CUTTING EDGE

COPCs Research Advances

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This e-newsletter - published by 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 April and June 2023.

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Pathophysiology Studies

Stimulated Whole-Blood Cytokine/Chemokine Responses are Associated with Interstitial Cystitis/Bladder Pain Syndrome Phenotypes and Features of Nociplastic Pain: A Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research Network Study.
Schrepf A, Kaplan C, Harris RE, Williams DA, Clauw DJ, As-Sanie S, Till S, Clemens JQ, Rodriguez LV, Van Bokhoven A, Landis R, Gallop R, Bradley C, Naliboff B, Pontari M, O'Donnell M, Luo Y, Kreder K, Lutgendorf SK, Harte SE.
Pain. 2023 May 1;164(5):1148-1157. doi: 10.1097/j.pain.0000000000002813. PMID: 36279178; PMCID: PMC10106356.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a common and debilitating disease with poor treatment outcomes. Studies from the multidisciplinary approach to the study of chronic pelvic pain research network established that IC/BPS patients with chronic overlapping pain conditions (COPCs) experience poorer quality of life and more severe symptoms, yet the neurobiological correlates of this subtype are largely unknown. We previously showed that ex vivo toll-like receptor 4 (TLR4) cytokine/chemokine release is associated with the presence of COPCs, as well as widespread pain and experimental pain sensitivity women with IC/BPS. Here, we attempt to confirm these findings in the multisite multidisciplinary approach to the study of chronic pelvic pain Symptom Patterns Study using TLR4-stimulated whole blood (female IC/BPS patients with COPC n = 99; without n = 36). Samples were collected in tubes preloaded with TLR4 agonist, incubated for 24 hours, and resulting supernatant assayed for 7 cytokines/chemokines. These were subject to a principal components analysis and the resulting components used as dependent variables in general linear models. Controlling for patient age, body mass index, and site of collection, we found that greater ex vivo TLR4-stimulated cytokine/chemokine release was associated with the presence of COPCs ($P < 0.01$), extent of widespread pain ($P < 0.05$), but not experimental pain sensitivity ($P > 0.05$). However, a second component of anti-inflammatory, regulatory, and

chemotactic activity was associated with reduced pain sensitivity (P < 0.01). These results confirm that the IC/BPS + COPCs subtype show higher levels of ex vivo TLR4 cytokine/chemokine release and support a link between immune priming and nociplastic pain in IC/BPS.

Multiple Chemical Sensitivity: It's Time to Catch up to the Science.
Molot J, Sears M, Anisman H.
Neurosci Biobehav Rev. 2023 May 10:105227. doi: 10.1016/j.neubiorev.2023.105227. Epub ahead of print. PMID: 37172924.

Multiple chemical sensitivity (MCS) is a complex medical condition associated with low dose chemical exposures. MCS is characterized by diverse features and common comorbidities, including fibromyalgia, cough hypersensitivity, asthma, and migraine, and stress/anxiety, with which the syndrome shares numerous neurobiological processes and altered functioning within diverse brain regions. Predictive factors linked to MCS comprise genetic influences, gene-environment interactions, oxidative stress, systemic inflammation, cell dysfunction, and psychosocial influences. The development of MCS may be attributed to the sensitization of transient receptor potential (TRP) receptors, notably TRPV1 and TRPA1. Capsaicin inhalation challenge studies demonstrated that TRPV1 sensitization is manifested in MCS, and functional brain imaging studies revealed that TRPV1 and TRPA1 agonists promote brain-region specific neuronal variations. Unfortunately, MCS has often been inappropriately viewed as stemming exclusively from psychological disturbances, which has fostered patients being stigmatized and ostracized, and often being denied accommodation for their disability. Evidence-based education is essential to provide appropriate support and advocacy. Greater recognition of receptor-mediated biological mechanisms should be incorporated in laws, and regulation of environmental exposures.

Insights from Mendelian Randomization and Genetic Correlation Analyses into the Relationship between Endometriosis and its Comorbidities.
McGrath IM, Montgomery GW, Mortlock S.
Hum Reprod Update. 2023 May 9:dmad009. doi: 10.1093/humupd/dmad009. Epub ahead of print. PMID: 37159502.

Background: Endometriosis remains a poorly understood disease, despite its high prevalence and debilitating symptoms. The overlap in symptoms and the increased risk of multiple other traits in women with endometriosis is becoming increasingly apparent through epidemiological data. Genetic studies offer a method of investigating these comorbid relationships through the assessment of causal relationships with Mendelian randomization (MR), as well as identification of shared genetic variants and genes involved across traits. This has the capacity to identify risk factors for endometriosis as well as provide insight into the aetiology of disease. Objective and rationale: We aim to review the current literature assessing the relationship between endometriosis and other traits using genomic data, primarily through the methods of MR and genetic correlation. We critically examine the limitations of these studies in accordance with the assumptions of the utilized methods. Search methods: The PubMed database was used to search for peer-reviewed original research articles using the terms 'Mendelian randomization endometriosis' and '"genetic correlation" endometriosis'. Additionally, a Google Scholar search using the terms '"endometriosis" "mendelian randomization" "genetic correlation"' was performed. All relevant publications (n = 21) published up until 7 October 2022 were included in this review. Upon compilation of all traits with published MR and/or genetic correlation with endometriosis, additional epidemiological and genetic information on their comorbidity with endometriosis was sourced by searching for the trait in conjunction with 'endometriosis' on Google Scholar. Outcomes: The association between endometriosis and multiple pain, gynaecological, cancer, inflammatory, gastrointestinal, psychological, and anthropometric traits has been assessed using MR analysis and genetic correlation analysis. Genetic correlation analyses provide evidence that genetic factors contributing to endometriosis are shared with multiple traits: migraine, uterine fibroids, subtypes of ovarian cancer, melanoma, asthma, gastro-oesophageal reflux disease, gastritis/duodenitis, and depression, suggesting the involvement of multiple biological mechanisms in endometriosis. The assessment of causality with MR has revealed several potential causes (e.g. depression) and outcomes (e.g. ovarian cancer and uterine fibroids) of a genetic predisposition to endometriosis; however, interpretation of these results requires consideration of potential violations of the MR assumptions. Wider implications: Genomic studies have demonstrated that there is a molecular basis for the co-occurrence of endometriosis with other traits. Dissection of this overlap has identified shared genes and pathways, which provide insight into the biology of endometriosis. Thoughtful MR studies are necessary to ascertain causality of the comorbidities of endometriosis. Given the significant diagnostic delay of endometriosis of 7-11 years, determining risk factors is necessary to aid diagnosis and reduce the disease burden. Identification of traits for which endometriosis is a risk factor is important for holistic treatment and counselling of the patient. The use of genomic data to disentangle the overlap of endometriosis with other traits has provided insights into the aetiology of endometriosis.

The Immunomodulatory Effects of Ethosuximide and Sodium Butyrate on Experimentally Induced Fibromyalgia: The Interaction between IL-4, Synaptophysin, and TGF-β1/NF-κB Signaling.

Abd Elmaaboud MA, Awad MM, El-Shaer RAA, Kabel AM.
Int Immunopharmacol. 2023 May;118:110061. doi: 10.1016/j.intimp.2023.110061. Epub 2023 Mar 28. PMID: 36989891.

Background and aims: Fibromyalgia is a widespread chronic pain syndrome associated with several comorbid conditions that affect the quality of patients' life. Its pathogenesis is complex, and the treatment strategies are limited by partial efficacy and potential adverse effects. So, our aim was to investigate the possible ameliorative effects of ethosuximide and sodium butyrate on fibromyalgia and compare their effects to pregabalin. Materials and methods: In a mouse model of reserpine induced fibromyalgia, the effect of ethosuximide, sodium butyrate, and pregabalin was investigated. Evaluation of mechanical allodynia, cold hypersensitivity, anxiety, cognitive impairment, and depression was performed. Also, the brain and spinal cord tissue serotonin, dopamine and glutamate in addition to the serum levels of interleukin (IL)-4 and transforming growth factor beta 1 (TGF-β1) were assayed. Moreover, the expression of nuclear factor kappa B (NF-κB) synaptophysin was immunoassayed in the hippocampal tissues. Key findings: Ethosuximide and sodium butyrate restored the behavioral tests to the normal values except for the antidepressant effect which was evident only with ethosuximide. Both drugs elevated the levels of the anti-inflammatory cytokines IL-4 and TGF-β1, reduced the hippocampal NF-κB, and increased synaptophysin expression with superiority of sodium butyrate. Ethosuximide reduced only spinal cord and brain glutamate while improved brain dopamine while sodium butyrate elevated spinal cord dopamine and serotonin with no effect on glutamate. Also, sodium butyrate elevated brain serotonin and reduced glutamate with no effect on brain dopamine. Significance: Each of sodium butyrate and ethosuximide would serve as a promising therapeutic modality for management of fibromyalgia and its comorbid conditions.

Influence of Chronic Fatigue Syndrome Codiagnosis on the Relationship between Perceived and Objective Psychoneuro-Immunoendocrine Disorders in Women with Fibromyalgia.

Otero E, Gálvez I, Ortega E, Hinchado MD.
Biomedicines. 2023 May 20;11(5):1488. doi: 10.3390/biomedicines11051488. PMID: 37239159; PMCID: PMC10216026.

Although the predominant symptom in fibromyalgia (FM) is muscle pain, and fatigue in chronic fatigue syndrome (CFS), differential diagnosis is very difficult. This research investigates the psychoneuroimmunoendocrine disorders of FM patients and ascertains whether a previous CFS diagnosis affected them. Through accelerometry objective parameters, physical activity/sedentarism levels in relation to fatigue are studied, as well as whether perceived levels of stress, anxiety, and pain correspond to objective biomarkers, all of these with respect to a reference group (RG) of women without FM. FM patients have a worse psychological state and perceived quality of life than those with RG. These perceived outcomes are consistent with impaired objective levels of a sedentary lifestyle, higher systemic levels of cortisol and noradrenaline, and lower levels of serotonin. However, FM patients with a previous CFS diagnosis had lower systemic levels of IL-8, cortisol, oxytocin, and higher levels of adrenaline and serotonin than FM patients without diagnosed CFS. In conclusion, while perceived health parameters do not detect differences, when objective neuroimmunoendocrine parameters related to stress, inflammation, pain, and fatigue are used, people with CFS could be overdiagnosed with FM. This reinforces the need for objective biomarker assessment of these patients for better diagnostic discrimination between both syndromes.

Distinct Neural Signaling Characteristics between Fibromyalgia and Provoked Vestibulodynia Revealed by Means of Functional Magnetic Resonance Imaging in the Brainstem and Spinal Cord.

Ioachim G, Warren HJM, Powers JM, Staud R, Pukall CF, Stroman PW.
Front Pain Res (Lausanne). 2023 May 22;4:1171160. doi: 10.3389/fpain.2023.1171160. PMID: 37283704; PMCID: PMC10240076.

Introduction: Fibromyalgia and provoked vestibulodynia are two chronic pain conditions that disproportionately affect women. The mechanisms underlying the pain in these conditions are still poorly understood, but there is speculation that both may be linked to altered central sensitization and autonomic regulation. Neuroimaging studies of these conditions focusing on the brainstem and spinal cord to explore changes in pain regulation and autonomic regulation are emerging, but none to date have directly compared pain and autonomic regulation in these conditions. This study compares groups of women with fibromyalgia and provoked vestibulodynia to healthy controls using a threat/safety paradigm with a predictable noxious heat stimulus. Methods: Functional magnetic resonance imaging data were acquired at 3 tesla in the cervical spinal cord and brainstem with previously established methods. Imaging data were analyzed with structural equation modeling and ANCOVA methods during: a period of noxious stimulation, and a period

before the stimulation when participants were expecting the upcoming pain. Results: The results demonstrate several similarities and differences between brainstem/spinal cord connectivity related to autonomic and pain regulatory networks across the three groups in both time periods. Discussion: Based on the regions and connections involved in the differences, the altered pain processing in fibromyalgia appears to be related to changes in how autonomic and pain regulation networks are integrated, whereas altered pain processing in provoked vestibulodynia is linked in part to changes in arousal or salience networks as well as changes in affective components of pain regulation.

Ectopic Endometriosis in the Pelvic Cavity Evokes Bladder Hypersensitivity via Transient Receptor Potential Ankyrin 1 Hyperexpression in Rats.
Hayashi N, Kawamorita N, Ishizuka Y, Kimura S, Satake Y, Ito A.
Int Urogynecol J. 2023 Jun;34(6):1211-1218. doi: 10.1007/s00192-022-05335-x. Epub 2022 Aug 30. PMID: 36040506.

