CUTTING EDGE

COPCs Research Advances

a publication of CHRONIC PAIN Research Alliance

Issue 29 - January 2025

COPCs Research Advances is published by the CPRA to keep the medical-scientific and patient communities informed about current research on Chronic Overlapping Pain Conditions (COPCs).

This issue contains abstracts of studies published between August 2024 and December 2025.

Prior issues are available on our website. If you are not already on our mailing list, you can sign up to receive future issues here. To read or download the CPRA's White Paper, click here.

Enhancing the Trustworthiness of Pain Research: A Call to Action.

ENTRUST-PE Network; O'Connell NE, Belton J, Crombez G, Eccleston C, Fisher E, Ferraro MC, Hood A, Keefe F, Knaggs R, Norris E, Palermo TM, Pickering G, Pogatzki-Zahn E, Rice AS, Richards G, Segelcke D, Smart KM, Soliman N, Stewart G, Tölle T, Turk D, Vollert J, Wainwright E, Wilkinson J, Williams ACC.
J Pain. 2024 Nov 16:104736. doi: 10.1016/j.jpain.2024.104736. Epub ahead of print. PMID: 39551457.

The personal, social and economic burden of chronic pain is enormous. Tremendous research efforts are being directed toward understanding, preventing, and managing chronic pain. Yet patients with chronic pain, clinicians and the public are sometimes poorly served by an evidence architecture that contains multiple structural weaknesses. These include incomplete research governance, a lack of diversity and inclusivity, inadequate stakeholder engagement, poor methodological rigour and incomplete reporting, a lack of data accessibility and transparency, and a failure to communicate findings with appropriate balance. These issues span pre-clinical research, clinical trials and systematic reviews and impact the development of clinical guidance and practice. Research misconduct and inauthentic data present a further critical risk. Combined, they increase uncertainty in this highly challenging area of study and practice, drive the provision of low value care, increase costs and impede the discovery of more effective solutions. In this focus article, we explore how we can increase trust in pain science, by examining critical challenges using contemporary examples, and describe a novel integrated conceptual framework for enhancing the trustworthiness of pain science. We end with a call for collective action to address this critical issue. PERSPECTIVE: Multiple challenges can adversely impact the trustworthiness of pain research and health research more broadly. We present ENTRUST-PE, a novel, integrated framework for more trustworthy pain research with recommendations for all stakeholders in the research ecosystem, and make a call to action to the pain research community.

PATHOPHYSIOLOGY STUDIES

Brain Predicted Age in Chronic Pelvic Pain: A Study by the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research Network.
Leech KA, Kettlety SA, Mack WJ, Kreder KJ, Schrepf A, Kutch JJ.
Pain. 2024 Oct 16. doi: 10.1097/j.pain.0000000000003424. Epub ahead of print. PMID: 39432808.

The effect of chronic pain on brain-predicted age is unclear. We performed secondary analyses of a large cross-sectional and 3-year longitudinal data set from the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research Network to test the hypothesis that chronic pelvic pain accelerates brain aging and brain aging rate. Brain-predicted ages of 492 chronic pelvic pain patients and 72 controls were determined from T1-weighted MRI scans and used to calculate the brain-predicted age gap estimation (brainAGE; brain-predicted - chronological age). Separate regression models determined whether the presence of chronic pelvic pain could explain brainAGE and brain aging rate when accounting for covariates. We performed secondary analyses to understand whether brainAGE was associated with factors that subtype chronic pelvic pain patients (inflammation, widespread pain, and psychological comorbidities). We found a significant association between chronic pelvic pain and brainAGE that differed by sex. Women with chronic pelvic pain had higher brainAGE than female controls, whereas men with chronic pelvic pain exhibited lower brainAGE than male controls on average-however, the effect was not statistically significant in men or women when considered independently. Secondary analyses demonstrated preliminary evidence of an association between inflammatory load and brainAGE. Further studies of brainAGE and inflammatory load are warranted.

"Neuroinflammation": Does it Have a Role in Chronic Pain? Evidence from Human Imaging.
Loggia ML.
Pain. 2024 Nov 1;165(11S):S58-S67. doi: 10.1097/j.pain.0000000000003342. PMID: 39560416.

Despite hundreds of studies demonstrating the involvement of neuron-glia-immune interactions in the establishment and/or maintenance of persistent pain behaviors in animals, the role (or even occurrence) of so-called "neuroinflammation" in human pain has been an object of contention for decades. Here, I present the results of multiple positron emission tomography (PET) studies measuring the levels of the 18 kDa translocator protein (TSPO), a putative neuroimmune marker, in individuals with various pain conditions. Overall, these studies suggest that brain TSPO PET signal: (1) is elevated, compared to healthy volunteers, in individuals with chronic low back pain (with additional elevations in spinal cord and neuroforamina), fibromyalgia, migraine and other conditions characterized by persistent pain; (2) has a spatial distribution exhibiting a degree of disorder specificity; (3) is parametrically linked to pain characteristics or comorbid symptoms (eg, nociplastic pain, fatigue, depression), as well as measures of brain function (ie, functional connectivity), in a regionally-specific manner. In this narrative, I also discuss important caveats to consider in the interpretation of this work (eg, regarding the cellular source of the signal and the complexities inherent in its acquisition and analysis). While the biological and clinical significance of these findings awaits further work, this emerging preclinical literature supports a role of neuron-glia-immune interactions as possible pathophysiological underpinnings of human chronic pain. Gaining a deeper understanding of the role of neuroimmune function in human pain would likely have important practical implications, possibly paving the way for novel interventions.

Sleep and Circadian Rhythm Disturbances as Risk and Progression Factors for Multiple Chronic Overlapping Pain Conditions: A Protocol for a Longitudinal Study.
Mun CJ, Youngstedt SD, Petrov ME, Pituch KA, Elliott JA, George SZ, LoVecchio F, Mardian AS, Elam KK, Winsick N, Eckert R, Sajith S, Alperin K, Lakhotia A, Kohler K, Reid MJ, Davis MC, Fillingim RB.
Pain Rep. 2024 Oct 24;9(6):e1194. doi: 10.1097/PR9.0000000000001194. PMID: 39465006; PMCID: PMC11512637.

Introduction: Chronic overlapping pain conditions (COPCs), such as chronic low back pain (cLBP) and fibromyalgia, frequently cooccur and incur substantial healthcare costs.

However, to date, much focus has been placed on individual anatomically based chronic pain conditions, whereas little is known about the mechanisms underlying progression to multiple (more than 1) COPCs. This study aims to address the gap by investigating the role of common and modifiable risk factors, specifically sleep and circadian rhythm disturbances, in the development of multiple COPCs.
Methods: The study will enroll 300 participants with cLBP, including 200 with cLBP only and 100 with cLBP plus other COPCs (ie, fibromyalgia, temporomandibular disorders, irritable bowel syndrome, and chronic headaches) and follow them up for 12 months. Sleep and circadian rhythms will be assessed using wireless sleep electroencephalography, 24-hour evaluation of the rhythm of urinary 6-sulfatoxymelatonin, actigraphy, and sleep diaries. Pain amplification using quantitative sensory testing, psychological distress using validated self-report measures, and the number of pain sites using a pain body map will also be assessed.
Perspectives: This research aims to (1) comprehensively characterize sleep/circadian disturbances in individuals with single and multiple COPCs using multimodal in-home assessments; (2) examine the associations between sleep/circadian disturbances, changes in pain amplification, and psychological distress; and (3) investigate the relationship among these factors and the progression in the number of pain sites, a proxy for multiple COPCs. The findings will provide insights into the mechanisms leading to multiple COPCs, potentially informing treatment and prevention strategies for these complex conditions.

Discriminating Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Comorbid Conditions using Metabolomics in UK Biobank.
Huang K, G C de Sá A, Thomas N, Phair RD, Gooley PR, Ascher DB, Armstrong CW. Commun Med (Lond). 2024 Nov 26;4(1):248. doi: 10.1038/s43856-024-00669-7. PMID: 39592839; PMCID: PMC11599898.

Background: Diagnosing complex illnesses like Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is complicated due to the diverse symptomology and presence of comorbid conditions. ME/CFS patients often present with multiple health issues, therefore, incorporating comorbidities into research can provide a more accurate understanding of the condition's symptomatology and severity, to better reflect real-life patient experiences.
Methods: We performed association studies and machine learning on 1194 ME/CFS individuals with blood plasma nuclear magnetic resonance (NMR) metabolomics profiles, and seven exclusive comorbid cohorts: hypertension ($n = 13,559$), depression ($n = 2522$), asthma ($n = 6406$), irritable bowel syndrome ($n = 859$), hay fever ($n = 3025$), hypothyroidism ($n = 1226$), migraine ($n = 1551$) and a non-diseased control group ($n = 53,009$).
Results: We present a lipoprotein perspective on ME/CFS pathophysiology, highlighting gender-specific differences and identifying overlapping associations with comorbid conditions, specifically surface lipids, and ketone bodies from 168 significant individual biomarker associations. Additionally, we searched for, trained, and optimised a machine learning algorithm, resulting in a predictive model using 19 baseline characteristics and nine NMR biomarkers which could identify ME/CFS with an AUC of 0.83 and recall of 0.70. A multi-variable score was subsequently derived from the same 28 features, which exhibited ~2.5 times greater association than the top individual biomarker.
Conclusions: This study provides an end-to-end analytical workflow that explores the potential clinical utility that association scores may have for ME/CFS and other difficult to diagnose conditions.

Unfavourable Glucose Metabolism is Associated with Functional Somatic Disorders. A Cross-Sectional General Population-Based Study: The DanFunD Study.
Dantoft TM, Jørgensen SW, Wellnitz KB, Ørnbøl E, Gormsen L, Fink P, Linneberg A, Jørgensen NR, Petersen MW, Bjerregaard AA, Jørgensen T. Psychoneuroendocrinology. 2024 Dec 12;172:107258. doi: 10.1016/j.psyneuen.2024.107258. Epub ahead of print. PMID: 39673833.

Objectives: Several studies have observed associations between unfavorable levels of blood glucose metabolic markers (i.e., fasting glucose, fasting insulin, glycated hemoglobin (HbA1c), and insulin resistance (HOMA-IR)) and functional somatic disorder (FSD). However, such associations have not yet been systematically analyzed in a general population-based sample using various FSD delimitations simultaneously. The aim of this study was to assess whether an unfavorable glucose metabolism is associated with FSD.
Design: Cross-sectional population-based study SETTING: Ten municipalities in the

western part of greater Copenhagen area in Denmark PARTICIPANTS: A total of 8183 men and women aged 18-76 years were included. Various delimitations of FSD, i.e., chronic fatigue (CF), chronic widespread pain (CWP), irritable bowel (IB), and bodily distress syndrome (BDS), were measured using validated self-administrated questionnaires. In a stratified subsample, BDS was also assessed by diagnostic interviews.
Outcome measures: Logistic regression models were estimated for each delimitation of FSD as outcome and fasting glucose, fasting insulin, HbA1c, and estimated insulin resistance. Results were adjusted for age, sex (model 1), lifestyle, and social factors (model 2) and presented as odds ratios (OR) with 95 % confidence intervals (CI).
Results: When only adjusting for sex and age, positive associations were found between all FSD delimitations and glucose, insulin, and HbA1c, except for between IB and HbA1c. Positive associations were also found between all questionnaire-based BDS groups, and men with BDS confirmed by diagnostic interviews and elevated insulin resistance. After adjusting for lifestyle and social factors, associations remained significant between both CF and glucose and HbA1c and between multi-organ BDS and glucose and HbA1c. Further, CF, single-organ BDS, multi-organ BDS, and women with overall-BDS also remained associated with increased levels of insulin resistance.
Conclusion: FSD seems to be associated with especially an increase in plasma insulin levels and increased levels of insulin resistance. Elevated levels of blood glucose and HbA1c among all FSD groups could also completely be explained by unhealthy lifestyle. Prospective studies are needed for further clarification of the clinical relevance of this observation.

Shared Genetics of Migraine and Gastrointestinal Disorders Implicates Underlying Neurologic Mechanisms Yet Heterogeneous Etiologies.
Chasman DI, Guo Y, Chan AT, Rist PM, Staller K.
Neurol Genet. 2024 Dec 10;10(6):e200201. doi: 10.1212/NXG.0000000000200201. PMID: 39677849; PMCID: PMC11637577.

Background and objectives: Migraine is strongly comorbid with irritable bowel syndrome (IBS), one of several gastrointestinal (GI) conditions that are distinguished by symptomatic profiles that are partly overlapping. Potential shared mechanisms of migraine and the GI conditions were investigated by assessing shared genetics on a genome-wide basis.
Methods: Analyses leveraged genome-wide summary statistics from large-scale genetic studies for migraine, including by aura status, IBS, peptic ulcer disease (PUD), gastrointestinal reflux (GERD), functional dyspepsia (FD), diverticular disease (DD), and the immune-related inflammatory bowel disease (IBD) or its constituents, ulcerative colitis (UC) and Crohn disease (CD). Genetic correlation was evaluated on a genome-wide basis and at independent local regions, including those related to therapeutic targeting of serotonin and the calcitonin gene-related peptide. Genetic correlation was assessed for enrichment at genes according to tissue specificity of gene expression. Potential causality between migraine and the GI conditions was assessed by Mendelian randomization.
Results: Genetic correlation with migraine was strongly significant among the nonimmune GI disorders, maximally for IBS (rg [SE] = 0.37[0.04], $p = 10^{-21}$) and minimally for DD (0.18 (0.04), 7.5×10^{-7}), but null for IBD. There were distinct patterns of local genetic sharing with migraine across the GI conditions at 22 significant segments of the genome, 7 of which were novel for either migraine or GI or both. Enrichment analysis suggested involvement of the CNS in genetic overlap of GERD, IBS, and PUD with migraine. There was local genetic sharing with migraine at *CALCA/CALCB* (encoding calcitonin gene-related peptide [CGRP]) in an inverse sense for GERD and PUD, but with concordance and greater significance for DD, IBD, and UC. Mendelian randomization supported causal effects of PUD, GERD and particularly DD (OR[SE] = 1.90 (1.35-2.68, $p = 2.2 \times 10^{-4}$) on migraine, but not of migraine on any GI condition.
Discussion: Genetic sharing of migraine and non-immune-related GI disorders was extensive yet distinct across GI disorders that have overlapping symptoms, with enrichment signals that imply neurologic mechanisms. Causal effects of some GI conditions on migraine were supported. A concordant local correlation at *CALCA/CALCB* of migraine with both DD and the immune-related disorders suggests potential benefit to these conditions from repurposed migraine therapeutics targeting CGRP.

