for managing vulvodynia in Italy. Study design: A cross-sectional study (the VuNet -Vulvodynia Network project) was performed in consecutive female patients with chronic vulvar pain attending 21 Italian medical centers (public hospitals, university clinics and private outpatient services) in the period December 2016 to November 2018. Study data were entered by healthcare professionals in a special web-based medical record system (PRIDE- Progetto Rete Italiana Dolore vulvarE). These data covered epidemiological aspects, demographic characteristics, obstetric and gynecological history, presence and duration of current and/or past symptoms, associated disorders, details of physical examination and treatment approaches. Results: A total of 1183 subjects with a diagnosis of chronic vulvar pain were included in the study. The main reason for consultation was superficial dyspareunia, present in 64.2 % of the women. 43.4 % of the sample reported comorbid sexual disorders (of desire in 22.1 % and arousal in 21.3 %). 48.3 % of the patients reported prolonged pain lasting between one and five years. Factors associated with vulvar pain included a relatively high family history of diabetes mellitus (father = 8.6 %; mother = 8.4 %), recurrent vulvovaginal candidiasis (32 %), and urinary tract infections (37.4 %: recurrent cystitis in 19.5 % and post-coital cystitis in 17.9 %). Irritable bowel syndrome (28 %), constipation (23.5 %), headache (25.7 %: migraine in 18.0 % and menstrual headache in 7.7 %), allergies (17.5 %: food allergies in 10.1 %, respiratory allergies in 7.4 %), anxiety (15.0 %), dyschezia (11.7 %), invalidating dysmenorrhea/endometriosis (11.1 %), and major depression (7.6 %) were also reported. Vestibulodynia was diagnosed in 837 of the 1183 patients (70.8 %) and generalized vulvodynia in 323 (27.3 %). Notably, 69.1 % of the patients stated that

previous therapies had not changed their pain. Conclusions: The diagnoses of vestibulodynia and vulvodynia must be considered in patients with chronic vulvar pain. The VuNet study contributes to a more comprehensive reading of the predisposing, precipitating and maintaining factors that contribute to vulvar pain, and of the key comorbidities.

Chronic facial pain: different comorbidities and characteristics between neuropathic and nonneuropathic conditions.
Puerta MY, Galhardoni R, Teixeira MJ, Tesseroli de Siqueira J, Tesseroli de Siqueira SRD.
Oral Surg Oral Med Oral Pathol Oral Radiol 2020 May 24;S2212-4403(20)31010-5.

Objective: The aim of this study was to investigate the association between comorbidities and chronic diseases and neuropathic and nonneuropathic orofacial pain diagnoses to suggest subclassifications of disease. Study design: This was a cross-sectional, retrospective, case-control study. We evaluated 174 patients with orofacial pain and 132 controls by using a systematic protocol that consisted of medical history and demographic, pain, and orofacial characteristics. Patients were grouped according to their diagnosis-neuropathic or non-neuropathic pain; medical comorbidities; and exclusion criteria. Analyses included Z-score normalization, χ^2 test, Fisher's exact test, 1-way analysis of variance (ANOVA), Student t test, Pearson's correlation coefficient, 2-step clustering, and logistic regression at 95% confidence level. Results: Functional chronic diseases were prevalent and correlated with pain and orofacial features. Three groups were identified in the cluster analysis: neuropathic facial pain, other orofacial pain syndromes, and fibromyalgia / temporomandibular disorders (TMDs). Logistic regression showed that hypothyroidism and gastritis were predictors for nonneuropathic orofacial conditions. Psychiatric diseases and gastritis were more prevalent among patients with generalized pain syndromes and TMDs and less prevalent among patients with neuropathic pain. Conclusions: Functional comorbidities were associated with orofacial and dental features and may correspond to multimorbidity states in patients with chronic orofacial pain. The findings support the hypothesis that nonneuropathic orofacial pain syndromes could be functional disorders.