Introduction and hypothesis: In women with chronic pelvic pain (CPP), interstitial cystitis/bladder pain syndrome (IC/BPS) and endometriosis frequently coexist. The mechanism of these diseases coexisting is explained by cross-sensitization between endometriosis and IC/BPS. The overlapped symptoms may be related to cross-sensitization with transient receptor potential vanilloid 1 (TRPV1) and/or transient receptor potential ankyrin 1 (TRPA1) hyperexpression. This study was aimed at exploring whether bladder hypersensitivity is evoked in the surgically induced ectopic endometriosis rat and whether TRPV1 and/or TRPA1 play a vital role. Methods: A total of 63 Sprague-Dawley female rats were divided into two groups, 39 for physiological examination and 24 for molecular analysis. Surgical induction of ectopic endometriosis (ENDO, n=27), surgical sham treatment (n=18), and treatment for endometriosis by GnRH analog (ENDO-G) (n=18) were performed. Bladder function was investigated by cystometry (for TRPV1 in the sham [n=6] and ENDO [n=9] groups and for TRPA1 in the sham [n=6], ENDO [n=9], and ENDO+G [n=9] groups), and TRPV1 and TRPA1 mRNA expressions were measured using real-time qPCR in the bladder and dorsal root ganglia (DRGs). Results: On cystometry, the relative intercontraction interval (ICI) after/before resiniferatoxin (RTx; TRPV1 activator) infusion to the bladder showed no significant difference between the two groups, whereas relative ICI after/before allyl isothiocyanate (AITC; TRPA1 activator) infusion was significantly lower in the ENDO group than in the sham group. TRPA1 mRNA expression in the bladder and L5 DRG was considerably higher in the ENDO group than in the sham group on real-time qPCR. TRPA1 mRNA hyperexpression and bladder hypersensitivity after AITC infusion were reduced in the ENDO-G group. Conclusions: Bladder cross-sensitization in ENDO rats occurs in association with hyperexpression of TRPA1 at both the DRG and the bladder mucosa. This can be understood by the "cross-sensitization of endometriosis to bladder" theory explaining overlapping symptoms among BPS/IC and ectopic endometriosis.

Connecting Dots in Disorders of Gut-Brain Interaction: The Interplay of Stress and Sex Hormones in Shaping Visceral Pain.
Labrenz F, Merz CJ, Icenhour A.
Front Psychiatry. 2023 May 19;14:1204136. doi: 10.3389/fpsyt.2023.1204136. PMID: 37275987; PMCID: PMC10235543.

Visceral pain and stress are tightly intertwined bodily and emotional phenomena, which enable a flexible adaptation to environmental challenges by activating a response repertoire to restore homeostasis along the gut-brain axis. However, visceral pain and stress can persist widely independent of the initial cause, acquiring independent disease values and posing major health burdens as predominant features in disorders of gut-brain interaction (DGBI). Epidemiological data consistently documents an increased prevalence for women to suffer from chronic visceral pain, possibly shaped by sex hormones and modulated by stress and its biological and psychosocial correlates. Yet, mechanisms underlying the complex interactions between altered visceroception, stress and sex remain widely elusive, especially in clinical populations with DGBI. We herein selectively review mechanisms of interactions between stress and sex in the complex pathophysiology of DGBI. A particular emphasis is laid on visceral pain, in which stress constitutes a major risk factor as well as mediator, and sex-related differences are particularly pronounced. Building on the neurobiology of stress and mechanisms of gut-brain interactions, we highlight putative target mechanisms *via* which visceral pain and stress may converge with sex effects into a triad. Accommodating a global demographic shift, we propose a lifespan perspective in future research, which may enable a more fine-tuned evaluation of this complex interplay exerting distinct challenges during vulnerable developmental phases. This viewpoint may advance our understanding of pathophysiological processes and can ultimately inspire novel tailored prevention strategies and therapeutic approaches in the treatment of chronic visceral pain and DGBI across the lifespan.

Developing a 3-D Computational Model of Neurons in the Central Amygdala to Understand Pharmacological Targets for Pain.
Miller Neilan R, Reith C, Anandan I, Kraeuter K, Allen HN, Kolber BJ.

Front Pain Res (Lausanne). 2023 May 30;4:1183553. doi: 10.3389/fpain.2023.1183553. PMID: 37332477; PMCID: PMC10270735.

Neuropathic and nociplastic pain are major causes of pain and involve brain areas such as the central nucleus of the amygdala (CeA). Within the CeA, neurons expressing protein kinase c-delta (PKCδ) or somatostatin (SST) have opposing roles in pain-like modulation. In this manuscript, we describe our progress towards developing a 3-D computational model of PKCδ and SST neurons in the CeA and the use of this model to explore the pharmacological targeting of these two neural populations in modulating nociception. Our 3-D model expands upon our existing 2-D computational framework by including a realistic 3-D spatial representation of the CeA and its subnuclei and a network of directed links that preserves morphological properties of PKCδ and SST neurons. The model consists of 13,000 neurons with cell-type specific properties and behaviors estimated from laboratory data. During each model time step, neuron firing rates are updated based on an external stimulus, inhibitory signals are transmitted between neurons via the network, and a measure of nociceptive output from the CeA is calculated as the difference in firing rates of pro-nociceptive PKCδ neurons and anti-nociceptive SST neurons. Model simulations were conducted to explore differences in output for three different spatial distributions of PKCδ and SST neurons. Our results show that the localization of these neuron populations within CeA subnuclei is a key parameter in identifying spatial and cell-type pharmacological targets for pain.

Alterations of Pain Pathways by Experimental Sleep Disturbances in Humans: Central Pain-Inhibitory, Cyclooxygenase, and Endocannabinoid Pathways.
Haack M, Engert LC, Besedovsky L, Goldstein MR, Devine JK, Dang R, Olia K, Molina V, Bertisch SM, Sethna N, Simpson N.
Sleep. 2023 Jun 13;46(6):zsad061. doi: 10.1093/sleep/zsad061. PMID: 36881901; PMCID: PMC10262178.

Study objectives: There is strong evidence that sleep disturbances are an independent risk factor for the development of chronic pain conditions. The mechanisms underlying this association, however, are still not well understood. We examined the effect of experimental sleep disturbances (ESDs) on three pathways involved in pain initiation/resolution: (1) the central pain-inhibitory pathway, (2) the cyclooxygenase (COX) pathway, and (3) the endocannabinoid (eCB) pathway. Methods: Twenty-four healthy participants (50% females) underwent two 19-day long in-laboratory protocols in randomized order: (1) an ESD protocol consisting of repeated nights of short and disrupted sleep with intermittent recovery sleep; and (2) a sleep control protocol consisting of nights with an 8-hour sleep opportunity. Pain inhibition (conditioned pain modulation, habituation to repeated pain), COX-2 expression at monocyte level (lipopolysaccharide [LPS]-stimulated and spontaneous), and eCBs (arachidonoylethanolamine, 2-arachidonoylglycerol, docosahexaenoylethanolamide [DHEA], eicosapentaenoylethanolamide, docosatetraenoylethanolamide) were measured every other day throughout the protocol. Results: The central pain-inhibitory pathway was compromised by sleep disturbances in females, but not in males ($p < 0.05$ condition × sex effect). The COX-2 pathway (LPS-stimulated) was activated by sleep disturbances ($p < 0.05$ condition effect), and this effect was exclusively driven by males ($p < 0.05$ condition × sex effect). With respect to the eCB pathway, DHEA was higher ($p < 0.05$ condition effect) in the sleep disturbance compared to the control condition, without sex-differential effects on any eCBs. Conclusions: These findings suggest that central pain-inhibitory and COX mechanisms through which sleep disturbances may contribute to chronic pain risk are sex specific, implicating the need for sex-differential therapeutic targets to effectively reduce chronic pain associated with sleep disturbances in both sexes.

TRPA1 Rare Variants in Chronic Neuropathic and Nociplastic Pain Patients.
Marchi M, Salvi E, Andelic M, Mehmeti E, D'Amato I, Cazzato D, Chiappori F, Lombardi R, Cartelli D, Devigili G, Dalla Bella E, Gerrits M, Almomani R, Malik RA, Ślęczkowska M, Mazzeo A, Gentile L, Dib-Hajj S, Waxman SG, Faber CG, Vecchio E, de Tommaso M, Lauria G.
Pain. 2023 Apr 19. doi: 10.1097/j.pain.0000000000002905. Epub ahead of print. PMID: 37079850.

No abstract available.

Microbiological and Physiological Effects of Pain.
Jin MY, Everett ES, Abd-Elsayed A.
Curr Pain Headache Rep. 2023 Jun;27(6):165-173. doi: 10.1007/s11916-023-01114-5. Epub 2023 Apr 22. PMID: 37086365; PMCID: PMC10122082.

Pain is an important innate defense mechanism that can dramatically alter a person's quality of life. Understanding the microbiological and physiological effects of pain may be important in the pursuit of novel pain interventions. The three descriptors of pain recognized by the International Association for the Study of Pain are nociceptive, neuropathic, and nociplastic pain. Our review examined the current understanding of all three pain types, focusing on the key molecules involved in the manifestation of each type as well as physiological effects. Additionally, we compared the

differences in painful and painless neuropathies and discussed the neuroimmune interaction involved in the manifestation of pain.

Antinociceptive Effects of an Anti-CGRP Antibody in Rat Models of Colon-Bladder Cross Organ Sensitization.
Mohammadi EN, Ligon CO, Mackenzie KD, Stratton J, Shnider SJ, Greenwood-Van Meerveld B.
J Pharmacol Exp Ther. 2023 May 10:JPET-AR-2022-001480. doi: 10.1124/jpet.122.001480. Epub ahead of print. PMID: 37164371.

Irritable bowel syndrome (IBS) and bladder pain syndrome/interstitial cystitis (BPS/IC) are comorbid visceral pain disorders seen commonly in women with unknown etiology, limited treatment options and can involve visceral organ cross-sensitization. Calcitonin gene-related peptide (CGRP) is a mediator of nociceptive processing and may serve as a target for therapy. In three rodent models, we employed a monoclonal anti-CGRP $F(ab')_2$ to investigate the hypothesis that visceral organ cross-sensitization is mediated by abnormal CGRP signaling. Visceral organ cross-sensitization was induced in adult female rats via transurethral infusion of protamine sulfate (PS) into the urinary bladder or infusion into the colon of trinitrobenzene sulfonic acid (TNBS). Colonic sensitivity was assessed via the visceromotor response (VMR) to colorectal distension (CRD). Bladder sensitivity was assessed as the frequency of abdominal withdrawal responses (AWR) to von Frey filaments applied to the suprapubic region. PS- or TNBS-induced changes in colonic and bladder permeability were investigated *in vitro* via quantification of transepithelial electrical resistance (TEER). Peripheral administration of an anti-CGRP $F(ab')_2$ inhibited PS-induced visceral pain behaviors and colon hyperpermeability. Similarly, TNBS-induced pain behaviors and colon and bladder hyperpermeability were attenuated by anti-CGRP $F(ab')_2$ treatment. PS into the bladder or TNBS into the colon significantly increased the VMR to CRD and AWR to suprapubic stimulation and decreased bladder and colon TEER. These findings suggest an important role of peripheral CGRP in visceral nociception and organ cross-sensitization and support the evaluation of CGRP as a therapeutic target for visceral pain in patients with IBS and/or BPS/IC. Significance Statement A monoclonal antibody against calcitonin gene-related peptide (CGRP) was found to reduce concomitant colonic and bladder hypersensitivity and hyperpermeability. The results of this study suggest that CGRP-targeting antibodies, in addition to migraine prevention, may provide a novel treatment strategy for multi-organ abdominopelvic pain following injury or inflammation.

Size Reduction of the Right Amygdala in Chronic Pain Patients with Emotional Stress: A Systematic Review and Meta-Analysis.
Chen MH, Sun CK, Lin IM, Suen MW, Sue YR, Chen IL, Lin CL, Yeh PY.
Pain Med. 2023 May 2;24(5):556-565. doi: 10.1093/pm/pnac162. PMID: 36308460.

The structural impact of chronic pain on amygdala in chronic pain (CP) patients remains unclear, although major depression and anxiety are known to be associated with its increase and decrease in size, respectively. This study aimed at examining the relationship between emotional stress and amygdala size in CP patients. The effects of mediating and moderating variables were also examined. The PubMed, Embase, and Web of Science databases were searched for English clinical trials from inception to February 2022 using the appropriate keyword strings. We compared the differences in amygdala size assessed with magnetic resonance imaging between CP patients with emotional stress and healthy counterparts. Of the 49 full-text articles identified, 13 studies enrolling 1,551 participants including 738 CP patients with emotional stress and 813 controls were analyzed. Emotional stress evaluated with questionnaires based on Beck depression inventory, Hamilton depression/anxiety scale, state-trait anxiety inventory, and hospital anxiety and depression scale revealed significant differences between CP patients with emotional stress and controls, indicating a subclinical but significant level of emotional stress in CP patients. The results demonstrated an amygdala shrinkage among CP patients with emotional stress compared to the controls, especially the right side ($P = .02$). Besides, pain from a single body region was more likely to impact the amygdala size compared to diffuse pain ($P = .02$). Regression analysis revealed no significant association between continuous variables (age, gender, pain duration/intensity) and amygdala size. Our findings demonstrated that emotional stress was associated with a reduced right amygdala size in CP patients.

The Waiting Game: Investigating the Neurobiological Transition from Acute to Persistent Pain in Adolescent Rats.
Salberg S, Doshen A, Yamakawa GR, Miller JV, Noel M, Henderson L, Mychasiuk R.
Cereb Cortex. 2023 May 9;33(10):6382-6393. doi: 10.1093/cercor/bhac511. PMID: 36610738; PMCID: PMC10183733.

Persistent postsurgical pain affects 20% of youth undergoing a surgical procedure, with females exhibiting increased prevalence of chronic pain compared with males. This study sought to examine the sexually-dimorphic neurobiological changes underlying the transition from acute to

persistent pain following surgery in adolescence. Male and female Sprague Dawley rats were randomly allocated to a sham or injury (plantar-incision surgery) condition and assessed for pain sensitivity while also undergoing magnetic resonance imaging at both an acute and chronic timepoint within adolescence. We found that injury resulted in persistent pain in both sexes, with females displaying most significant sensitivity. Injury resulted in significant gray matter density increases in brain areas including the cerebellum, caudate putamen/insula, and amygdala and decreases in the hippocampus, hypothalamus, nucleus accumbens, and lateral septal nucleus. Gray matter density changes in the hippocampus and lateral septal nucleus were driven by male rats whereas changes in the amygdala and caudate putamen/insula were driven by female rats. Overall, our results indicate persistent behavioral and neurobiological changes following surgery in adolescence, with sexually-dimorphic and age-specific outcomes, highlighting the importance of studying both sexes and adolescents, rather than extrapolating from male adult literature.