The Role and Treatment Potential of the Complement Pathway in Chronic Pain .
Vygonskaya M, Wu Y, Price TJ, Chen Z, Smith MT, Klyne DM, Han FY.
J Pain. 2024 Oct 1:104689. doi: 10.1016/j.jpain.2024.104689. Epub ahead of print. PMID:

39362355.

The role of the complement system in pain syndromes has garnered attention on the back of preclinical and clinical evidence supporting its potential as a target for new analgesic pharmacotherapies. Of the components that make up the complement system, component 5a (C5a) and component 3a (C3a) are most strongly and consistently associated with pain. Receptors for C5a are widely found in immune resident cells (microglia, astrocytes, sensory neuron-associated macrophages (sNAMs)) in the central nervous system (CNS) as well as hematogenous immune cells (mast cells, macrophages, T-lymphocytes, etc.). When active, as is often observed in chronic pain conditions, these cells produce various inflammatory mediators including pro-inflammatory cytokines. These events can trigger nervous tissue inflammation (neuroinflammation) which coexists with and potentially maintains peripheral and central sensitization. C5a has a likely critical role in initiating this process highlighting its potential as a promising non-opioid target for treating pain. This review summarises the most up-to-date research on the role of the complement system in pain with emphasis on the C5 pathway in peripheral tissue, dorsal root ganglia (DRG) and the CNS, and explores advances in complement-targeted drug development and sex differences. A perspective on the optimal application of different C5a inhibitors for different types (e.g., neuropathic, post-surgical and chemotherapy-induced pain, osteoarthritis pain) and stages (e.g., acute, subacute, chronic) of pain is also provided to help guide future clinical trials.
PERSPECTIVE: This review highlights the role and mechanisms of complement components and their receptors in physiological and pathological pain. The potential of complement-targeted therapeutics for the treatment of chronic pain is also explored with a focus on C5a inhibitors to help guide future clinical trials.

Identifying microRNAs Possibly Implicated in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Fibromyalgia: A Review.
Tsamou M, Kremers FAC, Samaritakis KA, Roggen EL.
Int J Mol Sci. 2024 Sep 3;25(17):9551. doi: 10.3390/ijms25179551. PMID: 39273498; PMCID: PMC11395538.

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and fibromyalgia (FM) are chronic syndromes of unknown etiology, accompanied by numerous symptoms affecting neurological and physical conditions. Despite frequent revisions of the diagnostic criteria, clinical practice guidelines are often outdated, leading to underdiagnosis and ineffective treatment. Our aim was to identify microRNA (miRNA) biomarkers implicated in pathological mechanisms underlying these diseases. A comprehensive literature review using publicly accessible databases was conducted. Interesting miRNAs were extracted from relevant publications on ME/CFS and/or FM, and were then linked to pathophysiological processes possibly manifesting these chronic diseases. Dysregulated miRNAs in ME/CFS and FM may serve as promising biomarkers for these diseases. Key identified miRNAs, such as miR-29c, miR-99b, miR-128, miR-374b, and miR-766, were frequently mentioned for their roles in immune response, mitochondrial dysfunction, oxidative stress, and central sensitization, while miR-23a, miR-103, miR-152, and miR-320 were implicated in multiple crucial pathological processes for FM and/or ME/CFS. In summary, both ME/CFS and FM seem to share many dysregulated biological or molecular processes, which may contribute to their commonly shared symptoms. This miRNA-based approach offers new angles for discovering molecular markers urgently needed for early diagnosis or therapeutics to tackle the pathology of these medically unexplained chronic diseases.

Structural MRI findings in the Brain Related to Pain Distribution in Chronic Overlapping Pain Conditions: An Explorative Case-control Study in Females with Fibromyalgia, Temporomandibular Disorder-related Chronic Pain and Pain-free Controls.
Lam J, Mårtensson J, Westergren H, Svensson P, Sundgren PC, Alstergren P.
J Oral Rehabil. 2024 Nov;51(11):2415-2426. doi: 10.1111/joor.13842. Epub 2024 Aug 16. PMID: 39152537.

Background: Few neuroimaging studies have investigated structural brain differences associated with variations in pain distribution.
Objective: To explore structural differences of the brain in fibromyalgia (FM), temporomandibular disorder pain (TMD) and healthy pain-free controls (CON) using structural and diffusion MRI.
Methods: A case-control exploratory study with three study groups with different pain

distribution were recruited: FM (n = 16; mean age [standard deviation]: 44 [14] years), TMD (n = 17, 39 [14] years) and CON (n = 10, 37 [14] years). Participants were recruited at the University Dental Clinic in Malmö, Sweden. T1-weighted and diffusion MRIs were acquired, clinical and psychosocial measures were obtained. Main outcome measures were subcortical volume, cortical thickness, white matter microstructure and whole brain grey matter intensity.
Results: Patients with FM had smaller volume in the right thalamus than patients with TMD (p = .020) and CON (p = .030). The right thalamus volume was negatively correlated to pain intensity (r = -0.37, p = .022) and pain-related disability (r = -0.45, p = .004). The FM group had lower cortical thickness in the right anterior prefrontal cortex than CON (p = .005). Cortical thickness in this area was negatively correlated to pain intensity (r [37] = - 0.48, p = .002).
Conclusions: This study suggests that thalamus grey matter alterations are associated with FM and TMD, and that anterior prefrontal cortex grey matter alterations are associated with FM but not TMD. Studies on chronic overlapping pain conditions are needed in relation to possible nociplastic pain mechanisms in the brain and central nervous system.

Nociplastic Pain Mechanisms and Toll-like Receptors as Promising Targets for its Management.
Rodríguez-Palma EJ, Huerta de la Cruz S, Islas-Espinoza AM, Castañeda-Corral G, Granados-Soto V, Khanna R.
Pain. 2024 Oct 1;165(10):2150-2164. doi: 10.1097/j.pain.0000000000003238. Epub 2024 Apr 5. PMID: 38595206.

Nociplastic pain, characterized by abnormal pain processing without an identifiable organic cause, affects a significant portion of the global population. Unfortunately, current pharmacological treatments for this condition often prove ineffective, prompting the need to explore new potential targets for inducing analgesic effects in patients with nociplastic pain. In this context, toll-like receptors (TLRs), known for their role in the immune response to infections, represent promising opportunities for pharmacological intervention because they play a relevant role in both the development and maintenance of pain. Although TLRs have been extensively studied in neuropathic and inflammatory pain, their specific contributions to nociplastic pain remain less clear, demanding further investigation. This review consolidates current evidence on the connection between TLRs and nociplastic pain, with a specific focus on prevalent conditions like fibromyalgia, stress-induced pain, sleep deprivation-related pain, and irritable bowel syndrome. In addition, we explore the association between nociplastic pain and psychiatric comorbidities, proposing that modulating TLRs can potentially alleviate both pain syndromes and related psychiatric disorders. Finally, we discuss the potential sex differences in TLR signaling, considering the higher prevalence of nociplastic pain among women. Altogether, this review aims to shed light on nociplastic pain, its underlying mechanisms, and its intriguing relationship with TLR signaling pathways, ultimately framing the potential therapeutic role of TLRs in addressing this challenging condition.

Investigating the Overlapping Presentation of Irritable Bowel Syndrome and Vulvodynia: A Scoping Review of the Evidence and Mechanisms.
Perelmuter S, Soogoor A, Maliszewski K, Grimshaw A.
Sex Med Rev. 2024 Sep 25;12(4):559-568. doi: 10.1093/sxmrev/qeae053. PMID: 39084679.

Introduction: Vulvodynia is a complex and multifactorial medical condition characterized by pain in the vulvar area without any identifiable cause. Vulvodynia is underdiagnosed, leading to increased risk of sexual dysfunction and reduced quality of life. Irritable bowel syndrome (IBS) is a gastrointestinal disorder predominantly affecting women. Vulvodynia and IBS frequently co-occur in women, with a 2- to 4-fold increased likelihood of IBS diagnosis in those with vulvodynia. These conditions may share underlying causes, highlighting the need for research to better understand their shared pathophysiology and develop effective therapeutics.
Objective: The aim of this scoping review was to assess the evidence of simultaneous presentation of IBS and vulvodynia.
Methods: A comprehensive search was conducted in 6 databases between inception of database and August 2023: PubMed, Web of Science, Scopus, Science Direct, Google Scholar, and Cochrane Library. Studies included primary research about IBS and vulvodynia in terms of presentation overlap, diagnosis, or treatment. Data were extracted

from eligible studies, summarized, and collated.
Results: Of the 306 unique articles identified, 33 were included in the final analysis: 20 cross-sectional studies, 4 case-control studies, 2 case reports, 4 cohort studies, 2 quasi-experimental studies, and 1 randomized trial. Common themes included a high prevalence of overlapping vulvodynia and IBS with a significant diagnostic delay in vulvodynia, mast cell involvement and visceral hypersensitization as common pathophysiology, and the need for a multimodal treatment.
Conclusion: Our review adds to the evidence that there is an association between vulvodynia and IBS. Despite this, research on the underlying molecular mechanisms of this association is scarce, and diagnostic delays persist for vulvodynia. Increasing awareness of the overlap of these conditions will improve screening for vulvodynia in the patient population with IBS, thereby improving the diagnostic delay, and understanding the pathophysiology will enable treatment strategies that address both conditions.

Sensory Profiles Predict Symptoms of Central Sensitization in Low Back Pain: A Predictive Model Research Study.
Gräper PJ, Scafoglieri A, Clark JR, Hallegraeff JM.
J Clin Med. 2024 Aug 9;13(16):4677. doi: 10.3390/jcm13164677. PMID: 39200819; PMCID: PMC11355633.

Background: Acute low back pain has a high prevalence, and when persisting into chronicity, it results in enormous socio-economic consequences. Sensory preferences may be key factors in predicting central sensitization as the main mechanism of nociplastic pain and chronicity.
Objectives: Build a model to predict central sensitization symptoms using sensory profiles based on the PROGRESS framework.
Methods: A Prognostic Model Research study was carried out to predict central sensitization symptoms at 12 weeks, using baseline sensory profiles, based on 114 patients with acute low back pain. Independent variables were sensory profiles, state and trait anxiety, age, duration, pain severity, depressive symptoms, and pain catastrophizing.
Results: This model, based on continuous data, significantly predicts central sensitization symptoms at 12 weeks. It contains two significantly contributing variables: sensory profile Sensory Sensitive (unstandardized B-value = 0.42; $p = 0.01$) and trait anxiety (unstandardized B-value = 0.53; $p \leq 0.001$). The model has a predictive value of $R^2 = 0.38$.
Conclusions: This model significantly predicts central sensitization symptoms based on sensory profile Sensory Sensitive and trait anxiety. This model may be a useful tool to intervene in a bottom-up and top-down approaches to prevent chronicity in clinical practice, including individual sensory preferences and behavioral responses to sensory stimulation in rehabilitation strategies.

Nociplastic Pain in Axial Spondyloarthritis and Psoriatic Arthritis: Role of JAK Kinases in Immunopathology and Therapeutic Impact of JAK Inhibitors.
Horbal N, Maksymowych WP.
Expert Rev Clin Immunol. 2024 Sep 8:1-16. doi: 10.1080/1744666X.2024.2400294. Epub ahead of print. PMID: 39225245.

Introduction: Pain in both peripheral and axial joints is a major symptom in patients with psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA). Emerging evidence demonstrates pain mechanisms, beyond those related to inflammation or joint damage, based on aberrant processing of nociceptive stimuli peripherally as well as centrally. The Janus kinase/signal transducers and activators of transcription (JAK-STAT) signaling pathway has been implicated in the processing of pain beyond its role in mediating inflammation and inhibitors of this pathway approved for the treatment of axSpA and PsA have been shown to alleviate a broad array of pain outcomes in both axial and peripheral joints.
Areas covered: We review recent definitions and standardization of the nomenclature for categorizing chronic pain according to causality, assessment tools to evaluate nociplastic pain, the pathophysiologic role of JAK-STAT signaling in nociplastic pain, evidence for the presence of nociplastic pain in axSpA and PsA, and the impact of JAK inhibitors (JAKi) on pain outcomes in clinical trials (PubMed: 01/01/2019-04/01-2024).
Expert opinion: Nociplastic pain assessment has been confined almost entirely to the use of a limited number of questionnaires in cross-sectional studies of these diseases. Though effective for alleviating pain, it is unclear if JAKi specifically impact nociplastic pain.

Connecting the Dots: Network Structures of Internalizing and Functional Symptoms in a Population-Based Cohort.

Saini U, Rosmalen JGM, Oldehinkel AJ, van Loo HM.