Comorbidities of self-reported fibromyalgia in United States adults: A cross-sectional study from The National Epidemiological Survey on Alcohol and Related Conditions (NESARC-III).
Sleurs D, Tebeka S, Scognamiglio C, Debertret C, Le Strat Y.
Eur J Pain. 2020 May 7. doi: 10.1002/ejp.1585. Online ahead of print.

Background: Fibromyalgia has been associated with various physical and mental disorders. However, these comorbidities need to be quantified in a population-based study. Method: We compared participants with and without self-reported fibromyalgia to assess (a) The prevalence of self-reported fibromyalgia and its sociodemographic characteristics in a US representative sample, (b) The associations between self-reported fibromyalgia and lifetime and past 12-month mental and physical disorders and (c) The quality of life associated with self-reported fibromyalgia. This cross-sectional study used a large national sample (n = 36,309) of the US population, the National Epidemiologic Survey on Alcohol and Related Conditions-III. Face to face interviews were conducted, collecting sociodemographic characteristics, diagnostic and statistical manual of mental disorders-5 structured diagnosis and self-reported medical conditions (including fibromyalgia). Results: The past 12-month prevalence of self-reported fibromyalgia was estimated at 2.05%. Participants with self-reported fibromyalgia were significantly at higher risk to report a lifetime history of mental disorder (adjusted odds ratio [aOR] = 2.32). Self-reported fibromyalgia was also positively associated with 24 of the 27 physical conditions assessed in this study. Participants with self-reported fibromyalgia were more likely to report a past 12-month

history of suicide attempts (aOR = 5.81), substance use disorders (aOR = 1.40), mood disorders (aOR = 2.67), anxiety disorders (aOR = 2.75) and eating disorders (aOR = 2.45). Participants with self-reported fibromyalgia had lower levels of both mental and physical quality of life than those without fibromyalgia. Conclusions: Participants with self-reported fibromyalgia have a higher prevalence of comorbid mental and physical disorders, and lower mean levels of mental and physical quality of life than their counterparts without fibromyalgia. Significance: We showed here a strong association of self-reported fibromyalgia with both mental and physical comorbidities. We showed that among participants with self-reported fibromyalgia, more than 8 out of 10 had at least three other physical comorbidities, and almost half had at least three mental comorbidities. This is a cross-sectional study using a representative sample of the US population with highly reliable psychiatric diagnosis that makes our results generalizable. Practitioners managing fibromyalgia should search and treat these comorbidities.

Prevalence and risk factors of dry eye in 79,866 participants of the population-based Lifelines cohort study in the Netherlands.
Vehof J, Snieder H, Jansonius N, Hammond CJ.
Ocul Surf. 2020 May 4;S1542-0124(20)30069-0. doi: 10.1016/j.jtos.2020.04.005.

Purpose: To investigate the prevalence of dry eye among all adult age categories and to discover independent risk factors by investigating a wide range of etiological categories. Methods: A cross-sectional association study including 79,866 voluntary participants aged 20-94 years of the population-based Lifelines Cohort Study in the Netherlands.
Results: Overall, 9.1% of participants had dry eye disease as measured by the Women's Health Study dry eye questionnaire. Prevalence of dry eye symptoms were particularly prevalent in 20-30 years olds. Dry eye was associated with comorbidities in almost all body systems, including musculoskeletal, gastro-intestinal, ophthalmic, autoimmune, psychiatric, pain, functional, dermatological and atopic disorders. Numerous independent risk factors were discovered or confirmed, with strong associations for female sex, contact lens use, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, eye surgery including cataract and laser refractive surgery, keratoconus, osteoarthritis, connective tissue diseases, atherosclerosis, Graves' disease, autistic disorder, depression, 'burnout', Crohn's disease, sarcoid, lichen planus, rosacea, liver cirrhosis, sleep apnea, sinusitis, thyroid function, and air pollution (NO_2). High blood pressure and high BMI were strongly associated with less dry eye, as was current smoking, while ex-smokers had more dry eye. No clear link between dry eye and lipid or blood glucose levels was found. Conclusions: This study on dry eye confirmed but also refuted many risk factors from smaller epidemiological studies, and discovered numerous new risk factors in multiple etiological categories. The finding that dry eye symptoms are particularly common in young adults is concerning, and warrants further study.