Microglia Polarization in Nociplastic Pain: Mechanisms and Perspectives.
Atta AA, Ibrahim WW, Mohamed AF, Abdelkader NF
Inflammopharmacology. 2023 Jun;31(3):1053-1067. doi: 10.1007/s10787-023-01216-x. Epub 2023 Apr 17. PMID: 37069462; PMCID: PMC10229465.

Nociplastic pain is the third classification of pain as described by the International Association for the Study of Pain (IASP), in addition to the neuropathic and nociceptive pain classes. The main pathophysiological mechanism for developing nociplastic pain is central sensitization (CS) in which pain amplification and hypersensitivity occur. Fibromyalgia is the prototypical nociplastic pain disorder, characterized by allodynia and hyperalgesia. Much scientific data suggest that classical activation of microglia in the spinal cord mediates neuroinflammation which plays an essential role in developing CS. In this review article, we discuss the impact of microglia activation and M1/M2 polarization on developing neuroinflammation and nociplastic pain, besides the molecular mechanisms engaged in this process. In addition, we mention the impact of microglial modulators on M1/M2 microglial polarization that offers a novel therapeutic alternative for the management of nociplastic pain disorders. Illustrating the mechanisms underlying microglia activation in central sensitization and nociplastic pain. LPS lipopolysaccharide, TNF-α tumor necrosis factor-α, INF-γ Interferon gamma, ATP adenosine triphosphate, 49 P2Y12/13R purinergic P2Y 12/13 receptor, P2X4/7R purinergic P2X 4/7 receptor, SP Substance P, NK-1R Neurokinin 1 receptor, CCL2 CC motif ligand 2, CCR2 CC motif ligand 2 receptor, CSF-1 colony-stimulating factor 1, CSF-1R colony-stimulating factor 1 receptor, CX3CL1 CX3C motif ligand 1, CX3XR1 CX3C motif ligand 1 receptor, TLR toll-like receptor, MAPK mitogen-activated protein kinases, JNK jun N-terminal kinase, ERK extracellular signal-regulated kinase, iNOS Inducible nitric oxide synthase, IL-1β interleukin-1β, IL-6 interleukin-6, BDNF brain-derived neurotrophic factor, GABA γ-Aminobutyric acid, GABAR γ-Aminobutyric acid receptor, NMDAR N-methyl-D-aspartate receptor, AMPAR α-amino-3-hydroxy-5-methyl-4-isoxazolepropi-onic acid receptor, IL-4 interleukin-4, IL-13 interleukin-13, IL-10 interleukin-10, Arg-1 Arginase 1, FGF fibroblast growth factor, GDNF glial cell-derived neurotrophic factor, IGF-1 insulin-like growth factor-1, NGF nerve growth factor, CD Cluster of differentiation.

The Neurophysiological Lesion: A Scoping Review.
Taylor DN.
J Chiropr Med. 2023 Jun;22(2):123-130. doi: 10.1016/j.jcm.2022.09.002. Epub 2023 Apr 1. PMID: 37346242; PMCID: PMC10280090.

Objective: The purpose of this study was to examine the extent of the literature on the neurophysiological lesion as referenced in functional neurology. Methods: A literature search was performed within the period from 2010 to March 2021. Search terms included central sensitization, central sensitivity syndrome, nociplastic pain, cold hyperalgesia, heat hyperalgesia, mechanical hyperalgesia, dynamic mechanical allodynia, temporal summation, spatial summation, and descending inhibition. A qualitative synthesis summarized the research findings, including clinical conditions and effect of spinal manipulation. Results: There were 30 studies, which included 7 high-level studies (meta-analysis or systematic reviews), 22 randomized controlled studies, and 1 scoping review. The findings suggest the existence of the changes in the central integrated state of a population of neurons with various disorders, experimentally induced stimulation, and treatment. The current literature suggests plasticity of the central integrative state (CIS) with the onset of pathologies and the changes in the CIS with different conservative nonpharmacologic treatments. Conclusions: This review suggests changes in the resting state of the CIS of a population of neurons that exist in the physiologic lesion may change in response to various therapies, including manipulative therapy. The findings from this review provide support of the hypothesis that nonpharmacologic conservative care may affect the neurophysiological lesion. However, studies were heterogeneous and evidence was lacking in the translation of targeting the therapies to distinct neuronal areas for clinical outcomes to treat specific disease states.

Clinical Studies

Systemic Factors in Temporomandibular Disorder Pain.
Thomas DC, Eliav E, Garcia AR, Fatahzadeh M.
Dent Clin North Am. 2023 Apr;67(2):281-298. doi: 10.1016/j.cden.2022.10.002. Epub 2023 Feb 1. PMID: 36965931.

The science of temporomandibular disorder (TMD) pain and its management has gone through significant changes during the last several decades. The authors strongly feel that the effect of systemic factors influencing TMD pain has been largely overlooked and poorly accounted for, even in established pain-management programs and protocols. The hope is that this article will act as a wake-up call for the pain management community to consider the importance of adequate knowledge of the systemic factors that affect the experience of TMD pain by the patient.

Pathogenesis and Differential Diagnosis of Temporomandibular Joint Disorders.
Khan J, Singer SR, Young A, Tanaiutchawoot N, Kalladka M, Mupparapu M.
Dent Clin North Am. 2023 Apr;67(2):259-280. doi: 10.1016/j.cden.2022.10.001. Epub 2023 Feb 1. PMID: 36965930.

Temporomandibular disorders (TMDs) are an umbrella term including disorders of the temporomandibular joint and muscles of the masticatory system. They are the most common nonodontogenic cause of pain in the orofacial region. A clear understanding of various conditions, underlying mechanisms, clinical presentation, and examination skills is required to effectively diagnose and manage these patients.

Diagnosing Nociplastic Pain in Cancer Survivors: A Major Step Forward.
Verspyck E, Attal N.
Br J Anaesth. 2023 May;130(5):515-518. doi: 10.1016/j.bja.2023.02.006. Epub 2023 Mar 6. PMID: 36890060.

Nociplastic pain syndromes include particular fibromyalgia, irritable bowel syndrome, headache, complex regional pain syndrome, and idiopathic orofacial pain. Several mechanisms have been proposed to account for nociplastic pain including central sensitisation, alterations of pain modulatory controls, epigenetic changes, and peripheral mechanisms. Importantly, nociplastic pain might also be present in patients with cancer pain, particularly those with pain related to complications of cancer treatment. Increased awareness of nociplastic pain associated with cancer should have important implications for monitoring and managing such patients.

High Overlap in Patients Diagnosed with Hypermobile Ehlers-Danlos Syndrome or Hypermobile Spectrum Disorders with Fibromyalgia and 40 Self-Reported Symptoms and Comorbidities.
Fairweather D, Bruno KA, Darakjian AA, Bruce BK, Gehin JM, Kotha A, Jain A, Peng Z, Hodge DO, Rozen TD, Munipalli B, Rivera FA, Malavet PA, Knight DRT.
Front Med (Lausanne). 2023 Apr 25;10:1096180. doi: 10.3389/fmed.2023.1096180. PMID: 37181352; PMCID: PMC10166812.

Background: Joint pain is a common symptom in patients with hypermobile Ehlers-Danlos Syndrome (hEDS), hypermobility spectrum disorders (HSD) and fibromyalgia. The goal of this study was to determine whether symptoms and comorbidities overlap in patients diagnosed with hEDS/HSD and/or fibromyalgia. Methods**:** We retrospectively examined self-reported data from an EDS Clinic intake questionnaire in patients diagnosed with hEDS/HSD, fibromyalgia, or both vs. controls with an emphasis on joint issues. Results**:** From 733 patients seen at the EDS Clinic, 56.5% (n = 414) were diagnosed with hEDS/HSD and fibromyalgia (Fibro), 23.8% (n = 167) hEDS/HSD, 13.3% (n = 98) fibromyalgia, or 7.4% (n = 54) none of these diagnoses. More patients were diagnosed with HSD (76.6%) than hEDS (23.4%). Patients were primarily White (95%) and female (90%) with a median age in their 30s (controls 36.7 [18.0, 70.0], fibromyalgia 39.7 [18.0, 75.0], hEDS/HSD 35.0 [18.0, 71.0], hEDS/HSD&Fibro 31.0 [18.0, 63.0]). There was high overlap in all 40 symptoms/comorbidities that we examined in patients diagnosed with fibromyalgia only or hEDS/HSD&Fibro, regardless of whether they had hEDS or HSD. Patients that only had hEDS/HSD without fibromyalgia had far fewer symptoms/comorbidities than patients with hEDS/HSD&Fibro. The top self-reported issues in patients that only had fibromyalgia were joint pain, hand pain when writing or typing, brain fog, joint pain keeping from daily activities, allergy/atopy and headache. Five issues that significantly and uniquely characterized patients diagnosed with hEDS/HSD&Fibro were subluxations (dislocations in hEDS patients), joint issues like sprains, the need to stop sports due to injuries, poor wound healing, and migraine. Conclusion: The majority of patients seen at the EDS Clinic had a diagnosis of hEDS/HSD plus fibromyalgia that was associated with more severe disease. Our findings indicate that fibromyalgia should be routinely assessed in patients with hEDS/HSD and vis-a-versa to improve patient care.

Comorbid Extra-Intestinal Central Sensitization Conditions Worsen Irritable Bowel Syndrome in Primary Care Patients.

Wang XJ, Ebbert JO, Loftus CG, Rosedahl JK, Philpot LM.
Neurogastroenterol Motil. 2023 Apr;35(4):e14546. doi: 10.1111/nmo.14546. Epub 2023 Feb 19. PMID: 36807964.

Background: Irritable bowel syndrome (IBS) is characterized as a central sensitization syndrome (CSS), a group of conditions including fibromyalgia, chronic fatigue, and restless leg syndrome (RLS) among others with frequent comorbidities of anxiety, depression, and chemical sensitivity. The prevalence of comorbid conditions and their impact on IBS symptom severity and quality of life in rural community populations has not been described. Methods: We administered a cross-sectional survey to patients with a documented CSS diagnosis in rural primary care practices to evaluate the relationship between CSS diagnoses, quality of life, symptom severity, and interactions with healthcare providers utilizing validated questionnaires. Subgroup analysis was performed on the IBS cohort. Mayo Clinic IRB approved the study. Key results: Seven hundred seventy-five individuals out of 5000 completed the survey (15.5% response rate) with 264 (34%) reporting IBS. Only 3% (n = 8) of IBS patients reported IBS alone without comorbid CSS condition. Most respondents reported overlapping migraine (196, 74%), depression (183, 69%), anxiety (171, 64%), and fibromyalgia (139, 52%). IBS patients with more than two comorbid CS condition showed significantly higher symptom severity with linear increase. Quality of life was lower in IBS with comorbid conditions, particularly in patients with IBS and RLS (mean EQ5-D 0.36 vs. 0.8 in IBS only, $p < 0.01$). Quality of life declined as number of comorbid conditions increased. Conclusions & inferences: Patients with IBS often have multiple CS disorders which increases symptom severity and lowers quality of life. Understanding the impact of multiple CSS diagnoses and treating these as a global condition may improve patient experience.

A Call for Improving Research on Pain Neuroscience Education and Chronic Pain: An Overview of Systematic Reviews.

Martinez-Calderon J, Ho EK, Ferreira PH, Garcia-Muñoz C, Villar-Alises O, Matias-Soto J.
J Orthop Sports Phys Ther. 2023 May 10:1-44. doi: 10.2519/jospt.2023.11833. Epub ahead of print. PMID: 37161889.

OBJECTIVE: To summarize the evidence of the effects of pain neuroscience education delivered alone or combined with other interventions for chronic pain. DESIGN: An overview of systematic reviews with meta-analysis. LITERATURE SEARCH: CINAHL (via EBSCOhost), Embase, PsycINFO (via ProQuest), PubMed, and the Cochrane Library were searched from inception until November 14th, 2022. STUDY SELECTION CRITERIA: Systematic reviews (SRs) with meta-analyses including randomized clinical trials. The outcomes were pain and psychological symptoms. DATA SYNTHESIS: AMSTAR 2 assessed the methodological quality of SRs. The primary study overlap was evaluated by calculating the corrected covered area (CCA). RESULTS: We included eight SRs including 30 meta-analyses of interest that comprised 28 distinct clinical trials. In some meta-analyses, pain neuroscience education delivered alone or combined with other interventions was more effective than control interventions for reducing pain intensity, pain catastrophizing, kinesiophobia, anxiety symptoms, and depression symptoms at some time points. However, other meta-analyses found a lack of effects of pain neuroscience education, and there were inconsistencies between meta-analyses covering the same outcome. The methodological quality of all SRs was critically low. The overlap, including all SRs, was high (CCA= 13%), and very high for SRs covering trials on chronic low back pain (CCA= 40%), chronic spine pain (CCA= 27%), and fibromyalgia (CCA= 25%). CONCLUSION: It is impossible to make clear clinical recommendations for delivering pain neuroscience education based on current meta-analyses. Action is needed to increase and improve the quality of SRs in the field of pain neuroscience education.