J Psychosom Res. 2024 Dec;187:111932. doi: 10.1016/j.jpsychores.2024.111932. Epub 2024 Sep 13. PMID: 39298869.

Objective: Comorbidities between internalizing disorders (IDs) and functional disorders (FDs) are well-documented, indicating shared pathways. However, their symptom-level relationships have been largely unexplored. This exploratory study employs a network approach to investigate symptoms of major depressive disorder (MDD), generalized anxiety disorder (GAD), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), fibromyalgia (FM), and irritable bowel syndrome (IBS) to identify bridge symptoms explaining comorbidity between the two domains.
Methods: We used cross-sectional data on 72,919 adult subjects from the Lifelines Cohort Study, a Dutch general population sample. A total of 38 symptoms representing diagnostic criteria of IDs and FDs were assessed with validated questionnaires. Network models were estimated using eLasso, based on the Ising model, to identify bridge symptoms. The Network Comparison Test (NCT) was used to test whether there were differences in network structure and strength across sex and age.
Results: Symptoms were moderately connected, with a network density of 52.7%. ID and FD symptoms clustered in their respective domains, but were connected through the bridge symptoms, fatigue, difficulty concentrating, trouble sleeping, and unrefreshing sleep. Fatigue and difficulty concentrating had the most connections, associated with 86.6% and 78.9% of the other symptoms, respectively. NCTs indicated no differences in network connectivity between females versus males or younger versus older adults (>50 years).
Conclusions: ID and FD symptoms are moderately interconnected. Bridge symptoms displaying strong connections to multiple disorders may play a central role in the mechanisms underpinning the comorbidity between IDs and FDs.

Associations Between Endogenous Sex Hormones and Multisite Chronic Musculoskeletal Pain.

Kifle ZD, Tian J, Aitken D, Melton PE, Cicuttini F, Jones G, Pan F.

Br J Anaesth. 2024 Dec 19:S0007-0912(24)00698-6. doi: 10.1016/j.bja.2024.11.021. Epub ahead of print. PMID: 39706703.

Background: Sex-differences in pain perception have been documented; however, the role of sex hormones in chronic musculoskeletal pain (CMP) remains unclear. Therefore, this study investigated whether sex hormones and sex hormone-binding globulin (SHBG) are associated with CMP.
Methods: We utilised data from the UK Biobank (n=357 424; females: 51.6%; white: 95.2%). Serum concentrations of oestradiol (E2), testosterone (T), and SHBG were measured at baseline. Chronic pain (≥3 months) in the neck/shoulder, back, hip, knee, or 'all over the body' was assessed at baseline and three follow-ups. Mixed-effects multinomial/logistic regression models were used.
Results: In multivariable analyses, greater concentrations of T and T/SHBG were associated with a lower number of CMP sites in both males (T: relative risk ratio=0.81 per standard deviation, 95% confidence interval [0.77-0.86] and T/SHBG: 0.85 [0.80-0.92]) and females (T: 0.85 [0.81-0.89] and T/SHBG: 0.93 [0.89-0.97] [all P-values for trend ≤0.001]). Greater T concentrations and T/SHBG were also associated with lower odds of CMP across all sites, while higher concentrations of SHBG were associated with lower odds of neck/shoulder CMP in both sexes. There was no association between concentrations of E2, SHBG, or E2/SHBG and number of CMP or site-specific CMP in either sex.
Conclusion: In both sexes, greater T concentrations and T/SHBG were associated with lower number of CMP sites and site-specific CMP, while greater concentrations of SHBG were linked to lower odds of neck/shoulder CMP. These findings suggest a potential involvement of sex steroids in the pathogenesis of CMP and underscore the need for further investigation into their potential in chronic pain management strategies.

Sex Differences in Functional and Structural Alterations of Hippocampus Region in Chronic Pain: A DTI and Resting-state fMRI Study.

Zhou JZ, Deng J, Luo DX, Mai JW, Wu JY, Duan YJ, Dong B, Xin WJ, Xu T, Wei JY.

Front Neurosci. 2024 Sep 6;18:1428666. doi: 10.3389/fnins.2024.1428666. PMID: 39308951; PMCID: PMC11412943.

Introduction: It is well known that there are significant differences in the prevalence of chronic pain between males and females. Human and animal imaging studies have shown that chronic pain profoundly alters the structure and function of brain regions. However, there is limited research on the sex-specific mechanisms underlying the brain plasticity and adaptive changes associated with chronic pain. In this article, we conducted a multimodal study to evaluate how nerve injury-induced chronic pain affects the brain.
Methods: Male and female Sprague-Dawley (SD) rats with spared nerve injury (SNI) model underwent resting-state functional magnetic resonance imaging (rs-fMRI) (male sham group: n = 18; male SNI group: n = 18; female sham group: n = 20; female SNI group: n = 18) and magnetic resonance diffusion tensor imaging (DTI) (male sham group: n = 23; male SNI group: n = 21; female sham group: n = 20; female SNI group: n = 21) scanning. ICA method, Fractional amplitude of low-frequency fluctuations (fALFF), immunofluorescence staining, and graph theory analysis was utilized to extract the rs-fMRI changes of brain regions of each group.
Results: Using SNI model, which promotes long-lasting mechanical allodynia, we found that neuropathic pain deeply modified the intrinsic organization of the brain functional network in male and female rats (main effect of operation: F = 298.449, P < 0.001). 64 independent components (ICs) in the brain were divided and assigned to 16 systems. In male rats, we observed significant alterations in the microstructure of the hippocampal cornu ammonis 1 and cornu ammonis 2 (CA1/CA2) region, as indicated by increased mean diffusivity (MD) (CA1_L: P = 0.02; CA1_R: P = 0.031; CA2_L: P = 0.035; CA2_R: P = 0.015) and radial diffusivity (RD) (CA1_L: P = 0.028; CA1_R: P = 0.033; CA2_L: P = 0.037; CA2_R: P = 0.038) values, along with enhanced activating transcription factor 3 (ATF3) expression. Conversely, in female rats, we found significant increases in the fractional amplitude of low frequency fluctuations (fALFF) value within the hippocampal dentate gyrus (DG) (F = 5.419, P = 0.023), accompanied by elevated c-Fos signal (F = 6.269, P = 0.031). Furthermore, graph theory analysis revealed notable differences in the small-world network of the hippocampal system in female rats, characterized by reduced small-world attributes and increased inter-nodal transmission efficiency.
Discussion: Our study indicates sex differences in structural and functional alterations in the hippocampal system in rats under chronic pain conditions. The results suggest that the hippocampus system plays an important role in the different mechanisms of chronic pain in different sexes. These findings provide reliable insights to explore the complex mechanisms underlying sex differences in chronic pain.

Comparison of the Symptom Networks of Long-COVID and Chronic Fatigue Syndrome: From Modularity to Connectionism.

Hyland ME, Antonacci Y, Bacon AM.
Scand J Psychol. 2024 Dec;65(6):1132-1140. doi: 10.1111/sjop.13060. Epub 2024 Jul 21.
PMID: 39034480.

The objective was to compare the symptom networks of long-COVID and chronic fatigue syndrome (CFS) in conjunction with other theoretically relevant diagnoses in order to provide insight into the etiology of medically unexplained symptoms (MUS). This was a cross-sectional comparison of questionnaire items between six groups identified by clinical diagnosis. All participants completed a 65-item psychological and somatic symptom questionnaire (GSQ065). Diagnostically labelled groups were long-COVID (N = 107), CFS (N = 254), irritable bowel syndrome (IBS, N = 369), fibromyalgia (N = 1,127), severe asthma (N = 100) and healthy group (N = 207). The 22 symptoms that best discriminated between the six groups were selected for network analysis. Connectivity, fragmentation and number of symptom clusters (statistically related symptoms) were assessed. Compared to long-COVID, the symptom networks of CFS, IBS and fibromyalgia had significantly lower connectivity, greater fragmentation and more symptom clusters. The number of clusters varied between 9 for CFS and 3 for severe asthma, and the content of clusters varied across all groups. Of the 33 symptom clusters identified over the six groups 30 clusters were unique. Although the symptom networks of long-COVID and CFS differ, the variation of cluster content across the six groups is inconsistent with a modular causal structure but consistent with a connectionist (network, parallel distributed processing) biological basis of MUS. A connectionist structure would explain why symptoms overlap and merge between different functional somatic syndromes, the failure to discover a biological diagnostic test and how psychological and behavioral interventions are therapeutic.

Induction of Orofacial Pain Potentiates Fibromyalgia Symptoms in Mice: Relevance of Nociceptin System.

Volkweis MCC, Tomasi LA, Santos GC, Dagnino APA, Estrázulas M, Campos MM.
Life Sci. 2024 Dec 1;358:123183. doi: 10.1016/j.lfs.2024.123183. Epub 2024 Oct 28. PMID: 39471900.

Aims: Fibromyalgia patients might experience temporomandibular disorder (TMD) as a comorbidity. However, the connection between these two syndromes is not fully understood. Nociceptin (N/OFQ) and NOP receptors are implicated in both conditions, but their relevance in the comorbidity needs investigation. This study featured a comorbidity model of fibromyalgia plus TMD in mice, attempting to evaluate the significance of the N/OFQ-NOP receptor in this paradigm.
Materials and methods: Female CF-1 mice were submitted to the fibromyalgia model induced by three daily consecutive injections of reserpine (0.25 mg/kg) and received an intra-masseter injection of complete Freund's adjuvant (CFA; 10 µl; diluted 1:1) on day four.
Key findings: There was a rise in nocifensive and depression-like behaviors in the comorbidity group, as evaluated by the Grimace scores and the tail suspension test (TST). This group displayed anxiogenic-like effects in the hole board and the elevated plus maze tests. The comorbidity group showed an increment of c-Fos immunopositivity in the ipsilateral side of CFA injection, in the trigeminal ganglion (TG) and thalamus. The administration of N/OFQ (1 nmol/kg, i.p.) boosted the Grimace scores in the comorbidity group, with no effect for the NOP receptor antagonist UFP-101 (1 nmol/kg, i.p.). Either NOP ligand failed to alter depression or anxiety behavioral changes. Alternatively, pregabalin (30 mg/kg; i.p.) reduced the nociceptive responses and the number of head dips in the hole board.
Significance: Data reveal new evidence suggesting that inducing TMD with CFA may worsen fibromyalgia symptoms in reserpine-treated mice, an effect partially regulated by systemic N/OFQ.

Up-regulation of IL-1β and sPLA2-III in the Medial Prefrontal Cortex Contributes to Orofacial and Somatic Hyperalgesia Induced by Malocclusion via Glial-neuron Crosstalk.
Feng HN, Zhong LQ, Xu CX, Wang TT, Wu H, Wang L, Traub RJ, Chen X, Cao DY.
Eur J Pharmacol. 2024 Nov 5;982:176933. doi: 10.1016/j.ejphar.2024.176933. Epub 2024 Aug 23. PMID: 39182540.

The medial prefrontal cortex (mPFC) has been identified as a key brain region involved in the modulation of chronic pain. Our recent study demonstrated that unilateral anterior crossbite (UAC) developed the comorbidity model of temporomandibular disorders (TMD) and fibromyalgia syndrome (FMS), which was characterized by both orofacial and somatic hyperalgesia. In the present study, UAC rats exhibited significant changes in gene expression in the mPFC. Enrichment analysis revealed that the significantly involved pathways were cytokines-cytokine receptor interaction and immune response. The expression of group III secretory phospholipase A2 (sPLA2-III) was significantly increased in the mPFC of UAC rats. Silencing sPLA2-III expression in the mPFC blocked the orofacial and somatic hyperalgesia. Immunofluorescence showed that sPLA2-III was mainly localized in neurons. The expression of interleukin-1β (IL-1β) in the mPFC significantly increased after UAC. Injection of IL-1β antibody into the mPFC blocked orofacial and somatic hyperalgesia. IL-1β was mainly localized in microglia cells. Furthermore, injection of IL-1β antibody significantly reduced the expression of sPLA2-III. These results indicate that neuroinflammatory cascade responses induced by glial-neuron crosstalk in the mPFC may contribute to the development of TMD and FMS comorbidity, and IL-1β and sPLA2-III are identified as novel potential therapeutic targets for the treatment of chronic pain in the comorbidity of TMD and FMS.

Predictive and Concurrent Validity of Pain Sensitivity Phenotype, Neuropeptidomics and Neuroepigenetics in the MI-RAT Osteoarthritic Surgical Model in Rats.
Otis C, Cristofanilli KA, Frezier M, Delsart A, Martel-Pelletier J, Pelletier JP, Beaudry F, Lussier B, Boyer A, Troncy E.
Front Cell Dev Biol. 2024 Aug 8;12:1400650. doi: 10.3389/fcell.2024.1400650. PMID: 39175874; PMCID: PMC11338919.