Analysis of clinical oral medicine practices at the University of Pennsylvania: a 5-year retrospective study.
Sun M, Sollecito TP, Greenberg MS, Pinto A, Stoopler ET.
Oral Surg Oral Med Oral Pathol Oral Radiol 2020 Mar;129(3):215-221.e6.

Objective: The aim of this study was to characterize oral medicine (OM) clinical practices at the University of Pennsylvania (Penn), determine the importance of OM clinical services, and emphasize aspects of training for OM specialists. Study design: Nonprobability sampling of OM resident patient logs for patients receiving clinical care from 2008 to 2013 was conducted. OM resident patient logs included clinical diagnosis, International Classification of Diseases, ninth edition code, medical history, clinical procedure, Current Procedural Terminology code, attending physician, and resident participation notes. Results: Outpatients in OM medical practices (n =

6024) averaged 1.56 diagnoses from OM specialists. Orofacial pain (45.02%) and oral mucosal diseases (34.28%) comprised the majority of OM diagnoses. The most common procedures were tissue biopsies (59.34%) and treatments for temporomandibular disorders (29.9%). Inpatients (n = 313) comprised 3.46% of Penn OM hospital services, and cardiovascular disorders (38.99%) were the most common admitting diagnoses in this group. In the OM dental practice (n = 1648), 42.05% of patients had a median of 3 medical comorbidities (range = 2-11), of which cardiovascular disorders (27.13%) were most prevalent. Conclusions: Analysis of Penn OM clinical practices emphasizes the breadth and multidisciplinary nature of OM services and importance of comprehensive postdoctoral training in all domains of OM.

Prevalence and overlap of somatic symptom disorder, bodily distress syndrome and fibromyalgia syndrome in the German general population: A cross sectional study.
Hauser W, Hausteiner-Wiehle C, Henningsen P, Brahler E, Schmalbach B, Wolfe F.
J Psychosom Res. 2020 Jun;133:110111. doi: 10.1016/j.jpsychores.2020.110111.

Objective: To study the prevalence and clinical characteristics of Somatic Symptom Disorder (SSD), Bodily Distress Syndrome (BDS) and fibromyalgia syndrome (FMS) and their overlap in the general German population. Methods: A cross-sectional nationally representative population survey was performed. 2531 participants (mean age 48.8 ± 17.85 years, 53.3% women) completed the Somatic Symptom Scale SSS-8, the Bodily Distress Syndrome (BDS) 25 checklist, the Whiteley Index 7 (WI-7), the self-administered comorbidity questionnaire and the Michigan Body Map. Case definitions of SSD, BDS and FMS were assigned using established criteria. Results: 4.5% of participants met the criteria of SSD (SSS - 8 at least one item "bothered very much" and WI- 7 total score ≥ 1). 9.6% met the criteria of single-organ BDS and 1.3% of multi-organ BDS. Prevalence of FMS according to 2016 criteria was 3.4%. 82.3% of FMS cases met any BDS criteria.28.1% of FMS cases satisfied SSD criteria. 28.8% of any BDS cases met the criteria of SSD. 75.1% of SSD cases met the criteria of any BDS. FMS cases reported the highest amount of somatic and psychological symptom burden and health anxieties. There were no differences in age and gender between any BDS and SSD cases. SSD cases reported worse general health and more fibromyalgia-related variables than any BDS cases. Conclusions: In the general population, there is a substantial overlap between FMS and BDS, but not of FMS and SSD, and not of SSD and any BDS. Case definitions of the three disorders partially captured different groups in the general population.

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. 2020 Apr;47(4):624-631. doi: 10.3899/jrheum.190149.