Pelvic Pain Comorbidities Associated with Quality-of-life after Endometriosis Surgery.

Tucker MDR, Noga MHL, Lee DC, Chiu MDS, Bedaiwy DMA, Williams DC, Allaire DC, Talhouk DA, Yong DPJ.
Am J Obstet Gynecol. 2023 May 4:S0002-9378(23)00278-8. doi: 10.1016/j.ajog.2023.04.040. Epub ahead of print. PMID: 37148956.

Background: After endometriosis surgery, pain can persist or recur in a subset of patients. A possible reason for persistent pain post-surgery is central nervous system sensitization and associated pelvic pain comorbidities. Surgery addresses the peripheral component of endometriosis pain pathophysiology (by lesion removal) but may not treat this centralized pain. Therefore endometriosis patients with pelvic pain comorbidities related to central sensitization may experience worse pain-related outcomes after surgery, such as lower pain-related quality-of-life. Objective: To determine whether baseline (preoperative) pelvic pain comorbidities are associated with pain-related quality-of-life at follow-up after endometriosis surgery. Study design: This study utilized longitudinal prospective registry data from the Endometriosis and Pelvic Pain

Interdisciplinary Cohort at the BC Women's Center for Pelvic Pain and Endometriosis. Subjects were ≤ 50 years old with confirmed or clinically suspected endometriosis, who underwent surgery (fertility-sparing or hysterectomy) for endometriosis pain. Subjects completed the pain subscale of the Endometriosis Health Profile (EHP-30) quality-of-life questionnaire preoperatively and at follow-up (1-2 years). Linear regression was performed to measure the individual relationships between seven pelvic pain comorbidities at baseline and follow-up EHP-30 score, controlling for baseline EHP-30 and type of surgery received. These baseline (preoperative) pelvic pain comorbidities included abdominal wall pain, pelvic floor myalgia, painful bladder syndrome, irritable bowel syndrome, Patient Health Questionnaire (PHQ-9) depression score, General Anxiety Disorder (GAD-7) score, and Pain Catastrophizing Scale (PCS) score. LASSO regression was then performed to select the most important variables associated with follow-up EHP-30 from among seventeen covariates (including the seven pelvic pain comorbidities, baseline EHP-30 score, type of surgery, and other endometriosis-related factors such as stage and histologic confirmation of endometriosis). Using 1000 bootstrap samples, we estimated the coefficients and confidence intervals of the selected variables and generated a covariate importance rank. Results: The study included 444 subjects. The median follow-up time was 18 months. Pain-related quality-of-life (EHP-30) of the study population significantly improved at follow-up after surgery ($p<0.001$). The following pelvic pain comorbidities were associated with lower quality-of-life (higher EHP-30 score) after surgery controlling for baseline EHP-30 score and type of surgery (fertility-sparing vs. hysterectomy): abdominal wall pain ($p=0.013$), pelvic floor myalgia ($p=0.036$), painful bladder syndrome ($p=0.022$), PHQ-9 score ($p<0.001$), GAD-7 score ($p<0.001$), and PCS score ($p=0.007$). Irritable bowel syndrome was not significant ($p=0.70$). Of the seventeen covariates included for LASSO regression, six remained in the final model (lambda = 3.136). These included three pelvic pain comorbidities that were associated with higher follow-up EHP-30 scores or worse quality-of-life: abdominal wall pain ($\beta = 3.19$), pelvic floor myalgia ($\beta = 2.44$), and PHQ-9 depression score ($\beta = 0.49$). The other three variables in the final model were baseline EHP-30 score, type of surgery, and histologic confirmation of endometriosis. Conclusion: Pelvic pain comorbidities present at baseline before surgery, which may reflect underlying central nervous system sensitization, are associated with lower pain-related quality-of-life after endometriosis surgery. Particularly important were depression and musculoskeletal/myofascial pain (abdominal wall pain and pelvic floor myalgia). Therefore, these pelvic pain comorbidities should be candidates for a formal prediction model of pain outcomes after endometriosis surgery.

Fibromyalgia Increases Post-Operative Healthcare Utilization Following Total Hip Arthroplasty.

Morrell AT, Mildren ME, Smith S, Yoo J, Kagan R.
J Arthroplasty. 2023 Apr 20:S0883-5403(23)00365-0. doi: 10.1016/j.arth.2023.04.019. Epub ahead of print. PMID: 37084922.

Background: Preoperative factors can complicate the postoperative course and increase health care utilization following total hip arthroplasty (THA). Fibromyalgia is not generally recognized as a modifiable risk factor prior to THA. The aim of this investigation was to assess the effect of fibromyalgia on postoperative health care utilization following THA. Methods: Patients who underwent primary THA from 2018 to 2019 were identified from a large national database using Current Procedural Terminology and International Classification of Diseases, tenth revision (International Classification of Diseases-10) codes. Patient demographics, age, sex, and preoperative opioid use were collected. Analysis compared patients who did and did not have fibromyalgia for postoperative health care utilization metrics; lengths of stay (LOS), 90-day postoperative opioid usages, dislocations, and emergency room visits. Independent t-tests were used to compare LOS and rates of ongoing opioid use. Logistic regression analyses with adjusted odds ratios evaluated the risk of dislocation and emergency room visit after adjusting for demographic characteristics and comorbidities. Results: Compared to those who did not have fibromyalgia, patients who had fibromyalgia experienced longer LOS ($P < .0001$), increased odds of opioid use 90 days postoperatively ($P < .0001$) as well as increased odds of hip dislocation ($P < .0001$) and presentation to the emergency room ($P < .0001$). Patients who had fibromyalgia were also more likely to be "frequent flyers" with ≥5 emergency room visits after THA ($P < .0001$). Conclusions: Fibromyalgia can complicate postoperative care following THA with increased LOS, higher rates of opioid use, and increased odds of dislocation and emergency room visits. As focus shifts to preoperative optimization and risk stratification, more attention should be placed on fibromyalgia prior to THA.

Comorbidities, Biomarkers and Cause Specific Mortality in Patients with Irritable Bowel Syndrome: A Phenome-Wide Association Study.

Seeling KS, Hehl L, Vell MS, Rendel MD, Creasy KT, Trautwein C, Mehler DMA, Keszthelyi D, Schneider KM, Schneider CV. United European Gastroenterol J. 2023 Jun;11(5):458-470. doi: 10.1002/ueg2.12397. Epub 2023 May 7. PMID: 37151116; PMCID: PMC10256994.

Background: Irritable bowel syndrome (IBS) is one of the most common functional digestive disorders. Our understanding about its comorbidities, biomarkers, or long-term risks is still

incomplete. Objective: To characterize comorbidities and biomarkers for IBS and establish the effect of IBS on overall- and cause specific mortality. Methods: We analyzed data from the population-based cohort of the UK Biobank (UKB) with 493,974 participants, including self-reported physician-diagnosed (n = 20,603) and ICD-10 diagnosed (n = 7656) IBS patients, with a mean follow-up of 11 years. We performed a phenome-wide association study (PheWAS) and competing risk analysis to characterize common clinical features in IBS patients. Results: In PheWAS analyses, 260 PheCodes were significantly overrepresented in self-reported physician-diagnosed IBS patients, 633 in patients with ICD-10 diagnosed IBS (ICD-10-IBS), with 221 (40%) overlapping. In addition to gastrointestinal diseases, psychiatric, musculoskeletal, and endocrine/metabolic disorders represented the most strongly associated PheCodes in IBS patients. Self-reported physician-diagnosed IBS was not associated with increased overall mortality and the risk of death from cancer was decreased (hazard ratio [HR] = 0.78 [95% CI = 0.7-0.9]). Lastly, we evaluated changes in serum metabolites in IBS patients and identified glycoprotein acetyls (GlycA) as a potential biomarker in IBS. One standard deviation increase in GlycA raised the risk of self-reported IBS/ICD-10 coded by 9%-20% (odds ratio [OR] = 1.09 [95% CI = 1.1-1.1]/OR = 1.20 [95% CI = 1.1-1.3]) and the risk of overall mortality in ICD-10-IBS patients by 28% (HR = 1.28 [95% CI = 1.1-1.5]). Conclusion: Our large-scale association study determined IBS patients having an increased risk of several different comorbidities and that GlycA was increased in IBS patients.

Impact of Chronic Pelvic Pain and Painful Bladder Syndrome on the Pittsburgh Sleep Quality Index on Women with Deep Endometriosis: A Cross-Sectional Study.
de Souza RJ, Villela NR, Brollo LCS, Oliveira MAP.
Int Urogynecol J. 2023 May 20. doi: 10.1007/s00192-023-05560-y. Epub ahead of print. PMID: 37209169.

Introduction and hypothesis: Painful bladder syndrome (PBS) is frequently associated with deep endometriosis (DE), and both conditions cause chronic pelvic pain (CPP), which often impairs sleep quality. This study was aimed at analyzing the impact of CPP plus PBS in women with DE on the global sleep quality index using the Pittsburgh Sleep Quality Index (PSQI) and subsequently examine each sleep dimension. Methods: One hundred and forty women with DE were included and answered the PSQI and the O'Leary-Sant Interstitial Cystitis Symptoms and Problem Index questionnaires with or without CPP. Women were categorized into good or poor sleepers using the PSQI cutoff; subsequently, a linear regression model was used to analyze the PSQI score and a logistic regression model for each questionnaire's sleep component. Results: Only 13% of women with DE had a good sleep. Approximately 20% of those with DE but no/mild pain were good sleepers; 138 women with DE (88.5%), 94% with PBS, and 90.5% with moderate/severe pain were poor sleepers. For PSQI components, CPP worsened the subjective sleep quality by more than threefold ($p = 0.019$), increased sleep disturbances by nearly sixfold ($p = 0.03$), and decreased the sleep duration by practically sevenfold ($p = 0.019$). Furthermore, PBS increased sleep disturbances by nearly fivefold ($p < 0.01$). Conclusions: The addition of PBS to CPP in women with DE is devastating for overall sleep quality, probably because it impacts some sleep dimensions unaffected by CPP and amplifies the problem in those already affected by pain.

The Biology of Pain: Through the Rheumatology Lens.
Sunzini F, Schrepf A, Clauw DJ, Basu N.
Arthritis Rheumatol. 2023 May;75(5):650-660. doi: 10.1002/art.42429. Epub 2023 Mar 20. PMID: 36599071.

Chronic pain is a major socioeconomic burden globally. The most frequent origin of chronic pain is musculoskeletal. In inflammatory musculoskeletal diseases such as rheumatoid arthritis (RA), chronic pain is a primary determinant of deleterious quality of life. The pivotal role of peripheral inflammation in the initiation and perpetuation of nociceptive pain is well-established among patients with musculoskeletal diseases. However, the persistence of pain, even after the apparent resolution of peripheral inflammation, alludes to the coexistence of different pain states. Recent advances in neurobiology have highlighted the importance of nociplastic pain mechanisms. In this review we aimed to explore the biology of pain with a particular focus on nociplastic pain in RA.

Fibromyalgia and Centralized Pain in the Rheumatoid Arthritis Patient.
Minhas D, Murphy A, Clauw DJ.
Curr Opin Rheumatol. 2023 May 1;35(3):170-174. doi: 10.1097/BOR.0000000000000929. Epub 2023 Feb 10. PMID: 36795021; PMCID: PMC10065919.

Purpose of review: Individuals with rheumatoid arthritis (RA) have traditionally been characterized as having nociceptive pain, leading to the assumption that effective immunosuppression should be enough to provide effective pain management. However, despite therapeutic advancements providing excellent control of inflammation, patients continue to have significant pain and fatigue. The presence of concurrent fibromyalgia, driven by augmented central nervous system processing and largely unresponsive to peripheral therapies, may contribute to this pain persistence. This review provides updates on fibromyalgia and RA as relevant for the clinician. Recent

findings: Patients with RA have high levels of concomitant fibromyalgia and nociplastic pain. The presence of fibromyalgia can lead to higher scores on disease measures, erroneously indicating that worse disease is presently leading to the increased use of immunosuppressives and opioids. Disease scores that provide a comparison between patient-reported and provider-reported and clinical factors may be helpful to indicate centralized pain. IL-6 and Janus kinase inhibitors, in addition to targeting peripheral inflammation, may provide pain relief by acting on peripheral and central pain pathways. Summary: Central pain mechanisms that may be contributing to pain in RA are common and should be distinguished from pain directly arising from peripheral inflammation.

Clinical Profiling of Specific Diagnostic Subgroups of Women with Chronic Pelvic Pain.
Demetriou L, Krassowski M, Abreu Mendes P, Garbutt K, Vitonis AF, Wilkins E, Coxon L, Arendt-Nielsen L, Aziz Q, Birch J, Horne AW, Hoffman A, Hummelshoj L, Lunde CE, Meijlink J, Perro D, Rahmioglu N, Terry KL, Pogatzki-Zahn E, Sieberg CB, Treede RD, Becker CM, Cruz F, Missmer SA, Zondervan KT, Nagel J, Vincent K.
Front Reprod Health. 2023 May 30;5:1140857. doi: 10.3389/frph.2023.1140857. PMID: 37325239; PMCID: PMC10266100.