Background: Micro-RNAs could provide great insights about the neuropathological mechanisms associated with osteoarthritis (OA) pain processing. Using the validated *M*ontreal *I*nduction of *R*at *A*rthritis *T*esting (MI-RAT) model, this study aimed to characterize neuroepigenetic markers susceptible to correlate with innovative pain

functional phenotype and targeted neuropeptide alterations.
Methods: Functional biomechanical, somatosensory sensitization (peripheral-via tactile paw withdrawal threshold; central-via response to mechanical temporal summation), and diffuse noxious inhibitory control (via conditioned pain modulation) alterations were assessed sequentially in OA (n = 12) and Naïve (n = 12) rats. Joint structural, targeted spinal neuropeptides and differential expression of spinal cord micro-RNAs analyses were conducted at the sacrifice (day (D) 56).
Results: The MI-RAT model caused important structural damages (reaching 35.77% of cartilage surface) compared to the Naïve group ($P < 0.001$). This was concomitantly associated with nociceptive sensitization: ipsilateral weight shift to the contralateral hind limb (asymmetry index) from -55.61% ± 8.50% (D7) to -26.29% ± 8.50% (D35) ($P < 0.0001$); mechanical pain hypersensitivity was present as soon as D7 and persisting until D56 ($P < 0.008$); central sensitization was evident at D21 ($P = 0.038$); pain endogenous inhibitory control was distinguished with higher conditioned pain modulation rate ($P < 0.05$) at D7, D21, and D35 as a reflect of filtrated pain perception. Somatosensory profile alterations of OA rats were translated in a persistent elevation of pro-nociceptive neuropeptides substance P and bradykinin, along with an increased expression of spinal miR-181b ($P = 0.029$) at D56.
Conclusion: The MI-RAT OA model is associated, not only with structural lesions and static weight-bearing alterations, but also with a somatosensory profile that encompasses pain centralized sensitization, associated to active endogenous inhibitory/facilitatory controls, and corresponding neuropeptidomic and neuroepigenetic alterations. This preliminary neuroepigenetic research confirms the crucial role of pain endogenous inhibitory control in the development of OA chronic pain (not only hypersensitivity) and validates the MI-RAT model for its study.

Parabrachial Neurons Promote Nociplastic Pain.
Palmiter RD.
Trends Neurosci. 2024 Sep;47(9):722-735. doi: 10.1016/j.tins.2024.07.002. Epub 2024 Aug 14. PMID: 39147688.

The parabrachial nucleus (PBN) in the dorsal pons responds to bodily threats and transmits alarm signals to the forebrain. Parabrachial neuron activity is enhanced during chronic pain, and inactivation of PBN neurons in mice prevents the establishment of neuropathic, chronic pain symptoms. Chemogenetic or optogenetic activation of all glutamatergic neurons in the PBN, or just the subpopulation that expresses the Calca gene, is sufficient to establish pain phenotypes, including long-lasting tactile allodynia, that scale with the extent of stimulation, thereby promoting nociplastic pain, defined as diffuse pain without tissue inflammation or nerve injury. This review focuses on the role(s) of molecularly defined PBN neurons and the downstream nodes in the brain that contribute to establishing nociplastic pain.

CLINICAL STUDIES

Pain Can't be Carved at the Joints: Defining Function-Based Pain Profiles and Their Relevance to Chronic Disease Management in Healthcare Delivery Design.
Barron DS, Saltoun K, Kiesow H, Fu M, Cohen-Tanugi J, Geha P, Scheinost D, Isaac Z, Silbersweig D, Bzdok D.
BMC Med. 2024 Dec 18;22(1):594. doi: 10.1186/s12916-024-03807-z. PMID: 39696368; PMCID: PMC11656997.

Background: Pain is a complex problem that is triaged, diagnosed, treated, and billed based on which body part is painful, almost without exception. While the "body part framework" guides the organization and treatment of individual patients' pain conditions, it remains unclear how to best conceptualize, study, and treat pain conditions at the population level. Here, we investigate (1) how the body part framework agrees with population-level, biologically derived pain profiles; (2) how do data-derived pain profiles interface with other symptom domains from a whole-body perspective; and (3) whether biologically derived pain profiles capture clinically salient differences in medical history.
Methods: To understand how pain conditions might be best organized, we applied a carefully designed multi-variate pattern-learning approach to a subset of the UK Biobank (n = 34,337), the largest publicly available set of real-world pain experience data to define common population-level profiles. We performed a series of post hoc analyses to validate

that each pain profile reflects real-world, clinically relevant differences in patient function by probing associations of each profile across 137 medication categories, 1425 clinician-assigned ICD codes, and 757 expert-curated phenotypes.
Results: We report four unique, biologically based pain profiles that cut across medical specialties: pain interference, depression, medical pain, and anxiety, each representing different facets of functional impairment. Importantly, these profiles do not specifically align with variables believed to be important to the standard pain evaluation, namely painful body part, pain intensity, sex, or BMI. Correlations with individual-level clinical histories reveal that our pain profiles are largely associated with clinical variables and treatments of modifiable, chronic diseases, rather than with specific body parts. Across profiles, notable differences include opioids being associated only with the pain interference profile, while antidepressants linked to the three complimentary profiles. We further provide evidence that our pain profiles offer valuable, additional insights into patients' wellbeing that are not captured by the body-part framework and make recommendations for how our pain profiles might sculpt the future design of healthcare delivery systems.
Conclusion: Overall, we provide evidence for a shift in pain medicine delivery systems from the conventional, body-part-based approach to one anchored in the pain experience and holistic profiles of patient function. This transition facilitates a more comprehensive management of chronic diseases, wherein pain treatment is integrated into broader health strategies. By focusing on holistic patient profiles, our approach not only addresses pain symptoms but also supports the management of underlying chronic conditions, thereby enhancing patient outcomes and improving quality of life. This model advocates for a seamless integration of pain management within the continuum of care for chronic diseases, emphasizing the importance of understanding and treating the interdependencies between chronic conditions and pain.

Clinical Pain Management: Current Practice and Recent Innovations in Research.
Wang J, Doan LV.
Cell Rep Med. 2024 Oct 15;5(10):101786. doi: 10.1016/j.xcrm.2024.101786. Epub 2024 Oct 8. PMID: 39383871; PMCID: PMC11513809.

Chronic pain affects one in five adults. It is not only a major cause of disability for individual patients but also a driver of costs for entire healthcare systems. Treatment of pain remains a challenge, and the use of opioids has further led to a concurrent opioid epidemic. In this review, we discuss current standard treatment options for chronic pain, including pharmacological, behavioral, and interventional treatments. In addition, we review ongoing research in different areas that will potentially unlock new therapies.

Non-Opioid Psychiatric Medications for Chronic Pain: Systematic Review and Meta-analysis.
Ayub S, Bachu AK, Jain L, Parnia S, Bhivandkar S, Ahmed R, Kaur J, Karlapati S, Prasad S, Kochhar H, Ayisire OE, Mitra S, Ghosh B, Srinivas S, Ashraf S, Papudesi BN, Malo PK, Sheikh S, Hsu M, De Berardis D, Ahmed S.
Front Pain Res (Lausanne). 2024 Oct 10;5:1398442. doi: 10.3389/fpain.2024.1398442. PMID: 39449766; PMCID: PMC11499177.

Background: The escalating number of deaths related to opioid usage has intensified the pursuit of non-opioid alternatives for managing chronic pain. It's often observed that psychiatric comorbidities coexist in patients suffering from chronic pain. There are a variety of psychotropic medications that have demonstrated effectiveness in treating both psychiatric symptoms and pain. This systematic review and meta-analysis aim to assess the effectiveness of various psychiatric drugs in managing specific types of chronic pain, including fibromyalgia, neuropathic pain, and chronic low back pain.
Methods: A comprehensive search of five major databases was conducted through February 2023 to identify randomized controlled trials (RCTs) that met our inclusion criteria, focusing on outpatients Over 18 years of age with chronic pain. The study assessed the effectiveness of duloxetine, mirogabalin, pregabalin, gabapentin, and tricyclic antidepressants (TCAs), including serotonin-norepinephrine reuptake inhibitors (SNRIs), across various chronic pain conditions such as fibromyalgia, neuropathic pain, and chronic low back pain. The primary outcome measures included pain reduction, improvement in function, and quality of life. Of the 29 RCTs in the systematic review, 20 studies qualified for the meta-analysis. The analysis was stratified by pain type and treatment duration (short-term ≤14 weeks vs. long-term >14 weeks), using Hedge's g standardized mean differences and a random-effects model, along with sensitivity and subgroup analyses.

Results: The overall short-term intervention effect across all studies was significant (SMD −1.45, 95% CI −2.15 to −0.75, $p < 0.001$), with considerable heterogeneity ($I^2 = 99\%$). For fibromyalgia, both duloxetine and mirogabalin demonstrated substantial efficacy with SMDs of −2.42 (95% CI −3.67 to −1.18, $p < 0.0001$) and −2.10 (95% CI −3.28 to −0.92, $p = 0.0005$), respectively. Conversely, treatments for neuropathic pain and chronic low back pain, including those with amitriptyline and desipramine, did not show significant benefits. The effectiveness of gabapentin could not be conclusively determined due to limited representation in the data. Additionally, no consistent long-term benefits were observed for any of the medications.
Conclusions: While the results of this study underscore the importance of exploring non-opioid alternatives for chronic pain management, particularly in light of the opioid crisis, it is crucial to interpret the findings carefully. Our analysis suggests that certain psychiatric medications, such Duloxetine and mirogabalin demonstrated significant short-term efficacy in fibromyalgia patients. However, their effectiveness in treating neuropathic pain and chronic low back pain was not statistically significant. Additionally, the effectiveness of gabapentin and other medications, such as pregabalin for neuropathic pain, could not be conclusively determined due to limited data and high study heterogeneity. No consistent long-term benefits were observed for any of the drugs studied, raising questions about their sustained efficacy in chronic pain management. These findings highlight the need for further research to understand better the role of psychiatric medications in managing specific chronic pain conditions without prematurely concluding that they are ineffective or unsuitable for these purposes.

Widespread Pain Phenotypes Impact Treatment Efficacy Results in Randomized Clinical Trials for Interstitial Cystitis/Bladder Pain Syndrome: A Multidisciplinary Approach to the Study of Chronic Pelvic Pain Network Study.
Farrar JT, Locke KT Jr, Clemens JQ, Griffith JW, Harte SE, Kirkali Z, Kreder KJ, Krieger JN, Lai HH, Moldwin RM, Mullins C, Naliboff BD, Pontari MA, Rodríguez LV, Schaeffer AJ, Schrepf A, Stephens-Shields A, Sutcliffe S, Taple BJ, Williams DA, Landis JR.
Pain. 2024 Nov 5. doi: 10.1097/j.pain.0000000000003455. Epub ahead of print. PMID: 39499552.

Pain clinical trials are notoriously complex and often inefficient in demonstrating efficacy, even for known efficacious treatments. A major issue is the difficulty in the a priori identification of specific phenotypes to include in the study population. Recent work has identified the extent of widespread pain as an important determinant of the likelihood of response to therapy, but it has not been tested in clinical trials for the treatment of interstitial cystitis/bladder pain syndrome (IC/BPS). We explored this hypothesis using data from 3 previously published trials testing treatments for IC/BPS, which suggested modest benefits but did not meet a priori primary outcome statistical significance criteria. Importantly, these studies also collected symptom questionnaire data that allowed us to retrospectively identify participants with and without widespread pain. Analyzing the treatment by the degree of widespread pain revealed a difference in outcome and statistical significance level for each trial. Participants with predominately local pain (ie, limited widespread pain symptoms) responded to therapy targeting local symptoms, whereas those with widespread pain did not. Alternatively, participants with widespread pain beyond their local pelvic pain responded to more centrally acting treatments. Our results suggest that differentiating patients based on widespread vs more localized pain is a key consideration for designing future clinical trials for conditions with variable pain profiles, such as IC/BPS and potentially other pain-based syndromic disorders.

Relationship of Sex and Diagnosis with Symptoms and Illness Impact in Urologic Chronic Pelvic Pain; A Mapp Network Analysis.
Naliboff BD, McWilliams T, Clemens JQ, Pontari MA, Stephens-Shields AJ, Moldwin R, Sutcliffe S, Mullins C, Landis JR.
Neurourol Urodyn. 2024 Dec 20. doi: 10.1002/nau.25648. Epub ahead of print. PMID: 39704257.

Objective: To assess differences in clinical presentation and illness impact in men and women presenting with urologic chronic pelvic pain syndrome (UCPPS) and between men diagnosed with interstitial cystitis/bladder pain syndrome (IC/BPS) or chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).
Methods: 356 men and 605 women from six sites across the United States were assessed using a comprehensive set of demographic, symptom, and illness impact measures.

Multivariable regression analyses examined differences between men and women and between men previously diagnosed with CP/CPPS or IC/BPS. In a stepwise manner, analyses tested group differences, controlling for demographic variables including symptom duration and presence of bladder pain that varied with filling and voiding.
Results: Men diagnosed with IC/BPS had the most severe UCPPS symptoms, followed by women with IC/BPS, and then men with CP/CPPS only. While men and women showed similar patterns of symptoms across most of the variables, women had increased widespread non-pelvic pain, greater pelvic floor tenderness on exam, and higher self-reported sensory sensitivity compared to men. About 60% of men diagnosed with CP/CPPS only reported bladder symptoms of painful filling or relief with voiding.
Conclusions: A generally shared symptom pattern was found across men and women irrespective of diagnostic labels suggesting the use of key marker symptoms, such as severity of bladder symptoms and widespread pain, to better identify subgroups of UCPPS rather than diagnostic category. Women may have an increased likelihood of increased sensitivity and central sensitization than men, including those men with IC/BPS.

Disease Phenotypes in Refractory Musculoskeletal Pain Syndromes Identified by Unsupervised Machine Learning.
Hügle T, Prétat T, Suter M, Lovejoy C, Ming Azevedo P.
ACR Open Rheumatol. 2024 Nov;6(11):790-798. doi: 10.1002/acr2.11699. Epub 2024 Aug 29. PMID: 39210607; PMCID: PMC11557993.