Objective: To investigate the relation of physical (non-psychological) comorbidity and multimorbidity to quantitative measures of fibromyalgia (FM) and musculoskeletal pain. Methods: We studied 12,215 patients in a research databank with quantitative measures of FM-related variables (FMV) that included binary determinations of FM and widespread pain (WSP), and constituent variables of FM diagnosis that included the WSP index (WPI), the symptom severity score (SSS), and the polysymptomatic distress scale (PSD). We assessed 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 ≥ 1 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, respectively, 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 FM percent

increased stepwise. For patients with ≥ 4 conditions, the predicted prevalence of FM was 55.2%. Conclusion: FM and FMV are associated with an increase in the number of comorbidities, and the association can be measured quantitatively. However, the association of WSP and FM may be an effect of definitions of WSP and FM, because comorbidity increases are also present with subsyndromal levels of both conditions.

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, Eplov LF, Fink P.
Scand J Public Health. 2020 Jul;48(5):567-576. 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.

The unifying diagnostic construct of bodily distress syndrome (BDS) was confirmed in the general population.
Petersen MW, Schroder A, Jorgensen T, Ornbol E, Dantoft TM, Eliasen M, Thuesen BH, Fink P.
J Psychosom Res. 2020 Jan;128:109868. doi: 10.1016/j.jpsychores.2019.109868.

Objectives: Bodily distress syndrome (BDS) has been shown to encompass a range of functional somatic syndromes (FSS) such as irritable bowel syndrome (IBS), fibromyalgia (FM), and chronic fatigue syndrome (CFS) in clinical samples. This study aimed to explore symptom clusters and test classification of individuals with illness similar to the BDS criteria in a general population sample. Methods: A stratified subsample of 1590 individuals from the DanFunD part two cohort was included. Symptoms were assessed with the Research Interview for Functional somatic Disorders, performed by trained physicians. In 44 symptoms pooled from criteria of IBS, FM, CFS, and BDS, symptom clusters were explored with explorative factor analysis. Confirmation of symptom clusters of BDS in the previously described 25- and 30-item BDS checklists was performed with confirmatory factor analysis. Classification of individuals into illness groups was investigated with latent class analysis.
Results: Four symptom clusters (cardiopulmonary, gastrointestinal, musculoskeletal, general symptoms/fatigue) corresponding to the BDS subtypes and their corresponding FSS were identified and confirmed. A three-class model including 25 BDS items had the best fit for dividing participants into classes of illness: One class with low probability, one class with medium probability, and one class with high probability of having ≥4 symptoms in all symptom clusters. Conclusion: The BDS concept was confirmed in the general population and constitutes a promising approach

for improved FSS classification. It is highly clinical relevant being the only diagnostic construct defining the complex multi-organ type.

The impact of chronic widespread pain on health status and long-term health predictors: a general population cohort study.
Sylwander C, Larsson I, Andersson M, Bergman S.
BMC Musculoskelet Disord. 2020 Jan 16;21(1):36. doi: 10.1186/s12891-020-3039-5.

Background: Chronic widespread pain (CWP) has a negative impact on health status, but results have varied regarding gender-related differences and reported health status. The aim was to study the impact of CWP on health status in women and men aged 35-54 years in a sample of the general population. The aim was further to investigate lifestyle-related predictors of better health status in those with CWP in a 12- and 21-year perspective. Method: A general population cohort study including 975 participants aged 35-54 years, with a 12- and 21-year follow-up. CWP was measured with a pain mannequin, and the questionnaire included questions on lifestyles factors with SF-36 for measurement of health status. Differences in health status were analysed with independent samples t-test and health predictors with logistic regression analysis. Results: The prevalence of CWP was higher in women at all time points, but health status was reduced in both women and men with CWP ($p < 0.001$) with no gender differences of clinical relevance. At the 12-year follow-up, a higher proportion of women than men had developed CWP (OR 2.04; CI 1.27-3.26), and at the 21-year follow-up, a higher proportion of men had recovered from CWP (OR 3.79; CI 1.00-14.33). In those reporting CWP at baseline, a better SF-36 health status (Physical Functioning, Vitality or Mental Health) at the 12-year follow-up was predicted by male gender, having personal support, being a former smoker, and having no sleeping problems. In the 21-year follow-up, predictors of better health were male gender, a weekly intake of alcohol, and having no sleeping problems. Conclusion: Women and men with CWP have the same worsening of health status, but men recover from CWP to a greater extent in the long-term. Being male, having social support, being a former smoker, and having no sleeping problems were associated with better health status in those with CWP.