Introduction: Chronic pelvic pain (CPP) is a common condition affecting up to 26.6% of women, with many suffering for several years before diagnosis and/or treatment. Its clinical presentation is varied and there are frequently comorbid conditions both within and outside the pelvis. We aim to explore whether specific subgroups of women with CPP report different clinical symptoms and differing impact of pain on their quality of life (QoL). Methods: The study is part of the Translational Research in Pelvic Pain (TRiPP) project which is a cross-sectional observational cohort study. The study includes 769 female participants of reproductive age who completed an extensive set of questions derived from standardised WERF EPHect questionnaires. Within this population we defined a control group (reporting no pelvic pain, no bladder pain syndrome, and no endometriosis diagnosis, $N = 230$) and four pain groups: endometriosis-associated pain (EAP, $N = 237$), interstitial cystitis/bladder pain syndrome (BPS, $N = 72$), comorbid endometriosis-associated pain and BPS (EABP, $N = 120$), and pelvic pain only (PP, $N = 127$). Results: Clinical profiles of women with CPP (13-50 years old) show variability of clinical symptoms. The EAP and EABP groups scored higher than the PP group ($p < 0.001$) on the pain intensity scales for non-cyclical pelvic pain and higher than both the BPS and PP groups ($p < 0.001$) on the dysmenorrhoea scale. The EABP group also had significantly higher scores for dyspareunia ($p < 0.001$), even though more than 50% of sexually active participants in each pain group reported interrupting and/or avoiding sexual intercourse due to pain in the last 12 months. Scores for the QoL questionnaire (SF-36) reveal that CPP patients had significantly lower QoL across all SF-36 subscales ($p < 0.001$). Significant effects were also observed between the pain groups for pain interference with their work ($p < 0.001$) and daily lives ($p < 0.001$), with the EABP suffering more compared to the EAP and PP groups ($p < 0.001$). Discussion: Our results demonstrate the negative impact that chronic pain has on CPP patients' QoL and reveal an increased negative impact of pain on the comorbid EABP group. Furthermore, it demonstrates the importance of dyspareunia in women with CPP. Overall, our results demonstrate the need for further exploration of interventions targeting QoL more broadly and suggest that novel approaches to classifying women with CPP are needed.

Low Dose Naltrexone's Utility for Non-Cancer Centralized Pain Conditions - A Scoping Review.
Rupp A, Young E, Chadwick AL.
Pain Med. 2023 Jun 11:pnad074. doi: 10.1093/pm/pnad074. Epub ahead of print. PMID: 37302106.

Background: At low doses, naltrexone (LDN) has been shown to modulate inflammation through the interruption of microglial cell activation within the central nervous system. One of the most likely contributors to centralized pain is changes in microglial cell processing, therefore, it has been postulated that LDN can be used to manage patients with pain resulting from central sensitization due to this relationship. This scoping review aims to synthesize the relevant study data for LDN as a novel treatment strategy for various centralized pain conditions. Methods: A comprehensive literature search was conducted using PubMed, Embase, and Google Scholar guided by the Scale for Assessment of Narrative Review Articles (SANRA) criteria. Results: 47 studies related to centralized pain conditions were identified. Many of the studies were case reports/series and narrative reviews, however a few RCTs have been conducted. Overall, the body of evidence revealed improvement in patient-reported pain severity as well outcomes related to hyperalgesia, physical function, quality of life, and sleep. Variability in dosing paradigms and the time to patient response was present in the reviewed studies. Conclusions: Evidence synthesized for this scoping review supports the ongoing use of LDN for the treatment of refractory pain in various centralized chronic pain conditions. Upon review of the current available published studies, it is apparent that further high-quality, well-powered RCTs need to be conducted in order to establish efficacy, standardization for dosing, and determine response times. In summary, LDN continues to offer promising results in the management of pain and other distressing symptoms in patients with chronic centralized pain conditions.

Temporomandibular Joint Disorder Comorbidities.
Thomas DC, Khan J, Manfredini D, Ailani J.
Dent Clin North Am. 2023 Apr;67(2): 379-392. doi: 10.1016/j.cden.2022.10.005.

Comorbidity is a distinct additional condition that either existed or exists during the clinical course of a patient afflicted by the condition/entity in question. The clinician attempting to manage temporomandibular joint disorder (TMD) and TMD pain must realize that recognition and management of the comorbidities are essential to the successful management of the same with optimal pain control. When TMD presents with multiple comorbidities, the task for the clinician becomes more complex. It is the hope of the authors that this condensed version of TMD-associated comorbidities acts as a primer for understanding the significance of the same in pain management.

Prevalence of Clinical Signs and Symptoms of Temporomandibular Joint Disorders Registered in the EUROTMJ Database: A Prospective Study in a Portuguese Center.
Ângelo DF, Mota B, João RS, Sanz D, Cardoso HJ.
J Clin Med. 2023 May 18;12(10):3553. doi: 10.3390/jcm12103553. PMID: 37240658; PMCID: PMC10219561.

Temporomandibular joint disorders (TMDs) are characterized by their multifactorial etiology and pathogenesis. A 3-year prospective study was conducted in a Portuguese TMDs department to study the prevalence of different TMDs signs and symptoms and their association with risk factors and comorbidities. Five hundred ninety-five patients were included using an online database: EUROTMJ. Most patients were female (80.50%), with a mean age of 38.20 ± 15.73 years. The main complaints were: (1) temporomandibular joint (TMJ) clicking (13.26%); (2) TMJ pain (12.49%); (3) masticatory muscle tension (12.15%). The main clinical findings were myalgia (74%), TMJ clicking (60-62%), and TMJ arthralgia (31-36%). Risk factors such as clenching (60%) and bruxism (30%) were positively associated with TMJ pain and myalgia. Orthodontic treatment (20%) and wisdom tooth removal (19%) were positively associated with TMJ clicking, while jaw trauma (6%), tracheal intubation (4%) and orthognathic surgery (1%) were positively associated with TMJ crepitus, limited mandibular range of motion, and TMJ pain, respectively. In total, 42.88% of TMDs patients had other associated chronic diseases, most of them were mental behavioral or neurodevelopmental disorders (33.76%), namely, anxiety (20%) and depression (13%). The authors also observed a positive association of mental disorders with the degree of TMJ pain and myalgia. The online database seems to be a relevant scientific instrument for healthcare providers who treat TMDs. The authors expect that the EUROTMJ database can serve as a milestone for other TMDs departments.

Prevalence of Painful Temporomandibular Disorders in Endodontic Patients with Tooth Pain.
Daline IH, Slade GD, Fouad AF, Nixdorf DR, Tchivileva IE.
J Oral Rehabil. 2023 Jul;50(7):537-547. doi: 10.1111/joor.13457. Epub 2023 Apr 14. PMID: 37021602.

Background: Pain from temporomandibular disorders (TMDs) may mimic endodontic pain, but its prevalence in endodontic patients is unknown. Objectives: This cross-sectional study investigated the prevalence of painful TMDs in patients presenting for endodontic treatment of a painful tooth. Contribution of TMD pain to the chief complaint and characteristics associated with TMD prevalence were also assessed. Methods: Patients reporting tooth pain in the 30 days before attending university clinics for nonsurgical root canal treatment or retreatment were enrolled. Before endodontic treatment, they completed questionnaires and a board-certified orofacial pain specialist/endodontic resident diagnosed TMD using published Diagnostic Criteria for TMD. Log-binomial regression models estimated prevalence ratios to quantify associations with patient characteristics. Results: Among 100 patients enrolled, prevalence of painful TMDs was 54%. In 26% of patients, TMD pain was unrelated to endodontic pain; in 20%, TMD contributed to their chief pain complaint; and in 8%, TMD was a sole aetiology for pain. TMD prevalence was associated with greater intensity, frequency and duration of the chief pain complaint; pain in more than one tooth; tenderness to tooth percussion and palpation; a diagnosis of symptomatic apical periodontitis; pain medication use; and psychological distress. Conclusion: A majority of patients with tooth pain seeking endodontic treatment had painful TMDs; one quarter had TMD as a component or sole cause of their pain. TMD prevalence was associated with more severe symptoms and signs of tooth pain and with psychological factors. The high frequency of TMD comorbidity warrants consideration in management of endodontic patients with history of toothache.

Pelvic Mapping to Explore Patterns of Chronic Pelvic Pain.
Aibel K, Choi S, Moldwin R.
Neurourol Urodyn. 2023 Apr;42(4):837-844. doi: 10.1002/nau.25145. Epub 2023 Feb 25. PMID: 36840909.

Purpose: Chronic pelvic pain syndromes (CPPS) are commonly encountered by urologists and urogynecologists and pose diagnostic and therapeutic challenges. Body maps have been helpful adjuncts to verbal descriptions of pain and may serve a role in phenotyping what is known to be a heterogeneous patient population. The aim of this study was to assess whether patterns of pain as marked on a body map of the pelvis exist among common CPPS diagnoses. The secondary aim was to investigate the association between the total number of pain locations marked on the map and clinical indices in patients with 1 to 3 CPPS diagnoses. Materials and methods: Data was collected on patients who visited the Northwell Health Pelvic Pain Treatment Center (PPTC) from January to May 2022 and were diagnosed with at least one of four major CPPS diagnoses: interstitial cystitis/bladder pain syndrome (IC/BPS), pelvic floor myalgia (PFM), chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), and vulvodynia. Demographic data as well as survey data from pelvic pain maps, Genitourinary Pain Index (GUPI) forms, and the short form-6 of the Pain Catastrophizing Scale (PCS-6) were recorded. Descriptive statistics among CPPS groups and Pearson correlations among the number of CPPS diagnoses were computed. Results: One hundred seventy females and 125 males with CPPS were included in the study. Significant cross-over in mapping patterns was notable between IC/BPS and PFM groups, both most commonly marking "abdomen" and "genital" regions. The most distinct pattern of pain was seen in patients with CP/CPPS and in patients with vulvodynia. Among the total sample, as the mean number of pain locations marked within the pelvis increased, GUPI and PCS scores increased ($p < 0.05$). As the number of CPPS diagnoses increased, the strength of the relationship independently increased. Conclusions: Pelvic body mapping demonstrated that different forms of CPPS displayed different distributions of pain, but mapping was not predictive of any diagnostic group. Nevertheless, the pelvic body map proved useful in identifying precise locations of pain and may help uncover regions of pain that cannot be easily communicated. The total number of pain sites marked appeared to correlate with worse clinical features.

Psychosocial Factors Associated with Pain Outcomes in Patients with Painful Temporomandibular Disorders and Headaches.

van der Meer HA, Tol CHM, Speksnijder CM, van Selms MKA, Lobbezoo F, Visscher CM.
Eur J Oral Sci. 2023 Apr;131(2):e12919. doi: 10.1111/eos.12919. Epub 2023 Feb 19. PMID: 36802069.

The objective of this study was to assess the association between psychosocial factors (in terms of anxiety, somatization, depression, and optimism) and pain (in terms of headache pain intensity and pain-related disability), in patients with a painful temporomandibular disorder (TMD) and one of the following headache types: migraine, tension-type headache (TTH), or headache attributed to TMD, corrected for the influence of bruxism. A retrospective study was conducted at an orofacial pain and dysfunction (OPD) clinic. Inclusion criteria were painful TMD, with migraine, TTH, and/or headache attributed to TMD. Linear regressions were performed to assess the influence of psychosocial variables on pain intensity and on pain-related disability, stratified per headache type. The regression models were corrected for bruxism and the presence of multiple headache types. A total of 323 patients (61% female; mean age 42.9, SD 14.4 years) were included. Headache pain intensity only had significant associations in TMD-pain patients with headache attributed to TMD, and anxiety showed the strongest relation ($\beta = 0.353$) with pain intensity. Pain-related disability was most strongly associated with depression in TMD-pain patients with TTH ($\beta = 0.444$), and with somatization in patients with headache attributed to TMD ($\beta = 0.399$). In conclusion, the influence of psychosocial factors on headache pain intensity and pain-related disability depends on the headache type presenting.

Temporomandibular Disorders in Immune-Mediated Rheumatic Diseases of the Adult: A Systematic Review.

Hysa E, Lercara A, Cere A, Gotelli E, Gerli V, Paolino S, Pizzorni C, Sulli A, Smith V, Cutolo M.
Semin Arthritis Rheum. 2023 May 5;61:152215. doi: 10.1016/j.semarthrit.2023.152215. Epub ahead of print. PMID: 37167773.

Objective: To systematically review the literature concerning temporomandibular disorders (TMDs) in immune-mediated rheumatic diseases (IMRDs) of the adult. The temporomandibular joint (TMJ) outcomes used in clinical studies, the prevalence of TMDs in IMRDs and the risk factors for their development were qualitatively synthetized. Methods: A literature search on PubMed Central, Embase and Cochrane Library databases was performed for studies including TMJ outcomes in IMRDs patients compared with healthy controls, other rheumatic diseases or in the assessed IMRDs patients after follow-up and treatment. Among the IMRDs of the adult, original articles investigating TMJ involvement in inflammatory polyarthritides and/or autoimmune connective tissue diseases were considered. The quality of the studies was scored using the Newcastle-Ottawa scale (NOS). Results: Of the 3259 screened abstracts, 56 papers were included in the systematic review. Most of the papers (77%) investigated TMDs in rheumatoid arthritis (RA) with a prevalence of signs and symptoms varying from 8% to 70%. The risk factors for TMDs development in RA

were female sex, younger age, anti-citrulline peptide autoantibodies (ACPA) positivity, higher disease activity, cervical spine involvement, cardiovascular and neuropsychiatric comorbidities. Ten papers (18%) evaluated TMDs in spondylarthritides (SpA) reporting a prevalence of symptoms and signs in 12%-80% of patients with higher TMDs prevalence in patients with radiographic spine involvement, skin psoriasis and HLADRB1×01 positivity. Among autoimmune connective tissue diseases (CTDs), systemic sclerosis (SSc) displayed the highest evidence of TMDs patient-reported outcomes (PROs) and clinical findings (20-93%), followed by systemic lupus erythematosus (SLE) in 18-85%, primary Sjogren's syndrome (24-54%) and idiopathic inflammatory myopathies (4-26%). In SSc and SLE, TMDs were more frequent in patients with higher disease activity and duration, correlating with the extent of skin fibrosis in SSc and with renal involvement in SLE. Conclusion: TMDs in IMRDs display a significant relevance in the rheumatological clinical practice even if often misdiagnosed. This burden is epidemiologically important in terms of PROs and clinical findings which correlate with disease activity in RA, SpA, SSc and SLE. The early recognition and multidisciplinary management of TMDs is warranted and should be aimed at hindering the TMJ structural damage maximizing the quality of life of patients.