Objective: Overlapping chronic pain syndromes, including fibromyalgia, are heterogeneous and often treatment-resistant entities carrying significant socioeconomic burdens. Individualized treatment approaches from both a somatic and psychological side are necessary to improve patient care. The objective of this study was to identify and visualize patient clusters in refractory musculoskeletal pain syndromes through an extensive set of clinical variables, including immunologic, psychosomatic, wearable, and sleep biomarkers.
Methods: Data were collected during a multimodal pain program involving 202 patients. Seventy-eight percent of the patients fulfilled the criteria for fibromyalgia, 77% had a concomitant psychiatric-mediated disorder, and 22% a concomitant rheumatic immune-mediated disorder. Five patient phenotypes were identified by hierarchical agglomerative clustering as a form of unsupervised learning, and a predictive model for the Brief Pain Inventory (BPI) response was generated. Based on the clustering data, digital personas were created with DALL-E (OpenAI).
Results: The most relevant distinguishing factors among clusters were living alone, body mass index, peripheral joint pain, alexithymia, psychiatric comorbidity, childhood pain, neuroleptic or benzodiazepine medication, and response to virtual reality. Having an immune-mediated disorder was not discriminatory. Three of five clusters responded to the multimodal treatment in terms of pain (BPI intensity), one cluster responded in terms of functional improvement (BPI interference), and one cluster notably responded to the virtual reality intervention. The independent predictive model confirmed strong opioids, trazodone, neuroleptic treatment, and living alone as the most important negative predictive factors for reduced pain after the program.
Conclusion: Our model identified and visualized clinically relevant chronic musculoskeletal pain subtypes and predicted their response to multimodal treatment. Such digital personas and avatars may play a future role in the design of personalized therapeutic modalities and clinical trials.

From Fibrositis to Fibromyalgia to Nociplastic Pain: How Rheumatology Helped Get Us Here and Where Do We Go from Here?
Clauw DJ.
Ann Rheum Dis. 2024 Oct 21;83(11):1421-1427. doi: 10.1136/ard-2023-225327. PMID: 39107083; PMCID: PMC11503076.

Rheumatologists and rheumatology have had a prominent role in the conceptualisation of nociplastic pain since the prototypical nociplastic pain condition is fibromyalgia. Fibromyalgia had been previously known as fibrositis, until it became clear that this condition could be differentiatied from autoimmune disorders because of a lack of systemic inflammation and tissue damage. Nociplastic pain is now thought to be a third descriptor/mechanism of pain, in addition to nociceptive pain (pain due to peripheral damage or inflammation) and neuropathic pain. Nociplastic pain can occur in isolation, or as a co-morbidity with other mechanisms of pain, as commonly occurs in individuals with autoimmune disorders. We now know that the cardinal symptoms of nociplastic pain are

widespread pain (or pain in areas not without evidence of inflammation/damage), accompanied by fatigue, sleep and memory issues. There is objective evidence of amplification/augmentation of pain, as well as of non-painful stimuli such as the brightness of lights and unpleasantness of sound or odors. Nociplastic pain states can be triggered by a variety of stressors such as trauma, infections and chronic stressors. Together these features suggest that the central nervous system (CNS) is playing a major role in causing and maintaining nociplastic pain, but these CNS factors may in some be driven by ongoing peripheral nociceptive input. The most effective drug therapies for nociplastic pain are non-opioid centrally acting analgesics such as tricyclics, serotonin-norepinephrine reuptake inhibitors and gabapentinoids. However the mainstay of therapy of nociplastic pain is the use of a variety of non-pharmacological integrative therapies, especially those which improve activity/exercise, sleep and address psychological co-morbidities.

Application of the IASP Grading System to Identify Underlying Pain Mechanisms in Patients with Knee Osteoarthritis: A Prospective Cohort Study.
Vervullens S, Meert L, Meeus M, Heusdens CHW, Verdonk P, Foubert A, Abatih E, Durnez L, Verbrugghe J, Smeets RJEM.
2024 Oct 1;40(10):563-577. doi: 10.1097/AJP.0000000000001234. PMID: 39016267; PMCID: PMC11389887.

Objectives: This study aimed to apply the International Association for the Study of Pain (IASP) grading system for identifying nociplastic pain in knee osteoarthritis (KOA) awaiting total knee arthroplasty (TKA) and propose criteria to fine-tune decision-making. In addition, the study aimed to characterize a "probable" versus "no or possible" nociplastic pain mechanism using biopsychosocial variables and compare both groups in their 1-year post-TKA response.
Methods: A secondary analysis of baseline data of a longitudinal prospective study involving 197 patients with KOA awaiting total TKA in Belgium and the Netherlands was performed. Two approaches, one considering 4 and the other 3 pain locations (step 2 of the grading system), were presented. Linear mixed model analyses were performed to compare the probable and no or possible nociplastic pain mechanism groups for several preoperative biopsychosocial-related variables and 1-year postoperative pain. Also, a sensitivity analysis, comparing 3 pain mechanism groups, was performed.
Results: Thirty (15.22%-approach 4 pain locations) and 46 (23.35%-approach 3 pain locations) participants were categorized under probable nociplastic pain. Irrespective of the pain location approach or sensitivity analysis, the probable nociplastic pain group included more woman, was younger, exhibited worse results on various preoperative pain-related and psychological variables, and had more pain 1-year post-TKA compared with the other group.
Discussion: This study proposed additional criteria to fine-tune the grading system for nociplastic pain (except for discrete/regional/multifocal/widespread pain) and characterized a subgroup of patients with KOA with probable nociplastic pain. Future research is warranted for further validation.

Development, Validation and Use of Custom Software for the Analysis of Pain Trajectories.
van Ittersum MR, de Zoete A, Rubinstein SM, Al-Madfai H, Kongsted A, McCarthy P.
Sci Rep. 2024 Aug 12;14(1):18719. doi: 10.1038/s41598-024-69574-2. PMID: 39134589; PMCID: PMC11319648.

In chronic musculoskeletal conditions, the prognosis tends to be more informative than the diagnosis for the future course of the disease. Many studies have identified clusters of patients who seemingly share similar pain trajectories. In a dataset of low back pain (LBP) patients, pain trajectories have been identified, and distinct trajectory types have been defined, making it possible to create pattern recognition software that can classify patients into respective pain trajectories reflecting their condition. It has been suggested that the classification of pain trajectories may create clinically meaningful subgroups of patients in an otherwise heterogeneous population of patients with LBP. A software tool was created that combined the ability to recognise the pain trajectory of patients with a system that could create subgroups of patients based on their characteristics. This tool is primarily meant for researchers to analyse trends in large heterogeneous datasets without large losses of data. Prospective analysis of pain trajectories is not directly helpful for clinicians. However, the tool might aid in the identification of patient characteristics which have predictive capabilities of the most likely trajectory a patient might experience in the future. This will

help clinicians to tailor their advice and treatment for a specific patient.

Exploring the Associations of Sleep Bruxism and Obstructive Sleep Apnea with Migraine Among Patients with Temporomandibular Disorder: A Polysomnographic Study.

Błaszczyk B, Waliszewska-Prosół M, Smardz J, Więckiewicz M, Wojakowska A, Martynowicz H.

Headache. 2024 Dec 30. doi: 10.1111/head.14892. Epub ahead of print. PMID: 39740030.

Background: Migraine is the most common disabling headache disorder in the world. Temporomandibular disorders (TMDs) are a group of conditions characterized by pain/dysfunction of masticatory muscles or their associated structures. There is a lack of studies concerning the association between sleep disorders such as sleep bruxism (SB), obstructive sleep apnea (OSA), migraine, and TMD, despite the increased prevalence of these conditions in TMD patients.
Objective: Our case-control study assesses the potential relationship among SB, OSA, and migraine using polysomnography (PSG) among the group with TMD.
Methods: One hundred nineteen patients with TMD were recruited and hospitalized in the Department and Clinic of Internal Medicine, Occupational Diseases, Hypertension, and Clinical Oncology at Wroclaw Medical University. Their sleep parameters were assessed by PSG according to American Academy of Sleep Medicine guidelines. Migraine diagnosis was based on the third edition of the International Classification of Headache Disorders. The group of 30 patients with median age 35.0 years (interquartile range [IQR]: 26.0, 41.0) were diagnosed with migraine and this group consisted of 17 without aura (MwoA) and 13 with aura (MwA). Thirty patients with migraine were compared to 89 patients with TMD without migraine (controls) with median age 37.0 years (IQR: 26.0, 44.0).
Results: Sleep bruxism was detected in 86% of the migraine group and 71.9% of control participants. The median bruxism episode index (BEI) among patients with migraine was 3.8 n/h (IQR: 2.7, 5.8) and 3.5 n/h (IQR: 1.8, 6.0) in the control group. SB and severe SB (respectively, BEI > 2 and BEI > 4) were not associated with migraine (odds ratio [OR] = 2.68, 95% confidence interval [CI]: 0.84-8.55, p = 0.095; OR = 0.98, 95% CI: 0.42-2.32, p = 0.966). However, mixed bruxism episodes were more frequent in the migraine group compared to study participants not experiencing migraine (median 0.7 n/h [IQR: 0.4, 1.6] vs. median 0.5 n/h [IQR: 0.2, 0.9], p = 0.044; OR = 1.96 with 95% CI: 1.16-3.32, p = 0.013). The median average duration of SB episodes in the migraine group was longer than in the controls (7.0 s [IQR: 5.5, 8.4] vs. 5.9 s [IQR: 5.1, 6.6], p = 0.005). The apnea-hypopnea index (AHI) value was not associated with migraine compared to controls (OR = 1.01, 95% CI: 0.96-1.06, p = 0.605), but MwoA had significantly increased AHI values compared to MwA (mean AHI = -0.1, standard deviation [SD] = 1.5 for MwA vs. mean AHI = 0.9 with SD = 1.3 for MwoA, p = 0.049).
Conclusion: Sleep bruxism may not be associated with migraine among patients with TMD; however, mixed bruxism episodes were more frequent in the migraine group. The increased duration of SB episodes in patients with migraine may suggest the common background of these conditions. OSA is also not associated with migraine; however, MwoA might increase the odds of OSA. There is a need to further explore sleep disturbances and migraine, especially in groups with their increased prevalence, such as patients with TMD.

Prevalence of Central Sensitization and Somatization in Adults with Temporomandibular Disorders-A Prospective Observational Study.

Seweryn P, Waliszewska-Prosol M, Straburzynski M, Smardz J, Orzeszek S, Bombala W, Bort M, Jenca A Jr, Paradowska-Stolarz A, Wieckiewicz M.

J Oral Facial Pain Headache. 2024 Dec;38(4):33-44. doi: 10.22514/jofph.2024.037. Epub 2024 Dec 12. PMID: 39800954.

Temporomandibular disorders (TMD) comprise a group of conditions affecting the masticatory muscles, the temporomandibular joints and associated structures, often manifesting as orofacial pain and functional limitations of the mandible. Central sensitization (CS) is gaining increasing attention in research focused on pain syndromes and somatization, playing a significant role in the pain experience. This study investigates the prevalence of CS and somatization among TMD patients, analyzing their relationships with TMD diagnoses and the intensity of chronic masticatory muscle pain (MMP). A prospective observational study was conducted with 214 adult participants diagnosed with TMD, based on the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD). The Central Sensitization Inventory (CSI) and the Somatic Symptom Scale-8 (SSS-8) were

utilized to assess CS and the burden of somatic symptoms, respectively. Furthermore, the patients were assessed for MMP, and the average pain in these muscles was calculated. Statistical analysis investigated correlations between CSI and SSS-8 scores, specific TMD diagnoses and MMP intensity. Most participants did not surpass the subclinical level for CS as assessed by the CSI. Women reported higher SSS-8 scores than men, suggesting sex differences in somatic symptom reporting. No significant relationship was found between specific TMD diagnoses and levels of CS or the SSS-8. However, a significant correlation was observed between SSS-8 scores and the intensity of chronic MMP, underscoring the impact of the intensity of chronic MMP on the perception of somatic symptoms among TMD patients. Additionally, the group with subclinical levels of CS presented significantly lower SSS-8 scores than other groups. This study highlights a lower-than-expected prevalence of CS among TMD patients. Higher levels of somatization were related to higher levels of CS and greater MMP. The findings suggest that TMD management should not only address specific pain sources but also consider the broader psychosocial aspects of the disorders, especially in chronic types.

A Dual-Focus Approach for Evaluating Contributors to Chronic Pain: The Roles of Psychosocial Risk and Resilience Factors.
Wilson JM, Steinhilber K, Yamin JB, Edwards RR, Meints SM.
Curr Opin Psychol. 2024 Dec 19;62:101981. doi: 10.1016/j.copsyc.2024.101981. Epub ahead of print. PMID: 39721213.

There has been a predominant focus on psychosocial risk factors associated with poor pain outcomes among individuals with chronic pain. However, it is also important to identify resilience factors that may mitigate the negative impact of or confer successful adaptation to pain. We argue for a dual-focus approach that evaluates the contributions of both risk and resilience factors. Person-centered statistical techniques (cluster analysis) may be beneficial to phenotype individuals based on their psychosocial characteristics to help inform treatment selection. Identifying treatment moderators based on individual-level characteristics (race/ethnicity) may provide insight into differences in treatment efficacy. Utilizing a holistic approach can inform the development and implementation of culturally adapted and personalized treatments aimed at reducing risk and bolstering resilience factors.

Effectiveness of a Brief Multicomponent Intervention to Improve Physical Activity Level and Functional Capacity in Fibromyalgia and Chronic Fatigue Syndrome (Synchronize+).
Martín-Borràs C, González Serra G, Carrasco-Querol N, Sansano-Nadal O, Bueno Hernández N, Bestraten Del Pino P, Pastor Cazalla M, Caballol Angelats R, Montesó-Curto P, Castro Blanco E, Pozo Ariza M, Fernández-Sáez J, Dalmau Llorca MR, Gonçalves AQ, Aguilar Martín C.
Front Physiol. 2024 Dec 9;15:1441076. doi: 10.3389/fphys.2024.1441076. PMID: 39717828; PMCID: PMC11663864.