Functional somatic illnesses in patients with functional bowel disorders. A cross-sectional cohort study in western Saudi Arabia.
Khayyat YM.
Saudi Med J. 2020 Feb;41(2):203-206. doi: 10.15537/smj.2020.2.24901.

To study the prevalence of functional gastrointestinal disorders (FGID) in Saudi patients with irritable bowel syndrome (IBS). Methods: A cross-sectional study was conducted in patients with IBS treated at a private tertiary medical center in western Saudi Arabia between 2013 and 2017. We used ROME 3 criteria with data from the Generalized Anxiety Disorder 7-item (GAD-7) scale, the Patient Health Questionnaire-9 (PHQ-9) depression scale, and International Classification of Headache Disorders (ICHD) to assess the prevalence of psychosomatic illness. Statistical analysis of frequency and statistical correlation was performed using Chi-square. Results: The final analysis of 307 patients revealed a combined 425 diagnoses of psychosomatic illness, including diagnoses of headache in 104 patients (34%), migraine in 93 patients (30.5%), fibromyalgia in 169 patients (55%), and depression in 59 patients (19%). There was a statistically significant correlation between patients' ages and diagnoses of joint pain and migraines. Conclusion: Fibromyalgia and headache disorders were common in this cohort of Saudi patients with IBS. This coexistence of illness is partly explained by the functional nature of these illnesses. Collective efforts to provide multidisciplinary care is needed for these patients.

Presentation and characteristics of abdominal pain vary by irritable bowel syndrome subtype: Results of a nationwide population-based study.

Shah ED, Almario CV, Spiegel BM, Chey WD.
Am J Gastroenterol. 2020 Feb;115(2):294-301.

Introduction: Abdominal pain is a cardinal feature of irritable bowel syndrome (IBS); however, differences in abdominal pain among IBS subtypes remain unknown. We aimed to characterize abdominal pain symptoms among established IBS subtypes using data from the National Gastrointestinal (GI) Survey. Methods: Individuals participating in the National GI Survey completed National Institutes of Health GI Patient-Reported Outcomes Measurement Information System (GI-PROMIS) questionnaires. Adults meeting modified Rome III IBS criteria and reporting abdominal pain in the previous 7 days were eligible. Outcomes included abdominal pain severity, bothersomeness, interference with daily activities, frequency, and location. Results were stratified by subtype (diarrhea [IBS-D], constipation [IBS-C], and mixed [IBS-M]). Regression models adjusted for demographics and comorbidities. Results: One thousand one hundred fifty-eight individuals (245 IBS-D, 232 IBS-C, and 681 IBS-M) with active IBS symptoms (defined as abdominal pain in the past 7 days) were included. Demographics were similar among the subtypes except for age, race/ethnicity, education, and marital status. The GI-PROMIS score was lower for IBS-D (percentile score of 68.6, SD = 25.1; P = 0.001) and IBS-M (69.1, SD = 25.1; P < 0.001) compared with IBS-C (75.5, SD = 20.7). Abdominal pain was more bothersome (P = 0.001), caused more interference with daily activities (P = 0.03), and was more frequent (P = 0.047) for individuals with IBS-C compared with individuals with IBS-D. No differences in these domains were seen between individuals with IBS-D and IBS-M. Individuals with IBS-C and IBS-M had more widespread pain compared with those with IBS-D. Discussion: In this population-based study, we found that abdominal pain characteristics differ between the IBS subtypes. Namely, individuals with IBS-C experience more bothersome, frequent, and diffuse abdominal pain compared with those with IBS-D.