The Pharmacological Treatment of Chronic Pain: From Guidelines to Daily Clinical Practice.
Marcianò G, Vocca C, Evangelista M, Palleria C, Muraca L, Galati C, Monea F, Sportiello L, De Sarro G, Capuano A, Gallelli L.
Pharmaceutics. 2023 Apr 6;15(4):1165. doi: 10.3390/pharmaceutics15041165. PMID: 37111650; PMCID: PMC10144480.

In agreement with the International Association for the Study of Pain, chronic pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. To date, there are several types of pain: nociceptive, neuropathic, and nociplastic. In the present narrative review, we evaluated the characteristics of the drugs used for each type of pain, according to guidelines, and their effects in people with comorbidity to reduce the development of severe adverse events.

A Rose by Another Name? Characteristics that Distinguish Headache Secondary to Temporomandibular Disorder from Headache that is Comorbid with Temporomandibular Disorder.
Sharma S, Slade GD, Fillingim RB, Ohrbach R.
Pain. 2023 Apr 1;164(4):820-830. doi: 10.1097/j.pain.0000000000002770. Epub 2022 Aug 30. PMID: 36048529; PMCID: PMC9971346.

Co-occurring pain conditions that affect overlapping body regions are complicated by the distinction between primary vs secondary pain conditions. We investigate the occurrence of headache and painful temporomandibular disorder (TMD) in a community-based, cross-sectional study of US adults in the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA-II) study. A specific goal was to determine whether headache attributed to TMD is separable from primary headache. Using DC/TMD and International Classification of Headache Disorders-third edition criteria, 3 groups of individuals were created: (a) headache without TMD; (b) headache comorbid with TMD; and (c) headache attributed to TMD. Regression models compared study groups according to demographic and comorbid characteristics, and post hoc contrasts tested for differences. Descriptive statistics and Cohen d effect size were computed, by group, for each predictor variable. Differences in continuous predictors were analyzed using one-way analysis of variance. Nearly all demographic and comorbid variables distinguished the combined headache and TMD groups from the group with headache alone. Relative to the reference group with primary headache alone, markers related to headache, TMD, somatic pain processing, psychosocial, and health conditions were substantially greater in both headache comorbid with TMD and headache attributed to TMD, attesting to their qualitative similarities. However, effect sizes relative to the reference group were large for headache comorbid with TMD and larger again for headache attributed to TMD, attesting to their separability in quantitative terms. In summary, the presence of overlapping painful TMD and headache adds substantially to the biopsychosocial burden of headache and points to the importance of comprehensive assessment and differential management.

Cannabinoids as a Potential Alternative to Opioids in the Management of Various Pain Subtypes: Benefits, Limitations, and Risks.
Ang SP, Sidharthan S, Lai W, Hussain N, Patel KV, Gulati A, Henry O, Kaye AD, Orhurhu V.
Pain Ther. 2023 Apr;12(2):355-375. doi: 10.1007/s40122-022-00465-y. Epub 2023 Jan 13. PMID: 36639601; PMCID: PMC10036719.

Introduction: Pain is a global phenomenon encompassing many subtypes that include neuropathic, musculoskeletal, acute postoperative, cancer, and geriatric pain. Traditionally, opioids have been a mainstay pharmacological agent for managing many types of pain. However, opioids have been a subject of controversy with increased addiction, fatality rates, and cost burden on the US

healthcare system. Cannabinoids have emerged as a potentially favorable alternative or adjunctive treatment for various types of acute and chronic pain. This narrative review seeks to describe the efficacy, risks, and benefits of cannabinoids as an adjunct or even potential replacement for opioids in the treatment of various subtypes of pain. Methods: In June of 2022, we performed a comprehensive search across multiple databases for English-language studies related to the use of cannabinoids in the treatment of various types pain: neuropathic pain, musculoskeletal pain, acute postoperative pain, cancer pain, and geriatric pain. Data from meta-analyses, systematic reviews, and randomized control trials (RCTs) were prioritized for reporting. We sought to focus our reported analysis on more recent literature as well as include older relevant studies with particularly notable findings. Results: There is conflicting evidence for the use of cannabinoids in the management of pain. While cannabinoids have shown efficacy in treating specific chronic pain subtypes such as neuropathic pain, fibromyalgia pain, and geriatric pain, they do not show as clear benefit in acute postoperative and the majority of musculoskeletal pain syndromes. Data trends towards cannabinoids having a positive effect in treating cancer pain, but results are not as conclusive. To date, there is a paucity of data comparing cannabinoids directly to opioids for pain relief. Overall, the side effects of cannabinoids appear to be relatively mild. However, there is still potential for addiction, altered brain development, psychiatric comorbidities, and drug-drug interactions. Conclusion: Cannabinoids may be effective in specific subtypes of pain, but current evidence and guidelines do not yet support its use as the first-line treatment for any type of acute or chronic pain. Rather, it may be considered a good adjunct or alternative for patients who have failed more typical or conservative measures. Additional studies are needed with standardized forms of cannabinoids, route of delivery, and dosing for greater-powered analysis. Providers must weigh the individualized patient risks, benefits, and concurrent medication list in order to determine whether cannabinoids are appropriate for a patient's pain treatment plan.

Chronic Pain Trials Often Exclude People with Comorbid Depressive Symptoms: A Secondary Analysis of 346 Randomized Controlled Trials.

Cheng DK, Ullah MH, Gage H, Moineddin R, Sud A.

Clin Trials. 2023 Jun 22:17407745231182010. doi: 10.1177/17407745231182010. Epub ahead of print. PMID: 37345528.

Background: Chronic pain and depression are common comorbid conditions, but there is limited evidence-based guidance for management of the two conditions together. In recent years, there has been an increase in the number of chronic pain randomized controlled trials that collect depression outcomes, but it is unknown how often these trials include people with depression or significant depressive symptoms. If trials do not include participants representative of real-world populations, evidence and guidance generated from these trials risk being inapplicable for large proportions of the target population, or worse, risk harm. Thus, in order to identify pathways to improve the conduct of clinical trials, the aims of this study were to (1) estimate the proportion of randomized controlled trials evaluating chronic pain interventions and reporting depression outcomes that include participants with significant depressive symptoms; and (2) assess the variability of inclusion proportions by pain type, intervention type, gender, country of origin, and publication year. Methods: Studies were extracted from an umbrella review of interventions for chronic pain that reported depression outcomes. Screening and data extraction were completed in duplicate and conflicts were resolved by a third author. Randomized controlled trials with at least 50% adult participants and validated depression scales were included, and randomized controlled trials with populations whose mean scores were at or above depression thresholds at baseline were considered to have included participants with depression. Results: Of the 346 randomized controlled trials analyzed, 142 (41%) included participants with depression. Eight pain-type groups and nine intervention types were identified. Randomized controlled trials investigating fibromyalgia and mixed chronic pain had the highest proportion of participants with depression, whereas studies of arthritis and axial pain had among the lowest. Randomized controlled trials from the United States had a significantly lower inclusion proportion compared with non-US studies, especially for studies on arthritis. The increase in inclusion proportion by publication year was driven by the increase in fibromyalgia studies. Discussion and conclusion: This study highlights opportunities to improve the conduct of chronic pain clinical trials. The majority of randomized controlled trials s analyzed evaluated participants without significant depressive symptoms at baseline, thus the findings synthesized in systematic reviews and subsequent guidelines are most applicable to the subset of real-world populations that do not have significant depressive symptoms. As well, systemic biases around psychological conditions and gender may be important contributors to differences in the study of depression in fibromyalgia compared with common conditions such as arthritis and axial pain. In order to better inform clinical practice, future research must intentionally include individuals with comorbid depression in trials of common chronic pain conditions, and consider methods to mitigate biases that may distort study design.

Which Comorbid Conditions and Risk Factors affect the Outcome of and Progression to Total Temporomandibular Joint Replacement?

Handa S, Guastaldi FPS, Violette L, Abou-Ezzi J, Rosén A, Keith DA.

Int J Oral Maxillofac Surg. 2023 Jun 3:S0901-5027(23)00135-2. doi: 10.1016/j.ijom.2023.05.011. Epub ahead of print. PMID: 37277244.

Surgery is an effective modality to reduce pain and increase range of motion (ROM) in TMJ disorders. The aim of this study was to determine which comorbidities and risk factors affect outcomes and progression to total joint replacement (TJR). A retrospective cohort study of patients who underwent TJR between 2000- 2018 at MGH was conducted. Primary outcome was successful vs unsuccessful surgery. Success was defined as pain score ≤ 4 and ROM ≥ 30 mm; failure was defined as lack of either or both. Secondary outcome was differences between patients undergoing TJR only (group A) and those undergoing multiple surgeries progressing to TJR (group B). 99 patients (82 females, 17 males) were included. Mean follow-up was 4.1 years; mean age at first surgery was 34.2 (range 14-71) years. Unsuccessful outcomes were associated with high preoperative pain, low preoperative ROM, and higher number of surgeries. Male sex favored successful outcome. 75.0% group A and 47.6% group B had successful outcome. Group B had more females, higher postoperative pain, lower postoperative ROM, and used more opioids compared to group A. High preoperative pain, low preoperative ROM, and more surgeries were associated with poorer outcomes and frequent opioid use.

How Dental Teams can Help Patients with Temporomandibular Disorders Receive General Dental Care: An International Delphi Process.

Allison JR, Offen E, Cowley T, Clare D, Bergman S, Feldman JG, Schmidt LM, Kalinowski T, Türp JC, Manfredini D, Nixdorf DR, DePalma AC, Durham J; International Network for Orofacial Pain and Related Disorders Methodology (INfORM).
J Oral Rehabil. 2023 Jun;50(6):482-487. doi: 10.1111/joor.13444. Epub 2023 Mar 23. PMID: 36924116.

Background: Many patients with temporomandibular disorders (TMD) find it difficult to undergo dental care due to challenges caused by their condition, previous temporomandibular joint surgery or invasive dental procedures, and the impact of comorbid conditions. Managing routine dental care for some patients with TMD can be seen as challenging by some dental practitioners. Objective: The objective of this study was to work with patients experiencing TMD and clinicians to co-produce recommendations aimed at helping general dentists to provide routine dental care for patients with TMD. Methods: A modified Delphi process was used to co-produce recommendations. Six patients experiencing TMD, patient advocates and seven clinicians took part, including international TMD clinicians. Two meetings were held with patient participants, mediated by a trained facilitator. Recommendations suggested by patient participants were distributed to clinicians who were asked to add additional suggestions, but not to modify patients' recommendations unless to aid clarity. Additional themes were identified from the existing literature, and the recommendations were then reviewed by the International Network for Orofacial Pain and Related Disorders Methodology (INfORM) consortium. Results: Recommendations were given to support patients before, during and after dental treatment. Participants identified specific and practical recommendations to help patients with TMD receive routine dental care, but also emphasised the need for professionals to listen sensitively to patients' concerns and work with patients in an empathetic and non-judgmental way. Conclusion: These recommendations, co-developed with patients experiencing TMD, should help dental professionals to provide supportive general dental care for patients with TMD.

Life is pain: Fibromyalgia as a Nexus of Multiple Liability Distributions.

Moscati A, Faucon AB, Arnaiz-Yépez C, Lönn SL, Sundquist J, Sundquist K, Belbin GM, Nadkarni G, Cho JH, Loos RJF, Davis LK, Kendler KS.
Am J Med Genet B Neuropsychiatr Genet. 2023 Jun 19. doi: 10.1002/ajmg.b.32949. Epub ahead of print. PMID: 37334860.

Fibromyalgia is a complex disease of unclear etiology that is complicated by difficulties in diagnosis, treatment, and clinical heterogeneity. To clarify this etiology, healthcare-based data are leveraged to assess the influences on fibromyalgia in several domains. Prevalence is less than 1% of females in our population register data, and about 1/10th that in males. Fibromyalgia often presents with co-occurring conditions including back pain, rheumatoid arthritis, and anxiety. More comorbidities are identified with hospital-associated biobank data, falling into three broad categories of pain-related, autoimmune, and psychiatric disorders. Selecting representative phenotypes with published genome-wide association results for polygenic scoring, we confirm genetic predispositions to psychiatric, pain sensitivity, and autoimmune conditions show associations with fibromyalgia, although these may differ by ancestry group. We conduct a genome-wide association analysis of fibromyalgia in biobank samples, which did not result in any genome-wide significant loci; further studies with increased sample size are necessary to identify specific genetic effects on fibromyalgia. Overall, fibromyalgia appears to have strong clinical and likely genetic links to several disease categories, and could usefully be understood as a composite manifestation of these etiological sources.