Introduction: Fibromyalgia (FM) and chronic fatigue syndrome (CFS) are complex central sensitization syndromes that represent an important public health problem. Low cardiorespiratory fitness and muscle function with habitual intolerance to efforts are common characteristics of FM and CFS. This study aimed to examine the effect of a brief multicomponent intervention based on physical activity (PA), nutrition, and chronobiology on movement behaviors (PA, sedentary and sleep time), muscle strength, and cardiorespiratory capacity.
Methods: randomized controlled trial was conducted in primary healthcare in Catalonia. A total of 143 individuals with FM or FM and CFS concomitantly (age 50.8, SD 8.1; 94.4% women) were randomly allocated to the intervention (IG, n = 69) or control (CG, n = 74) groups. The IG participated in a brief multicomponent (PA, nutrition, and chronobiology) group-based intervention (4 sessions, 3 h/session) while the CG received usual primary care practice. Primary outcome measure was PA measured by the REGICOR-Short Physical Activity Questionnaire. Secondary outcomes were sedentary (International Physical Activity Questionnaire) and sleep time (Pittsburgh Sleep Quality Index), upper- and lower-body muscle strength (handgrip and sit-to-stand test, respectively), and aerobic capacity (6-min walk test). Data were collected at baseline and 3 months post-intervention.
Results: The IG showed positive differences at 3-month follow-up, with highly appreciably PA levels, less sedentary time, and significantly improved sleep time. Significant between-group differences were also observed at 3 months, with better health values in the IG: PA

and sleep time (370.3 ± 307.0 vs. 195.9 ± 289.1 min/week and 6.1 ± 1.6 vs. 5.5 ± 1.8 h/night, respectively) and less sedentary time (266.2 ± 153.3 vs. 209.4 ± 199.9 min/day). The IG also showed higher upper limb strength and significant lower-body strength both between and within groups, as well as significantly improved cardiorespiratory capacity.
Conclusion: The Synchronize + multicomponent program implemented at primary healthcare has shown short-term effectiveness in improving 24-h movement behaviors and health outcomes in individuals with FM, with or without CFS. This intervention may be a first step in educating and motivating people with FM and CFS to adopt an active lifestyle, leading to improved health. Long-term follow-up will determine whether the changes are maintained over time and their impact on quality of life and healthcare costs.

Effectiveness of the SYNCHRONIZE + Brief Intervention in Improving Mediterranean Diet Adherence, Nutritional Quality and Intake Pattern in Persons with Fibromyalgia and Chronic Fatigue Syndrome.
Carrasco-Querol N, Cabricano-Canga L, Bueno Hernández N, Martín-Borràs C, Gonçalves AQ, Vila-Martí A, Ribot B, Solà J, Valls-Llobet C, Caballol Angelats R, Montesó-Curto P, Castro Blanco E, Pozo Ariza M, Carreres Rey S, Pla Pagà L, Dearos Sanchís M, Fernández-Sáez J, Dalmau Llorca MR, Aguilar Martín C.
Nutrients. 2024 Dec 24;17(1):11. doi: 10.3390/nu17010011. PMID: 39796445; PMCID: PMC11723387.

Background: Multidisciplinary lifestyle interventions are being researched to treat fibromyalgia. However, the impact of nutrition as a key treatment component is little studied. This study aimed to evaluate the effectiveness of the SYNCHRONIZE + lifestyle multidisciplinary intervention in improving adherence to the Mediterranean diet, nutrition quality and dietary intake pattern in persons with fibromyalgia and chronic fatigue syndrome.
Methods: A pragmatic randomized clinical trial was conducted in primary care. Data were collected using the 17-item energy-restricted Mediterranean Adherence Screener (er-MEDAS), the food frequency questionnaire (sFFQ) and the 24 h recall questionnaire (24 HR), in addition to chrono-nutritional, anthropometric, and body composition data, at baseline and 3-, 6-, and 12- month follow-up visits, and statistically analyzed.
Results: A total of 158 participants were evaluated. Results showed the effectiveness of the intervention in improving adherence to the Mediterranean diet. The adherence depended on the group-time interaction being positive and significant at 3 and 6 months post-intervention in the INT group and on the participant age and educational level. Specifically, the intake of legumes, fruits, vegetables, nuts and blue fish was increased, while the intake of sweets and pastries, butter and cream and red and processed meat was reduced. Furthermore, the intake of chips and candies was also reduced, and the consumption of fermented food (yogurts, cheese, kefir) increased. Thus, general diet quality improved. Interestingly, the intake of key nutrients such as protein and iron increased. Furthermore, the number of night eaters was decreased significantly. Muscle mass index was also improved in the intervention group. These results were maintained in the medium to long term.
Conclusion: SYNCHRONIZE + is a brief, low-cost, multidisciplinary intervention effective in improving adherence to the Mediterranean diet and improving nutritional and dietary intake patterns in persons with fibromyalgia and chronic fatigue syndrome. Further evaluation of the effect on quality of life and symptoms is needed.

The Effect of Fibromyalgia Syndrome on Female Patients Diagnosed with Chronic Migraine.
Mengi A, Türk BG, Uygunoglu U.
Clin Neurol Neurosurg. 2024 Nov;246:108573. doi: 10.1016/j.clineuro.2024.108573. Epub 2024 Sep 23. PMID: 39321573.

Objective: To compare pain, quality of life, sleep, anxiety and depression, central sensitization, and functionality between chronic migraine (CM) patients with comorbid fibromyalgia syndrome (FMS) and patients with CM alone.
Method: Thirty three female patients with CM and thirty three female patients with CM+FMS were enrolled in the study. Demographic and clinical characteristics of the patients were recorded. FM was diagnosed based on the 2016 American College of Rheumatology diagnostic criteria. All participants were evaluated with Allodynia Symptom Checklist, Short Form-36 (SF-36), Pittsburgh Sleep Quality Index (PSQI), Hospital Anxiety and Depression Scale (HADS), Migraine Disability Assessment (MIDAS) and Headache

Impact Test (HIT-6) questionnaires, and Central Sensitization Inventory (CSI). FM patients were also evaluated with Fibromyalgia Impact Questionnaire (FIQ).
Results: The average number of headache days was significantly higher in patients with CM+FMS ($p = 0.006$). Among migraine accompanying symptoms, the number of patients with phonophobia was significantly higher in patients with CM+FMS ($p = 0.008$). While CSI score was 39.0 ± 11.7 in CM patients, it was 52.2 ± 9.2 in CM+FMS patients. CSI scores were higher in CM+FMS patients ($p < 0.001$). SF-36 sub-cores, including physical function, energy/fatigue, emotional well-being, and general health scores, were lower in CM+FMS patients ($p < 0.05$). Sleep duration was significantly lower and use of medication to sleep was more common in same group ($p < 0.05$). FIQ score in CM+FMS patients was associated with quality of life scores, sleep quality, anxiety, and central sensitization scores ($p < 0.05$).
Conclusion: In patients with chronic migraine, FMS comorbidity negatively affects the quality of life and significantly increases central sensitization.

Intense Symptoms of Pain are Associated with Poor Sleep, Fibromyalgia, Depression and Sleep Apnea in Patients with Rheumatoid Arthritis and Psoriatic Arthritis. A Register-based Study.
Weman L, Salo H, Kuusalo L, Huhtakangas J, Vähäsalo P, Backström M, Kärki J, Sokka-Isler T
Joint Bone Spine. 2024 Sep;91(5):105744. doi: 10.1016/j.jbspin.2024.105744. Epub 2024 May 23. PMID: 38795765.

Objectives: To study whether poor sleep and comorbidities are associated with high symptom levels of patient-reported outcomes (PROs) pain, patient global assessment and fatigue in patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA), in a nation-wide cross-sectional setting.
Methods: Clinical data were extracted from The Finnish Rheumatology Quality Register between 1.2021 and 9.2022. Self-reported sleep was categorized as "good" (little/no difficulties) or "poor" (great difficulties/can't) sleep. Data concerning comorbidities were collected from national registers. Descriptive statistics were used. Regression analyses were applied to analyze independent associations of sleep status, comorbidities and disease activity with pain in RA and PsA, adjusting for age and sex.
Results: Among 13,512 patients with RA, 6052 [mean (SD) age 62 (13), 71% female] had sleep status reported; in PsA 1861/3636 [age 55 (13), 48% female]. In RA, 5072 (84%) reported good and 980 (16%) poor sleep; the corresponding numbers in PsA were 1460 (78%) and 401 (22%). Median values for objective disease activity were low and similar in patients with poor sleep and good sleep in both diseases. Among patients with no swollen joints, the median values for PROs were approximately three times higher for patients with poor sleep vs. good sleep in both diagnoses ($P<0.001$). In regression analyses, "poor" sleep was independently associated with higher symptoms in pain [B (95%CI) 20 (18,22) in RA and 23 (19, 26) in PsA], followed by comorbid fibromyalgia, as well as depression in RA and sleep apnea in PsA.
Conclusion: "Poor" sleep quality and comorbidities are independently associated with pain. Patient's sleep status is important to know especially in patients with severe symptoms without objective disease activity.

Morphological and Mechanical Properties of Cervical Muscles in Fibromyalgia with Migraine: A Case-control Study.
Balaban M, Toprak Celenay S, Lalecan N, Akan S, Ozer Kaya D.
Musculoskelet Sci Pract. 2024 Nov;74:103185. doi: 10.1016/j.msksp.2024.103185. Epub 2024 Sep 14. PMID: 39305717.

Background: The precise manner in which morphological and mechanical properties of cervical muscles in patients with fibromyalgia and migraine are affected remains unclear.
Objectives: The objective of this study was to compare the morphological and mechanical properties of cervical muscles in individuals diagnosed with fibromyalgia who also experience migraine headaches with those who do not.
Methods: The study included two groups of fibromyalgia patients: one with migraine ($n = 18$, age = 44.7 ± 7.5 years, body mass index = 28.7 ± 6.9 kg/m^2) and one without migraine ($n = 21$, age = 42.6 ± 9.5 years, body mass index = 25.1 ± 4.4 kg/m^2). Body pain intensity related to fibromyalgia and migraine attack severity were evaluated with a Visual Analog Scale (VAS). The cervical muscle morphological and mechanical properties, including thickness, cross-sectional area (CSA), and stiffness, were measured using ultrasound

imaging.
Results: It was found that there was a greater decrease in longus colli muscle CSA scores ($p = 0.004$) and a greater increase in upper trapezius muscle stiffness scores ($p = 0.013$) in the fibromyalgia + migraine group compared to the fibromyalgia group. No statistically significant differences were observed in trapezius muscle thickness ($p = 0.261$), sternocleidomastoid muscle thickness ($p = 0.874$), multifidus CSA ($p = 0.963$), or sternocleidomastoid muscle stiffness ($p = 0.642$) between the two groups.
Conclusion: Patients with fibromyalgia and migraine exhibited diminished longus colli muscle CSA and heightened upper trapezius muscle stiffness compared to those with fibromyalgia but no migraine. It should be considered that migraine comorbidity in fibromyalgia may negatively affect cervical muscle morphological and mechanical properties.

Application of the Grading System for "Nociplastic Pain" in Chronic Primary and Chronic Secondary Pain Conditions: A Field Study.
Schmidt H, Drusko A, Renz MP, Schlömp L, Tost H, Schuh-Hofer S, Tesarz J, Meyer-Lindenberg A, Treede RD.
Pain. 2025 Jan 1;166(1):196-211. doi: 10.1097/j.pain.0000000000003355. Epub 2024 Aug 26. PMID: 39190340.

The concept "nociplastic pain" has been developed for patients with features of nociceptive system sensitization that are not explained as nociceptive or neuropathic. Here, we tested how well the recently published grading system differentiates between chronic primary and secondary pain conditions. We recruited patients with fibromyalgia (FMS, n = 41), complex regional pain syndrome (CRPS, n = 11), osteoarthritis (OA, n = 21), or peripheral nerve injury (PNI, n = 8). We used clinical history, pain drawings, quantitative sensory testing (QST), and questionnaires to classify their pains as possibly or probably "nociplastic." All patients with chronic primary pain exhibited widespread/regional pain not explainable by either nociceptive or neuropathic mechanisms. Widespread pain occurred in 12 patients with OA but was identified as nociceptive in 11 of 12. Regional pain occurred in 4 patients with PNI but was identified as neuropathic in 3 of 4. At this step, the grading system had 100% sensitivity and 93% specificity. Clinical evidence for pain hypersensitivity by QST, and history of hypersensitivity and mental comorbidities did not differentiate between chronic primary pain (QST: 36/52 = 69%, history: 43/52 = 83%) and secondary pain conditions (QST: 20/29 = 69%, history: 24/29 83%). Based on these data, specificity remained excellent (93%), but sensitivity dropped substantially (60%) due to lacking evidence for pain hypersensitivity in many patients with FMS. This low sensitivity suggests that the published grading system is not suitable for screening purposes. We suggest structural and content modifications to improve sensitivity, including placement of patient history before clinical examination and addition of a high tender point count as evidence for widespread pain hypersensitivity.

Pain from Internal Organs and Headache: The Challenge of Comorbidity .
Affaitati G, Costantini R, Fiordaliso M, Giamberardino MA, Tana C.
Diagnostics (Basel). 2024 Aug 12;14(16):1750. doi: 10.3390/diagnostics14161750. PMID: 39202238; PMCID: PMC11354044.