CLINICAL STUDIES

Tooth-related pain or not?
Renton T.
Headache. 2020 Jan;60(1):235-246. doi: 10.1111/head.13689

Dental pain is the most common acute pain presenting in the orofacial region; however, chronic pain conditions are also frequent and include; temporomandibular joint disorders (TMDs), primary headaches (neurovascular pain), painful post-traumatic trigeminal neuropathy (PPTTN) and less commonly referred pain and idiopathic or centralized pain conditions. All of these conditions can mimic toothache and vice versa. Many of these conditions are comorbid with high levels of tension headache and migraine reported in patients with TMD; however, dentists remain unfamiliar with headaches and medics unfamiliar with toothache's multiple presentations. The anatomical complexity of the region, the potential exhaustive differential diagnoses and the multiple siloed training of specialties, leads to incorrect and delayed diagnosis and often results in patients undergoing inappropriate surgical and medical treatments. The continued inappropriate interventions may also complicate the later presentation of the patient with pain, by changing its phenotype, preventing a timely and correct diagnosis. Due to the variable presentation of toothache, which can mimic many different chronic pains including; episodic throbbing pain of migraine, the dull continuous pain of myofascial and arthrogenous TMDs or centralized facial pain, diagnosis can be complex. Neuralgic pain occurs in the dentition in health and with disease, mimicking conditions like PPTTN, trigeminal neuralgia (TN), and trigeminal autonomic cephalalgias (TACs), many patients are inappropriately diagnosed and treated, either by general medical practitioners assuming that the neuralgia is due to TN rather than more commonly presenting toothache or by a dentists or other

surgeons continuing to treat TN or TACs with routine surgical care. Many patients are prescribed countless courses of antibiotics and undergo multiple surgical interventions simply as a result of poor education due to siloed specialty training. This must be addressed to improve patient safety.

A directional preference approach for chronic pelvic pain, bladder dysfunction and concurrent musculoskeletal symptoms: a case series.
Hughes C, May S.
J Man Manip Ther. 2020 Jul;28(3):170-180. doi: 10.1080/10669817.2019.1668994.

Background: Chronic pelvic pain (CPP) with concurrent musculoskeletal and bladder symptoms is a complex and challenging problem. However, clinically the co-existence of these symptoms is not routinely questioned, and their musculoskeletal source is not investigated thoroughly. The purpose of this case series is to present the use of Mechanical Diagnosis and Therapy (MDT) principles in seven patients with concurrent chronic pelvic pain, bladder dysfunction and musculoskeletal symptoms. Case descriptions: Seven patients with coexisting pelvic health and musculoskeletal signs and symptoms were retrospectively reviewed. Most common symptoms were urinary frequency, incontinence, pelvic pain, nocturia, dyspareunia, bladder dyssynergia, and lumbar, pelvic or hip pain. All patients failed to recognize the possible interconnectedness of the two sets of symptoms. Each exhibited a directional preference (DP) and subsequent MDT provisional classification of derangement was established; the use of DP forces abolished or dramatically improved both symptoms and mobility impairments. In all cases DP was for sustained sagittal forces initially, but ultimately lateral forces and mobilization were indicated. Outcomes: Changes in Pelvic Floor Impact Questionnaire, Care Connections Pelvic Floor and Lumbar spine were all clinically significant and exceeded minimally Clinical Important Differences several times. Average of 5.8 sessions per patient was noted. Follow-up at an average of 3.3 years revealed ongoing satisfaction and confidence in independent self-management. Discussion: These case studies highlight the importance of ensuring expansion of intake questions for possible co-existence of symptoms in both pelvic and musculoskeletal patients, possibly suggesting a mechanical intervention is indicated. Provisional subclassification into 'Mechanical Pelvic Syndrome' is proposed. Level of Evidence: 4.

Exercise and chronic pain.
Borisovskaya A, Chmelik E, Karnik A.
Adv Exp Med Bio. 2020;1228:233-253. doi: 10.1007/978-981-15-1792-1_16.