Effect on Orofacial Pain in Patients with Chronic Pain Participating in a Multimodal Rehabilitation Programme - a Pilot Study.
Holmström AK, Vallin S, Wänman A, Lövgren A, Stålnacke BM.
Scand J Pain. 2023 Jun 19. doi: 10.1515/sjpain-2023-0004. Epub ahead of print. PMID: 37327054.

Objectives: Orofacial pain in patients taking part in a multimodal rehabilitation programme (MMRP) due to chronic bodily pain is common but it is not known whether such a rehabilitation programme can also have an effect on the presence of orofacial pain. The first aim of this study was to evaluate the effect of an MMRP on orofacial pain frequency. The second aim was to evaluate differences in the effect on quality of life and on psychosocial factors related to chronic pain. Methods: MMRP was evaluated through validated questionnaires from the Swedish Quality Registry for Pain Rehabilitation (SQRP). Fifty-nine patients participating in MMRP filled out the two screening questions for orofacial pain in addition to the SQRP questionnaires before and after participation in MMRP during the period August 2016 to March 2018. Results: Pain intensity decreased significantly after the MMRP (p=0.005). Fifty patients (69.4 %) reported orofacial pain before MMRP and no significant decrease after the programme (p=0.228). Among individuals with orofacial pain, the self-reported level of depression decreased after participation in the programme (p=0.004). Conclusions: Even though orofacial pain is common among patients with chronic bodily pain, participation in a multimodal pain programme was not enough to reduce frequent orofacial pain. This finding implies that specific orofacial pain management including information about jaw physiology could be a justified component of patient assessment prior to a multimodal rehabilitation programme for chronic bodily pain.

Managing Vulvodynia with Central Sensitization: Challenges and Strategies.
Rubal C, Pereira A, Sastre LC, Pérez-Cejuela BA, Gámiz SH, Chaves P, Medina TP.
J Clin Med. 2023 Jun 5;12(11):3851. doi: 10.3390/jcm12113851. PMID: 37298046; PMCID: PMC10253424.

Background: Vulvodynia is defined as a chronic idiopathic vulvar pain condition. This study aimed to investigate the effect of central sensitization on the prognosis of neuromodulator treatment for vulvodynia. Method: A total of 105 patients with vulvodynia who underwent pelvic mapping pain exploration were included and scored according to the Convergence PP Criteria for pelvic pain and central sensitization. The patients were treated according to chronic pelvic pain guidelines, and their response to treatment was evaluated. Results: A total of 35 out 105 patients (33%) with vulvodynia had central sensitization, which was associated with comorbidities, dyspareunia, pain with micturition, and pain with defecation. Dyspareunia and pain with defecation were independent prognostic factors for central sensitization. Patients with central sensitization experienced more pain during intercourse, urination, or defecation, had more comorbidities, and responded worse to treatment. They required more treatment, with a longer response time (over 2 months). Patients with localized vulvodynia were treated with physiotherapy and lidocaine, while patients with generalized vulvodynia were treated with neuromodulators. Amitriptyline was effective in treating patients with generalized spontaneous vulvodynia and dyspareunia. Conclusions: Overall, this study highlights the importance of considering central sensitization in the diagnosis and treatment of vulvodynia and the need for individualized treatment based on the patient's symptoms and underlying mechanisms. Vulvodynia patients with central sensitization had more pain during intercourse, urination, or defecation, and responded worse to treatment, requiring more time and medication.

Epidemiology Studies

Estimated Rates of Incident and Persistent Chronic Pain Among US Adults, 2019-2020.
Nahin RL, Feinberg T, Kapos FP, Terman GW.
JAMA Netw Open. 2023 May 1;6(5):e2313563. doi: 10.1001/jamanetworkopen.2023.13563. PMID: 37191961; PMCID: PMC10189566.

Importance: Chronic pain risk and prognosis estimates are needed to inform effective interventions. Objective: To estimate rates of chronic pain and high-impact chronic pain (HICP) incidence and persistence in US adults across demographic groups. Design, setting, and participants: This cohort study examined a nationally representative cohort with 1 year of follow-up (mean [SD], 1.3 [0.3] years). Data from the 2019-2020 National Health Interview Survey (NHIS) Longitudinal Cohort were used to assess the incidence rates of chronic pain across demographic groups. The cohort was created using random cluster probability sampling of noninstitutionalized civilian US adults 18 years or older in 2019. Of 21 161 baseline participants in the 2019 NHIS who were randomly chosen for follow-up, 1746 were excluded due to proxy response(s) or lack of contact information, and 334 were deceased or institutionalized. Of the 19 081 remaining, the final analytic sample of 10 415 adults also participated in the 2020 NHIS. Data were analyzed from January 2022 to March

2023. Exposures: Self-reported baseline sex, race, ethnicity, age, and college attainment. Main outcomes and measures: Primary outcomes were the incidence rates of chronic pain and HICP, and secondary outcomes were the demographic characteristics and rates across demographic groups. A validated measure of pain status ("In the past 3 months, how often did you have pain? Would you say never, some days, most days, or every day?") yielded 3 discrete categories each year: pain free, nonchronic pain, or chronic pain (pain "most days" or "every day"). Chronic pain present in both survey years was considered persistent; HICP was defined as chronic pain that limited life or work activities on most days or every day. Rates were reported per 1000 person-years (PY) of follow-up, and age standardized based on the 2010 US adult population. Results: Among 10 415 participants included in the analytic sample, 51.7% (95% CI, 50.3%-53.1%) were female, 54.0% (95% CI, 52.4%-55.5%) were aged 18 to 49 years, 72.6% (95% CI, 70.7%-74.6%) were White, 84.5% (95% CI, 81.6%-85.3%) were non-Hispanic or non-Latino, and 70.5% (95% CI, 69.1%-71.9%) were not college graduates. Among pain-free adults in 2019, incidence rates of chronic pain and HICP in 2020 were 52.4 (95% CI, 44.9-59.9) and 12.0 (95% CI, 8.2-15.8) cases per 1000 PY, respectively. The rates of persistent chronic pain and persistent HICP in 2020 were 462.0 (95% CI, 439.7-484.3) and 361.2 (95% CI, 265.6-456.8) cases per 1000 PY, respectively. Conclusions and relevance: In this cohort study, the incidence of chronic pain was high compared with other chronic diseases. These results emphasize the high disease burden of chronic pain in the US adult population and the need for early management of pain before it becomes chronic.

Seventeen-Year National Pain Prevalence Trends Among U.S. Military Veterans.
Taylor KA, Kapos FP, Sharpe JA, Kosinski AS, Rhon DI, Goode AP.
medRxiv [Preprint]. 2023 Apr 10:2023.03.27.23287408. doi: 10.1101/2023.03.27.23287408. PMID: 37034604; PMCID: PMC10081421.

Importance: U.S. military veterans experience higher pain prevalence and severity than nonveterans. However, it is unclear how these differences have changed over time. Previous studies are limited to veterans receiving care from the Veterans Health Administration. Objective: To characterize pain prevalence trends in the overall population of U.S. veterans compared to nonveterans, using nationally-representative data. Design: Repeated cross-sectional study. Data: National Health Interview Survey, 2002-2018. Analysis: January 2023. Setting: Population-based survey of noninstitutionalized U.S. adults. Participants: Across the 17-year period, mean annual weighted population was 229.7 million adults (unweighted sample total: n=506,639; unweighted sample annual mean: n=29,802). Exposure: Veteran status. Main Outcomes: Crude and demographics-adjusted pain prevalence trend differences between veterans and nonveterans across five pain variables (severe headache or migraine, facial pain, neck pain, low back pain, and joint pain) and two composite variables (any pain [≥1 prevalent pain] and multiple pains [≥2 prevalent pain]). Results: Weighted proportion of veterans varied from 11.48% in 2002 (highest) to 8.41% in 2017 (lowest). Across the study period, crude prevalence was generally similar or higher among veterans than nonveterans for all pain variables except for severe headache or migraine and facial pain. When equalizing age, sex, race, and ethnicity, pain prevalence among veterans remained similar or higher than nonveterans for all pain variables. From 2002 to 2018 there was an absolute increase (95% CI) in pain prevalence among veterans (severe headache or migraine: 2.0% [1.6% to 2.4%]; facial pain: 1.9% [1.4% to 2.4%]; neck pain: 4.7% [4.1% to 5.2%]; joint pain: 11.4% [10.8% to 11.9%]; low back pain: 10.3% [9.5% to 11.1%]; any pain: 10.0% [9.6% to 10.4%]; and multiple pains: 9.9% [9.2% to 10.6%]. Crude and adjusted analyses indicated prevalence of all pain variables increased more among veterans than nonveterans from 2002 to 2018. Conclusion and Relevance: Veterans had similar or higher adjusted prevalence and higher rates of increase over time for all pain variables compared to nonveterans. Continued pain prevalence increase among veterans may impact healthcare utilization (within and outside of the VHA), underscoring the need for improved pain prevention and care programs for these individuals with disproportionate pain burden.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): A Preliminary Survey among Patients in Switzerland.
Tschopp R, König RS, Rejmer P, Paris DH.
Heliyon. 2023 Apr 20;9(5):e15595. doi: 10.1016/j.heliyon.2023.e15595. PMID: 37131449; PMCID: PMC10149204.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a multi-factorial systemic chronic debilitating disease of poorly understood etiology and limited systematic evidence. The questionnaire and interview-based survey included 169 ME/CFS patients from the Swiss ME/CFS association. The majority of patients were females (72.2%), single (55.7%) and without children (62.5%). Only one third were working (full/part-time). The mean onset of ME/CFS was 31.6 years of age with 15% of patients being symptomatic before their 18th birthday. In this cohort, patients had documented ME/CFS for a mean 13.7 years, whereby half (50.3%) stated their condition was progressively worsening. Triggering events and times of disease onset were recalled by 90% of the

participants. An infectious disease was associated with a singular or part of multiple events by 72.9% and 80.6%, respectively. Prior to disease onset, a third of the patients reported respiratory infections; followed by gastro-intestinal infections (15.4%) and tick-borne diseases (16.2%). Viral infections were recalled by 77.8% of the respondents, with Epstein Barr Virus being the most commonly reported agent. Patients self-reported an average number of 13 different symptoms, all described specific triggers of symptoms exacerbation and 82.2% suffered from co-morbidities. This study collated clinically relevant information on ME/CFS patients in Switzerland, highlighting the extent of disease severity, the associated factors negatively affecting daily life activities and work status as well as potential socio-economic impact.

Association of Fibromyalgia with Cancerous and Non-Cancerous Gastrointestinal Comorbidities: A Cross-Sectional Study.

Savin E, Tsur AM, Watad A, Gendelman O, Kopylov U, Cohen AD, Amital H.
Clin Exp Rheumatol. 2023 Apr 3. doi: 10.55563/clinexprheumatol/rp5lkn. Epub ahead of print. PMID: 37083168.

Objectives: Several studies have shown a higher prevalence of irritable bowel syndrome (IBS) among patients with fibromyalgia yet, data regarding association between fibromyalgia and other gastrointestinal disorders have been relatively overlooked. Our aim was to investigate the association between fibromyalgia and gastrointestinal disorders including both benign and malignant conditions. Methods: We conducted a retrospective cross-sectional study based on the comprehensive electronic database of the largest health maintenance organisation in Israel. All subjects with a diagnosis of fibromyalgia in their medical records and age- and sex-matched controls were included in the study. We investigated the association of fibromyalgia with benign gastrointestinal disorders including IBS, gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), celiac disease, Crohn's disease, ulcerative colitis, and with gastrointestinal malignancies including colorectal, pancreatic, stomach, liver, and bile duct cancers. Results: The study enrolled 18,598 patients with fibromyalgia and 36,985 controls. The mean age was 56.5 years (standard deviation=14) with a female predominance (91%). Fibromyalgia was significantly associated with IBS (OR 4.61, 95% CI 4.09-5.2, p<0.001), GERD (OR 2.62, 95% CI 2.5-2.75, p<0.001), PUD (OR 2.13, 95% CI 1.98-2.3, p<0.001), celiac disease (OR 2.08, 95% CI 1.63-2.65, p<0.001), Crohn's disease (OR 1.85, 95% CI 1.408-2.32, p<0.001) and ulcerative colitis (OR 1.81, 95%CI 1.4-2.33, p<0.001). Nonetheless, no significant differences were found regarding the prevalence of gastrointestinal malignancies between the fibromyalgia patients and controls. Conclusions: Our findings suggest that FM is positively associated with various benign but not malignant GI disorders.

Occurrence of Comorbidity Following Osteoarthritis Diagnosis: A Cohort Study in the Netherlands.

Kamps A, Runhaar J, de Ridder MAJ, de Wilde M, van der Lei J, Zhang W, Prieto-Alhambra D, Englund M, de Schepper EIT, Bierma-Zeinstra SMA.
Osteoarthritis Cartilage. 2023 Apr;31(4):519-528. doi: 10.1016/j.joca.2022.12.003. Epub 2022 Dec 15. PMID: 36528309.