Headache and visceral pain are common clinical painful conditions, which often co-exist in the same patients. Numbers relative to their co-occurrence suggest possible common pathophysiological mechanisms. The aim of the present narrative review is to describe the most frequent headache and visceral pain associations and to discuss the possible underlying mechanisms of the associations and their diagnostic and therapeutic implications based on the most recent evidence from the international literature. The conditions addressed are as follows: visceral pain from the cardiovascular, gastrointestinal, and urogenital areas and primary headache conditions such as migraine and tension-type headache. The most frequent comorbidities involve the following: cardiac ischemic pain and migraine (possible shared mechanism of endothelial dysfunction, oxidative stress, and genetic and hormonal factors), functional gastrointestinal disorders, particularly IBS and both migraine and tension-type headache, primary or secondary dysmenorrhea and migraine, and painful bladder syndrome and headache (possible shared mechanisms of peripheral and central sensitization processes). The data also show that the various visceral pain-headache associations are characterized by more than a simple sum of symptoms from each condition but often involve complex interactions with the frequent enhancement of symptoms from both, which is crucial for diagnostic and treatment purposes.

EPIDEMIOLOGY STUDIES

The Burden of Diseases, Injuries, and Risk Factors by State in the USA, 1990-2021: A Systematic Analysis for the Global Burden of Disease Study 2021.

GBD 2021 US Burden of Disease Colaborators

Lancet. 2024 Dec 7;404(10469):2314-2340. doi: 10.1016/S0140-6736(24)01446-6.

Background: The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2021 provides a comprehensive assessment of health and risk factor trends at global, regional, national, and subnational levels. This study aims to examine the burden of diseases, injuries, and risk factors in the USA and highlight the disparities in health outcomes across different states.

Methods: GBD 2021 analysed trends in mortality, morbidity, and disability for 371 diseases and injuries and 88 risk factors in the USA between 1990 and 2021. We used several metrics to report sources of health and health loss related to specific diseases, injuries, and risk factors. GBD 2021 methods accounted for differences in data sources and biases. The analysis of levels and trends for causes and risk factors within the same computational framework enabled comparisons across states, years, age groups, and sex. GBD 2021 estimated years lived with disability (YLDs) and disability-adjusted life-years (DALYs; the sum of years of life lost to premature mortality and YLDs) for 371 diseases and injuries, years of life lost (YLLs) and mortality for 288 causes of death, and life expectancy and healthy life expectancy (HALE). We provided estimates for 88 risk factors in relation to 155 health outcomes for 631 risk-outcome pairs and produced risk-specific estimates of summary exposure value, relative health risk, population attributable fraction, and risk-attributable burden measured in DALYs and deaths. Estimates were produced by sex (male and female), age (25 age groups from birth to ≥95 years), and year (annually between 1990 and 2021). 95% uncertainty intervals (UIs) were generated for all final estimates as the 2·5th and 97·5th percentiles values of 500 draws (ie, 500 random samples from the estimate's distribution). Uncertainty was propagated at each step of the estimation process.

Findings: We found disparities in health outcomes and risk factors across US states. Our analysis of GBD 2021 highlighted the relative decline in life expectancy and HALE compared with other countries, as well as the impact of COVID-19 during the first 2 years of the pandemic. We found a decline in the USA's ranking of life expectancy from 1990 to 2021: in 1990, the USA ranked 35th of 204 countries and territories for males and 19th for females, but dropped to 46th for males and 47th for females in 2021. When comparing life expectancy in the best-performing and worst-performing US states against all 203 other countries and territories (excluding the USA as a whole), Hawaii (the best-ranked state in 1990 and 2021) dropped from sixth-highest life expectancy in the world for males and fourth for females in 1990 to 28th for males and 22nd for females in 2021. The worst-ranked state in 2021 ranked 107th for males (Mississippi) and 99th for females (West Virginia). 14 US states lost life expectancy over the study period, with West Virginia experiencing the greatest loss (2·7 years between 1990 and 2021). HALE ranking declines were even greater; in 1990, the USA was ranked 42nd for males and 32nd for females but dropped to 69th for males and 76th for females in 2021. When comparing HALE in the best-performing and worst-performing US states against all 203 other countries and territories, Hawaii ranked 14th highest HALE for males and fifth for females in 1990, dropping to 39th for males and 34th for females in 2021. In 2021, West Virginia-the lowest-ranked state that year-ranked 141st for males and 137th for females. Nationally, age-standardised mortality rates declined between 1990 and 2021 for many leading causes of death, most notably for ischaemic heart disease (56·1% [95% UI 55·1-57·2] decline), lung cancer (41·9% [39·7-44·6]), and breast cancer (40·9% [38·7-43·7]). Over the same period, age-standardised mortality rates increased for other causes, particularly drug use disorders (878·0% [770·1-1015·5]), chronic kidney disease (158·3% [149·6-167·9]), and falls (89·7% [79·8-95·8]). We found substantial variation in mortality rates between states, with Hawaii having the lowest age-standardised mortality rate (433·2 per 100 000 [380·6-493·4]) in 2021 and Mississippi having the highest (867·5 per 100 000 [772·6-975·7]). Hawaii had the lowest age-standardised mortality rates throughout the study period, whereas Washington, DC, experienced the most improvement (a 40·7% decline [33·2-47·3]). Only six countries had age-standardised rates of YLDs higher than the USA in 2021: Afghanistan, Lesotho, Liberia, Mozambique, South Africa, and the Central African Republic, largely because the impact of musculoskeletal disorders, mental disorders, and substance use disorders on

age-standardised disability rates in the USA is so large. At the state level, eight US states had higher age-standardised YLD rates than any country in the world: West Virginia, Kentucky, Oklahoma, Pennsylvania, New Mexico, Ohio, Tennessee, and Arizona. Low back pain was the leading cause of YLDs in the USA in 1990 and 2021, although the age-standardised rate declined by 7·9% (1·8-13·0) from 1990. Depressive disorders (56·0% increase [48·2-64·3]) and drug use disorders (287·6% [247·9-329·8]) were the second-leading and third-leading causes of age-standardised YLDs in 2021. For females, mental health disorders had the highest age-standardised YLD rate, with an increase of 59·8% (50·6-68·5) between 1990 and 2021. Hawaii had the lowest age-standardised rates of YLDs for all sexes combined (12 085·3 per 100 000 [9090·8-15 557·1]), whereas West Virginia had the highest (14 832·9 per 100 000 [11 226·9-18 882·5]). At the national level, the leading GBD Level 2 risk factors for death for all sexes combined in 2021 were high systolic blood pressure, high fasting plasma glucose, and tobacco use. From 1990 to 2021, the age-standardised mortality rates attributable to high systolic blood pressure decreased by 47·8% (43·4-52·5) and for tobacco use by 5·1% (48·3%-54·1%), but rates increased for high fasting plasma glucose by 9·3% (0·4-18·7). The burden attributable to risk factors varied by age and sex. For example, for ages 15-49 years, the leading risk factors for death were drug use, high alcohol use, and dietary risks. By comparison, for ages 50-69 years, tobacco was the leading risk factor for death, followed by dietary risks and high BMI.
Interpretation: GBD 2021 provides valuable information for policy makers, health-care professionals, and researchers in the USA at the national and state levels to prioritise interventions, allocate resources effectively, and assess the effects of health policies and programmes. By addressing socioeconomic determinants, risk behaviours, environmental influences, and health disparities among minority populations, the USA can work towards improving health outcomes so that people can live longer and healthier lives.

Global and Regional Trends and Projections of Chronic Pain from 1990 to 2035: Analyses Based on Global Burden of Diseases Study 2019.
Zhu M, Zhang J, Liang D, Qiu J, Fu Y, Zeng Z, Han J, Zheng J, Lin L.
Br J Pain. 2024 Dec 24:20494637241310697. doi: 10.1177/20494637241310697. Epub ahead of print. PMID: 39726775; PMCID: PMC11669129.

Background: Chronic pain poses a significant public health challenge. We present the global and regional data on Prevalence, Incidence and Years Lived with Disability (YLDs) for Chronic pain from the Global burden of disease (GBD) study 2019 data and analyze their associations with Socio-demographic index (SDI), age, and gender, and the future trends from 2020 to 2035.
Methods: Regional trends in the burden of chronic pain and its association with age, gender, and SDI were assessed from 1990 to 2019. Joinpoint analysis was employed to describe trends in chronic pain burden across different SDI regions. Additionally, the Bayesian Age-Period-Cohort model (BAPC) was used for predicting future trends. Age-standardized rates (ASRs) of prevalence, incidence, and YLDs were employed to quantify the burden of chronic pain.
Results: Between 1990 and 2019, a significant increase was observed in global prevalence and YLDs rates of chronic pain. Higher rates were found among females, whereas a faster rise was noted among males. Notably, Low Back Pain (LBP) and Migraine accounted for predominant YLDs globally, particularly among those aged 75 and above. A notable prevalence of Tension-type Headache (TTH) was observed among younger populations. Furthermore, ASRs for chronic pain were highest in high-SDI regions. Projections suggest an increase in headache ASRs globally for both genders from 2020 to 2035.
Conclusion: From 1990 to 2019, the global burden of chronic pain increased significantly, with projections indicating a continued rise in headache burden over the next 15 years, underscoring the need for heightened attention to these issues.

Prevalence and Sociodemographic Correlates of Chronic Pain Among a Nationally Representative Sample of Older Adults in the United States.
LaRowe LR, Miaskowski C, Miller A, Mayfield A, Keefe FJ, Smith AK, Cooper BA, Wei LJ, Ritchie CS.
J Pain. 2024 Oct;25(10):104614. doi: 10.1016/j.jpain.2024.104614. Epub 2024 Jun 25. PMID: 38936750; PMCID: PMC11402580.

Subgroup analyses conducted among U.S. national survey data have estimated that 27 to 34% of adults aged ≥65 years have chronic pain. However, none of these studies focused specifically on older adults or examined disparities in chronic pain in those aged ≥65 years.

To obtain current information on the prevalence and sociodemographic correlates of chronic pain in U.S. older adults, a cross-sectional analysis was conducted of data collected from 3,505 older adults recruited from the AmeriSpeak Panel. Chronic pain was defined as pain on most or every day in the last 3 months. Nationally representative chronic pain prevalence estimates were computed by incorporating study-specific survey design weights. Logistic regression analyses evaluated differences in chronic pain status as a function of sociodemographic characteristics (eg, gender, race/ethnicity, and socioeconomic status). The results indicated that 37.8% of older adults reported chronic pain. Compared with White older adults, Black (odds ratio [OR] = .6, 95% CI: .4-.8) and Asian (OR = .2, 95% CI: .1-.8) older adults were less likely to report chronic pain. The prevalence of chronic pain was also lower among those who reported the highest (vs lowest) household income (OR = .6, 95% CI: .4-.8). Those who were not working due to disability (vs working as a paid employee) were more likely to report chronic pain (OR = 3.2, 95% CI: 2.1-5.0). This study was the first to recruit a large, representative sample of older adults to estimate the prevalence of chronic pain and extends prior work by identifying subgroups of older adults that are disproportionately affected. PERSPECTIVE: This study was the first to estimate the prevalence and sociodemographic correlates of chronic pain among a large, representative sample of U.S. older adults. The findings underscore the high prevalence of chronic pain and highlight disparities in chronic pain prevalence rates among this historically understudied population.

Does Pain Explain Trends in Disability? An Analysis of Middle-Aged and Older U.S. Adults, 2002-2018.

Ruan H, Zajacova A, Zimmer Z, Grol-Prokopczyk H. J Gerontol B Psychol Sci Soc Sci. 2024 Nov 1;79(11):gbae148. doi: 10.1093/geronb/gbae148. PMID: 39196710; PMCID: PMC11474771.

Objectives: This article investigates the role of pain in disability trends in the United States, within the context of recent unfavorable disability trends and the concurrent rise in pain.
Methods: We conducted a 2-part analysis using National Health Interview Survey data from 2002 to 2018 for U.S. adults aged 45-84. First, we assessed how changes in the prevalence of 5 site-specific types of pain (headaches/migraines, joint, low back, neck, and facial/jaw pain) associated with disability trends. Second, we used self-reported causes of disability and examined whether there has been a change in the proportion of individuals who attribute their disability to 1 of 5 chronic or acute painful conditions.
Results: The 5 site-specific types of pain, individually and collectively, were significantly associated with increases in disability. If site-specific chronic pain had not increased during the study period, the trend for functional limitations would have been 40% lower, and that for activity limitations would have shown a slight decline instead of an increase. Attributions of functional limitations to painful conditions increased by 23% during the 2002-2018 period, representing an additional 9.82 million Americans experiencing pain-attributable disability. Arthritis/rheumatism, back/neck problems, and other musculoskeletal/connective conditions were the primary sources of pain-related disability.
Discussion: Our research provides the first systematic, national examination of how pain is contributing to disability trends in the United States. The findings have implications for disability reduction policies and shed light on the far-reaching consequences of pain for overall population health.

Chronic Overlapping Pain Conditions in people with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): a sample from the Multi-site Clinical Assessment of ME/CFS (MCAM) study.

Fall EA, Chen Y, Lin JS, Issa A, Brimmer DJ, Bateman L, Lapp CW, Podell RN, Natelson BH, Kogelnik AM, Klimas NG, Peterson DL, Unger ER; MCAM Study Group.
BMC Neurol. 2024 Oct 18;24(1):399. doi: 10.1186/s12883-024-03872-0. PMID: 39425035; PMCID: PMC11488184.