In this chapter, we describe the impact and etiology of chronic pain, the associated changes in the nervous system, and the mechanisms by which exercise may be able to affect and reverse these changes. Evidence for efficacy of exercise in different conditions associated with chronic pain is presented, with focus on chronic low back pain, fibromyalgia, osteoarthritis, rheumatoid arthritis, and migraines. While the efficacy of exercise and level of evidence supporting it vary in different diseases, exercise has direct and indirect benefits for most patients suffering from chronic pain. Effective exercise regimens include education and cognitive restructuring to promote behavioral activation and reconceptualization of what pain means, with the goal of gradually reversing the vicious cycle of pain, inertia, sedentary behavior, and worsening disability. Long-term, consistent, individualized exercise-based treatment approaches are most likely to result in improvements in pain and function.

Chronic orofacial pain.
Ananthan S, Benoliel R.
J Neural Transm (Vienna). 2020 Apr;127(4):575-588. doi: 10.1007/s00702-020-02157-3.
While pain chronicity in general has been defined as pain lasting for more than 3

months, this definition is not useful in orofacial pain (OFP) and headache (HA). Instead, chronicity in OFP and HA is defined as pain occurring on more than 15 days per month and lasting for more than 4 h daily for at least the last 3 months. This definition excludes the periodic shortlasting pains that often recur in the face and head, but are not essentially chronic. Although the headache field has adopted this definition, chronic orofacial pain is still poorly defined. In this article, we discuss current thinking of chronicity in pain and examine the term 'chronic orofacial pain' (COFP). We discuss the entities that make up COFP and analyze the term's usefulness in clinical practice and epidemiology.

Chronic pain and sleep disturbances: A pragmatic review of their relationships, comorbidities, and treatments.
Husak AJ, Bair MJ.
Pain Med. 2020 Jun 1;21(6):1142-1152. 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.

Sleep and pain in humans with fibromyalgia and comorbid insomnia: double-blind, crossover study of suvorexant 20 mg versus placebo.
Roehrs T, Withrow D, Koshorek G, Verkler J, Bazan L, Roth T.
J Clin Sleep Med. 2020 Mar 15;16(3):415-421. doi: 10.5664/jcsm.8220.

Study objectives: The chronic pain disorder, fibromyalgia, is associated with sleep disturbance, typically sleep maintenance. No studies have evaluated the effect of sleep medication on pain sensitivity in this population. Suvorexant, an orexin antagonist approved for treatment of insomnia, was evaluated for effects on both sleep and the pain of fibromyalgia. Methods: Women age 21 to 65 years with fibromyalgia and comorbid insomnia (n = 10) were treated, double-blind, for 9 nights each with suvorexant, 20 mg and placebo in counterbalanced order. All were in good psychiatric and stable physical health and met American College of Rheumatology 2010 criteria for fibromyalgia and Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition criteria for insomnia. Screening 8-hour polysomnography (PSG) was used to rule out other sleep disorders. On nights 8 and 9 of each treatment 8-hour PSG were collected and on days 1 and 8 pain sensitivity was assessed at 1100 and 1500 hours

by measuring finger withdrawal latency (FWL) to a radiant heat stimulus at 5 randomly presented intensity levels. Results: Suvorexant versus placebo increased total sleep time (7.2 versus 6.7 hours, P < .05) and reduced wake after sleep onset (37 versus 67 minutes, P < .04) with no night effects or interaction. Latency to persistent sleep and sleep stage measures were not altered. FWL on both am and pm tests varied as a function of intensity (P < .001). Average FWL (over 5 intensities and both days) was increased relative to placebo on both the am (13.9 versus 13.1 seconds) and pm tests (15.8 versus 14.1 seconds, P < .03) following suvorexant the previous night. Conclusions: Suvorexant 20 mg in patients with fibromyalgia, improved sleep time and reduced next-day pain sensitivity on assessments of FWL to a radiant heat stimulus.

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.