Objective: To determine the risk of comorbidity following diagnosis of knee or hip osteoarthritis (OA). Design: A cohort study was conducted using the Integrated Primary Care Information database, containing electronic health records of 2.5 million patients from the Netherlands. Adults at risk for OA were included. Diagnosis of knee or hip OA (=exposure) and 58 long-term comorbidities (=outcome) were defined by diagnostic codes following the International Classification of Primary Care coding system. Time between the start of follow-up and incident diagnosis of OA was defined as unexposed, and between diagnosis of OA and the end of follow-up as exposed. Age and sex adjusted hazard ratios (HRs) comparing comorbidity rates in exposed and unexposed patient time were estimated with 99.9% confidence intervals (CI). Results: The study population consisted of 1,890,712 patients. For 30 of the 58 studied comorbidities, exposure to knee OA showed a HR larger than 1. Largest positive associations (HR with (99.9% CIs)) were found for obesity 2.55 (2.29-2.84) and fibromyalgia 2.06 (1.53-2.77). For two conditions a HR < 1 was found, other comorbidities showed no association with exposure to knee OA. For 26 comorbidities, exposure to hip OA showed a HR larger than 1. The largest were found for polymyalgia rheumatica 1.81 (1.41-2.32) and fibromyalgia 1.70 (1.10-2.63). All other comorbidities showed no associations with hip OA. Conclusion: This study showed that many comorbidities were diagnosed more often in patients with knee or hip OA. This suggests that the management of OA should consider the risk of other long-term-conditions.

The Bidirectional Association between Chronic Musculoskeletal Pain and Sleep-Related Problems: A Systematic Review and Meta-Analysis.

Santos M, Gabani FL, de Andrade SM, Bizzozero-Peroni B, Martínez-Vizcaíno V, González AD, Mesas AE.
Rheumatology (Oxford). 2023 Apr 27:kead190. doi: 10.1093/rheumatology/kead190. Epub ahead

of print. PMID: 37104741.

Objectives: This systematic review and meta-analysis synthesize the evidence on the prospective bidirectional associations between sleep-related problems (SRP) and chronic musculoskeletal pain (CMP). Methods: A literature search for cohort studies available in the PubMed, Scopus, Web of Science, PsycINFO, and Cochrane Library databases as of July 19, 2022, was performed. Pooled odds ratios and effect sizes were calculated through random effects meta-analysis. Subgroup and meta-regression analyses were performed to explore differences by follow-up time, proportion of each sex, and mean age. The Meta-analysis Of Observational Studies in Epidemiology guidelines were strictly followed. Results: Twenty studies with a total of 208 190 adults (aged 34.4-71.7 years) were included, with 17 of them being used in the meta-analysis. Individuals with SRP at baseline had a 1.79-fold higher incidence (odds ratio, OR = 1.79; 95% confidence interval, 95% CI : 1.55-2.08; I2=84.7%; p<0.001) and a 2.04-fold higher persistence (OR = 2.04; 95% CI : 1.42-2.94; I2=88.5%; p<0.005) of CMP than those without SRP. In the subgroup analysis of the association between SRP and CMP, the longer the follow-up time of the studies, the higher the heterogeneity between them. In the corresponding meta-regression, no significant effect was observed for follow-up time, sex proportion, or age. Individuals with CMP at baseline had a 2.02-fold higher incidence of SRP (OR = 2.02; 95% CI : 1.62-2.53; I2=90.0%; p<0.001) than those without CMP. Conclusion: This study provides robust evidence concerning the longitudinal association between SRP and incidence-persistence of CMP in adults. In addition, the available prospective studies support the existence of a bidirectional relationship between CMP and SRP.

Systematic Review and Meta-Analysis of Calculating Degree of Comorbidity of Irritable Bowel Syndrome with Migraine.
Todor TS, Fukudo S.
Biopsychosoc Med. 2023 Jun 8;17(1):22. doi: 10.1186/s13030-023-00275-4. PMID: 37291550; PMCID: PMC10251688.

Background: Irritable bowel syndrome (IBS) and migraines are often comorbid each other. These disorders are likely to be bidirectionally linked through the gut-brain axis and share several underlying mechanisms including central nervous system sensitization. However, quantitative analysis of comorbidity was not reported enough. The aim of this systematic review and meta-analysis was to calculate the present degree of comorbidity of these two disorders. Methods: A literature search was performed searching for articles describing IBS or migraine patients with the same inverse comorbidity. Pooled odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals (CIs) were then extracted. The total effect estimates were determined and presented by random effect forest plots for the group of articles with IBS patients with migraine and the group of articles on migraine sufferers with comorbid IBS separately. The average results of these plots were compared. Results: The literature search resulted in initial 358 articles and final 22 articles for the meta-analysis. The total OR values obtained were 2.09 [1.79 - 2.43] in IBS with comorbid migraine or headache, 2.51 [1.76 - 3.58] for migraineurs with comorbid IBS and an overall HR of 1 .62 [1.29 - 2.03] was found for cohort studies of migraine sufferers with comorbid IBS. A similar expression of a selection of other comorbidities was found in IBS and migraine patients, especially for depression and fibromyalgia a strong similarity was found in their expression rate. Conclusions: This systematic review with meta-analysis was the first to combine data on IBS patients with comorbid migraine and migraineurs with comorbid IBS. The fact that closely related existential rates were observed between these two groups should be used as motivation for future research to further investigate these disorders for why this similarity occurs. Mechanisms involved in central hypersensitivity such as genetic risk factors, mitochondrial dysfunction and microbiota are particularly good candidates. Experimental designs in which therapeutic methods for these conditions can be exchanged or combined may also lead to the discovery of more efficient treatment methods.

Association of Laparoscopically-Confirmed Endometriosis with Long COVID-19: A Prospective Cohort Study.
Wang S, Farland LV, Gaskins AJ, Mortazavi J, Wang YX, Tamimi RM, Rich-Edwards JW, Zhang D, Terry KL, Chavarro JE, Missmer SA.
Am J Obstet Gynecol. 2023 Jun;228(6):714.e1-714.e13. doi: 10.1016/j.ajog.2023.03.030. Epub 2023 Mar 25. PMID: 36972892; PMCID: PMC10101545.

Background: Women are at greater risk than men of developing chronic inflammatory conditions and "long COVID." However, few gynecologic health risk factors for long COVID-19 have been identified. Endometriosis is a common gynecologic disorder associated with chronic inflammation, immune dysregulation, and comorbid presentation with autoimmune and clotting disorders, all of which are pathophysiological mechanisms proposed for long COVID-19. Therefore, we hypothesized that women with a history of endometriosis may be at greater risk of developing long COVID-19. Objective: This study aimed to investigate the association between history of endometriosis before SARS-CoV-2 infection and risk of long COVID-19. Study design: We followed 46,579 women from 2 ongoing prospective cohort studies-the Nurses' Health Study II and the

Nurses' Health Study 3-who participated in a series of COVID-19-related surveys administered from April 2020 to November 2022. Laparoscopic diagnosis of endometriosis was documented prospectively in main cohort questionnaires before the pandemic (1993-2020) with high validity. SARS-CoV-2 infection (confirmed by antigen, polymerase chain reaction, or antibody test) and long-term COVID-19 symptoms (≥4 weeks) defined by the Centers for Disease Control and Prevention were self-reported during follow-up. Among individuals with SARS-CoV-2 infection, we fit Poisson regression models to assess the associations between endometriosis and risk of long COVID-19 symptoms, with adjustment for potential confounding variables (demographics, body mass index, smoking status, history of infertility, and history of chronic diseases). Results: Among 3650 women in our sample with self-reported SARS-CoV-2 infections during follow-up, 386 (10.6%) had a history of endometriosis with laparoscopic confirmation, and 1598 (43.8%) reported experiencing long COVID-19 symptoms. Most women were non-Hispanic White (95.4%), with a median age of 59 years (interquartile range, 44-65). Women with a history of laparoscopically-confirmed endometriosis had a 22% greater risk of developing long COVID-19 (adjusted risk ratio, 1.22; 95% confidence interval, 1.05-1.42) compared with those who had never been diagnosed with endometriosis. The association was stronger when we defined long COVID-19 as having symptoms for ≥8 weeks (risk ratio, 1.28; 95% confidence interval, 1.09-1.50). We observed no statistically significant differences in the relationship between endometriosis and long COVID-19 by age, infertility history, or comorbidity with uterine fibroids, although there was a suggestive trend indicating that the association may be stronger in women aged <50 years (<50 years: risk ratio, 1.37; 95% confidence interval, 1.00-1.88; ≥50 years: risk ratio, 1.19; 95% confidence interval, 1.01-1.41). Among persons who developed long COVID-19, women with endometriosis reported on average 1 additional long-term symptom compared with women without endometriosis. Conclusion: Our findings suggest that those with a history of endometriosis may be at modestly increased risk for long COVID-19. Healthcare providers should be aware of endometriosis history when treating patients for signs of persisting symptoms after SARS-CoV-2 infection. Future studies should investigate the potential biological pathways underlying these associations.

The Prevalence of Migraine in Inflammatory Bowel Disease, a Systematic Review and Meta-Analysis.

Olfati H, Mirmosayyeb O, Hosseinabadi AM, Ghajarzadeh M.

Int J Prev Med. 2023 May 27;14:66. doi: 10.4103/ijpvm.ijpvm_413_21. PMID: 37351058; PMCID: PMC10284239.

Background: Patients with inflammatory bowel disease (IBD) suffer from a wide range of comorbidities such as migraine. In studies, the prevalence of migraine in cases with IBD was reported differently. The goal of this systematic review and meta-analysis was to estimate the pooled prevalence of migraine in IBD cases. Methods: Two researchers independently and systematically searched PubMed, Scopus, EMBASE, Web of Science, and google scholar. They also searched the gray literature including references of the included studies and conference abstracts which were published up to May 2021. Cross-sectional studies were included. Results: The literature search revealed 840 articles, and after deleting duplicates, 650 remained. For the meta-analysis, 10 studies were included. Totally, 62,554 patients were evaluated. The pooled prevalence of migraine in patients with IBD was 19% (95% CI: 15-22%). The pooled prevalence of migraine in ulcerative colitis (UC) was 10% (95% CI: 4-15%) (I^2 = 99.8%, P < 0.001). The pooled prevalence of migraine in the Crohn's disease (CD) group was 24% (95% CI: 17-30%) (I^2 = 98.8%, P < 0.001). The pooled odds of developing migraine in IBD cases was 1.51 (95% CI: 1-2.27) (I^2 = 90.8%, P < 0.001). Conclusions: The result of this systematic review and meta-analysis showed that the pooled prevalence of migraine in patients with IBD was 19% (95% CI: 15-22%).

Temporomandibular Disorder, Otologic, Body Pain, and Psychological Symptoms: Their Inter-Relationships in Asian Youths.

Yap AU, Lee DZR.

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Purpose: This study aimed to establish the inter-relationships between Temporomandibular disorders (TMDs), otologic, pain, and psychological comorbidities in Asian youths. Methods: Youths, aged 17 to 24 years old, were enrolled from a local polytechnic and an electronic survey encompassing demographic variables, the DC/TMD TMD pain screener (TPS), Short-form Fonseca Anamnestic Index (SFAI), modified Maciel's Otologic/Pain Symptom Inventory, and Patient Health Questionnaire-4 was administered. Participants were subsequently categorized into "no TMD pain (NP)" and "with TMD pain (WP)" in addition to "no TMDs (NT)" and "with any TMDs (WT)" groups. Data were evaluated with the Chi-square test, non-parametric, and logistic regression analyses (α = 0.05). Results: Among the 198 participants (mean age 18.8 ± 1.7 years), 11.1% had painful TMDs and 18.2% experienced TMD pain and/or dysfunction. Significant differences in total-otologic symptom (total-OS), vertigo, and dizziness plus otalgia, tinnitus, and

hearing loss scores were observed between the WP-NP and WT-NT groups correspondingly. While total-comorbid pain (total-CP) and psychological distress (total-PD) scores varied substantially between the WT-NT group, only a significant difference in total-PD scores was discerned between the WP-NP group. Total-OS scores were moderately correlated to TPS/SFAI, total-CP, total-PD scores. and psychological distress was a risk factor for painful TMDs. Conclusion: Otologic and pain comorbidities were prevalent among Asian youths with TMDs and appear to be interrelated. The complex interaction of TMDs with otological, pain, and psychological comorbidities must be considered when caring for youths with multiple somatic complaints.

Masculine Gender Affects Sex Differences in the Prevalence of Chronic Health Problems - The Doetinchem Cohort Study.
Vader SS, Lewis SM, Verdonk P, Verschuren WMM, Picavet HSJ.
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Both (biological) sex and (socio-cultural) gender are relevant for health but in large-scale studies specific gender measures are lacking. Using a masculine gender-score based on 'traditional masculine-connotated aspects of everyday life', we explored how masculinity may affect sex differences in the prevalence of chronic health problems. We used cross-sectional data (2008-2012) from the Doetinchem Cohort Study to calculate a masculine gender-score (range 0-19) using information on work, informal care, lifestyle and emotions. The sample consisted of 1900 men and 2117 women (age: 40-80). Multivariable logistic regressions including age and SES were used to examine the role of masculine gender on sex differences in the prevalence of diabetes, coronary heart disease, CVA, arthritis, chronic pain and migraine. Men had higher masculine gender-scores than women (12.2 vs 9.1). For both sexes, a higher masculine gender-score was associated with lower prevalence of chronic health problems. Diabetes, CHD, and CVA were more prevalent in men, and gender-adjustment resulted in greater sex differences: e.g. for diabetes the ORsex changed from 1.21 (95 %CI 0.93-1.58) to 1.60 (95 %CI 1.18-2.17). Arthritis, chronic pain, and migraine were more prevalent in women, and gender-adjustment resulted in smaller sex differences: e.g. for chronic pain the ORsex changed from 0.53 (95 %CI 0.45-0.60) to 0.73 (95 %CI 0.63-0.86). Gender measured as 'everyday masculinity' is associated with lower prevalence of chronic health problems in both men and women. Our findings also suggest that the commonly found sex differences in the prevalence of chronic health problems have a large gender component.