Background: Chronic overlapping pain conditions (COPCs), pain-related conditions that frequently occur together, may occur in patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and could impact illness severity. This study aimed to identify comorbid COPCs in patients with ME/CFS and evaluate their impact on illness severity.
Methods: We used data from 923 participants in the Multi-Site Clinical Assessment of ME/CFS study, conducted in seven U.S. specialty clinics between 2012 and 2020, who completed the baseline assessment (595 ME/CFS and 328 healthy controls (HC)). COPCs included chronic low back pain (cLBP), chronic migraine/headache (cMHA), fibromyalgia

(FM), interstitial cystitis/irritable bladder (IC/IB), irritable bowel syndrome (IBS), temporomandibular disorder (TMD). Illness severity was assessed through questionnaires measuring symptoms and functioning. Multivariate analysis of variance and analysis of covariance models were used for analyses. Log-binomial regression analyses were used to compute prevalence of COPCs and prevalence ratios (PR) between groups with 95% confidence intervals. Both unadjusted and adjusted results with age and sex are presented.
Results: 76% of participants with ME/CFS had at least one COPCs compared to 17.4% of HC. Among ME/CFS participants, cMHA was most prevalent (48.1%), followed by FM (45.0%), cLBP (33.1%), and IBS (31.6%). All individual COPCs, except TMD, were significantly more frequent in females than males. The unadjusted PR (ME/CFS compared to HC) was highest for FM [147.74 (95% confidence interval (CI) = 20.83-1047.75], followed by cLBP [39.45 (12.73-122.27)], and IC/IB [13.78 (1.88-101.24)]. The significance and order did not change after age and sex adjustment. The COPC comorbidities of cLBP and FM each had a significant impact on most health measures, particularly in pain attributes (Cohen's d effect size 0.8 or larger). While the impact of COPC comorbidities on non-pain attributes and quality of life measures was less pronounced than that on pain, statistically significant differences between ME/CFS participants with and without COPCs were still evident.
Conclusions: More than 75% of ME/CFS participants had one or more COPCs. Multiple COPCs further exacerbated illness severity, especially among females with ME/CFS. Assessment and management of COPCs may help improve the health and quality of life for patients with ME/CFS.

Fluctuation of Functional Somatic Disorders in a Population-based Cohort. The DanFunD Study.
Schovsbo SU, Kårhus LL, Bjerregaard AA, Petersen MW, Frostholm L, Fink P, Carstensen TBW, Eplov LF, Benros ME, Brix S, Madsen AL, Linneberg A, Dantoft TM, Jørgensen T. PLoS One. 2024 Oct 16;19(10):e0312031. doi: 10.1371/journal.pone.0312031. PMID: 39413108; PMCID: PMC11482674.

Background: Evidence of incidence of functional somatic disorders (FSD) is hampered by unclear delimitations of the conditions and little is known about the possible interchangeability between syndromes. Further, knowledge on remission and persistence of FSD in the general population is limited. We aimed to assess the natural course of various FSD over 5 years in the general population.
Methods: A follow-up study (Danish Study of Functional Disorders—DanFunD) was conducted in a random sample of the general population comprising 5,738 participants aged 18–76 years at baseline. Both at baseline and five-year follow-up, participants filled in validated questionnaires on symptoms to delimitate two approaches of FSD, the bodily distress syndrome (BDS) and four functional somatic syndromes (FSS): irritable bowel (IB), chronic fatigue (CF), chronic widespread pain (CWP), and multiple chemical sensitivity (MCS).
Results: Both BDS and FSS showed a five-year incidence around 11%. Incidence of the individual FSS varied from 0.8% (MCS) to 5.7% (CF). BDS and FSS showed a remission proportion close to 50%. We found a high degree of interchangeability between each FSS varying from 15.0% to 23.4%.
Conclusion: We identified a marked fluctuation pattern of FSD during a five-year period, with a high degree of interchangeability between each FSS. The study stresses the importance of large population-based cohorts with transparent delimitation of FSD in future research to understand these complex conditions.

The Frequency of Fibromyalgia in Patients with Systemic Lupus Erythematosus and Associated Factors: A Systematic Review and Meta-analysis.
Mistry S, Daoud A, Magrey MN, Pamuk ON.
Clin Rheumatol. 2024 Oct 19. doi: 10.1007/s10067-024-07188-9. Epub ahead of print. PMID: 39424681.

Fibromyalgia (FM) in systemic lupus erythematosus (SLE) patients contributes to increased fatigue, anxiety, depression, and mental exhaustion. This study's objective is to systematically review the literature and to determine the frequency of FM in patients with SLE and its associated factors. A literature review was conducted to assess the prevalence of FM in SLE patients and to identify FM-associated factors. This involved searching the PubMed and Cochrane Library databases from 1959 to 2023. Cohorts, case-control, and population-based studies were included, while those not focusing on FM rates in SLE

patients were excluded. Data on FM-associated factors and FM frequency in control or connective tissue disease (CTD) groups were obtained if available. Secondary analyses compared FM frequencies in SLE and other groups (healthy controls or CTD groups). Fifty-six studies met the eligibility criteria. Out of the 56 studies, nine included comparative data between SLE patients and healthy controls, while six presented data comparing the frequency of FM in patients with SLE and other CTDs. The combined cohorts included 58,052 SLE patients. Among 5063 SLE patients, FM was detected. The overall random-effects pooled prevalence of FM was 15.8% (95% CI, 13.4-18.5) with high heterogeneity (I^2, 97.9%). Our analysis revealed a significantly higher risk of FM in patients with SLE compared to controls (OR, 3.7; 95% CI, 2.74-5.0). There was a higher risk of FM in SLE patients compared to other rheumatic diseases, but the difference was not significant. Our study showed that the prevalence of FM is higher in patients with SLE compared to the general population. FM in SLE may act as a confounding factor when assessing disease activity and treatment response. Research results indicate that concurrent FM is a frequent comorbidity in SLE, emphasizing the importance of recognizing its occurrence in SLE patients.

Fibromyalgia Comorbidity in Systemic Lupus Erythematosus Patients: Assessing Impact on Quality of Life.

Monteiro JAM, Gama ALH, Oliveira JCS, Falcao MV, Melo AKG, Egypto DCS, Braz AS. Adv Rheumatol. 2024 Dec 18;64(1):90. doi: 10.1186/s42358-024-00432-5. PMID: 39696564.

Introduction: The prevalence of Fibromyalgia in patients with Systemic Lupus Erythematosus (SLE) is significantly higher compared to the general population. Despite this frequent association, Fibromyalgia remains underdiagnosed and consequently inadequately treated, negatively affecting the quality of life of these patients.
Objective: This study aims to evaluate the occurrence of Fibromyalgia and its impact on the quality of life of Brazilian patients with SLE treated at a University Hospital in the state of Paraiba.
Materials and methods: This descriptive, observational, and cross-sectional study included patients with SLE diagnosed according to the 2012 criteria of the Systemic Lupus Erythematosus International Collaborating Clinics (SLICC). The occurrence of Fibromyalgia was assessed using the American College of Rheumatology (ACR) criteria of 1990 and 2010/2011, revised in 2016. Quality of life was evaluated using the Short-Form 36 (SF-36) questionnaire for all patients, while the Fibromyalgia Impact Questionnaire (FIQ) was applied to those diagnosed with Fibromyalgia.
Results: The sample comprised 107 SLE patients, with an average age of 54.1 years (SD:12.1), of whom 95.4% (102) were women. The prevalence of Fibromyalgia among SLE patients was 19.1% (21), all of whom were women with a mean age of 45.6 years (SD 9.6). The SF-36 scores of SLE patients with Fibromyalgia were consistently lower across all eight domains compared to those without Fibromyalgia, indicating a significant negative impact of this comorbidity.
Conclusion: These findings are consistent with existing literature, highlighting the significant negative impact of Fibromyalgia on the quality of life of patients with SLE.

Fibromyalgia, Mood Disorders and Chronic Damage are the Main Determinants of Worse Quality of Life in Systemic Lupus Erythematosus Patients: Results from a Cross-Sectional Analysis.

Ceccarelli F, Ciancarella C, Pirone C, Natalucci F, Picciariello L, Garufi C, Mancuso S, Truglia S, Spinelli FR, Alessandri C, Cont F.
Lupus. 2024 Dec;33(14):1584-1593. doi: 10.1177/09612033241299978. Epub 2024 Nov 11. PMID: 39526791.

Objective: As suggested by the EULAR recommendations, a comprehensive management of Systemic Lupus Erythematosus (SLE) should include the evaluation of disease activity, chronic damage, and quality of life (QoL). QoL is significantly impaired in SLE patients, even in those achieving a state of remission, suggesting the possible contribution of other factors. Thus, in the present study we aimed at analyzing QoL in a large SLE cohort by using LupusQoL, and at identifying the main determinant of poorer QoL.
Methods: We conducted a cross-sectional study by including consecutive SLE patients diagnosed according to the 2019 ACR/EULAR criteria. Clinical, laboratory and therapeutical data were collected. Disease activity was assessed by SLEDAI-2k, while chronic damage by the SLICC Damage Index (SDI). The diagnosis of fibromyalgia was made in accordance

with the ACR criteria (2016). At the time of the enrollment, all patients completed the following questionnaires: LupusQoL to assess quality of life and hospital anxiety and depression scale (HADS) for anxiety and depression.
Results: Our analysis included 237 SLE patients [92.4% female, median age 46 years (IQR 19.5), median disease duration 156.8 months (IQR 180.6)]. At the time of enrollment, we found a mean SLEDAI-2k of 1.7 (DS 2.4); 104 patients (43.9%) had chronic damage, with a mean SDI value of 0.8 (DS 1.3). Patients diagnosed with fibromyalgia were 69 (29.1%); moreover, HADS questionnaire identified a condition of anxiety and depression in 112 (47.3%) and 94 (39.7%) patients, respectively. The most compromised domain in the LupusQoL resulted "fatigue", followed by "burden to others". Patients with SDI ≥ 1 showed lower quality of life than patients without chronic damage, as demonstrated by significantly lower values in all items of the LupusQoL ($p < .01$). Furthermore, significantly lower values in all the LupusQoL domains were observed in patients with fibromyalgia, anxiety and depression, in comparison to those patients without these manifestations ($p < .0001$). No association was demonstrated between QoL and disease activity. Finally, the linear regression analysis confirmed mood disorders, in particular depression, and fibromyalgia as the main determinants of worse quality of life in our cohort.
Conclusions: The present study demonstrated the influence of different factors in the quality of life of SLE patients. In particular, the presence of mood disorders, fibromyalgia and chronic damage resulted the main determinants of poorer QoL. This evidence reinforces the need for a comprehensive patient care.

Discordant Dry Eye Disease and Chronic Pain: A Systematic Review and Meta-analysis.
Hoffmann M, Farrell S, Colorado LH, Edwards K.
Cont Lens Anterior Eye. 2024 Dec;47(6):102248. doi: 10.1016/j.clae.2024.102248. Epub 2024 Jun 8. PMID: 38851945.

Purpose: To evaluate the relative contributions of objective and subjective indicators of dry eye disease (DED) in individuals with chronic pain conditions compared with controls.
Methods: A systematic review and meta-analysis was conducted of studies that reported the signs and symptoms of DED and/or their prevalence in individuals with chronic pain compared with controls. International Association for the Study of Pain (IASP) International Classification of Diseases (ICD)-11 codes for chronic pain conditions were applied, and outcomes defined as DED signs and symptoms. A search strategy utilised the EMBASE, Web of Science, Cochrane Library and MEDLINE databases. Risk of bias assessment was performed with the Newcastle-Ottawa scale. Random effects meta-analysis calculated mean differences (MD) and odds ratios (OR), while subgroup analysis of different chronic pain conditions explored their relative association with the signs and symptoms of DED. Evidence certainty was evaluated using Grades of Recommendation, Assessment, Development, and Evaluation (GRADE).
Results: Fourteen observational studies comprising 3,281,882 individuals were included. Meta-analysis found high quality evidence that individuals with chronic pain were more likely to experience symptoms of DED than controls (OR = 3.51 [95 %CI: 3.45,3.57]). These symptoms were more severe (MD = 18.53 [95 %CI: 11.90, 25.15]) than controls with a clinically meaningful effect size. Individuals with chronic pain had more rapid tear film disruption (MD = -2.45 [95 %CI: -4.20, -0.70]) and reduced tear production (MD = -5.57 [95 %CI: -9.56, -1.57]) compared with controls (with moderate evidence quality). High quality evidence revealed individuals with chronic pain had lower basal tear production (anaesthetised) than controls (MD = -2.59 [95 %CI: -3.60, -1.58]). Tear film osmolarity showed no significant differences between the chronic pain and pain-free groups. Group differences for DED signs were not considered clinically meaningful.
Conclusion: More severe, clinically meaningful symptoms of DED were reported in individuals with chronic pain than controls, however group differences for the signs of DED were typically of limited or questionable clinical relevance. This ocular phenotype where DED is felt more than it is seen in chronic pain may reflect underlying sensory hypersensitivity, shared by both conditions and contributing to their frequent comorbidity. Advancing understanding of this potential pathophysiological mechanism may guide clinical management.

Prevalence and Clinical Correlates of Endometriosis in Patients With IC/BPS.
Namugosa M, El Haraki A, Ritts R, Ferrara K, Badlani G, Evans R, Walker SJ.
Urogynecology (Phila). 2024 Oct 18. doi: 10.1097/SPV.0000000000001589. Epub ahead of print. PMID: 39423149.

Importance: Interstitial cystitis/bladder pain syndrome (IC/BPS) presents as a complex heterogeneous disorder that poses a significant clinical challenge both for diagnosis and treatment. The identification of patient subgroups with significant overlap in their nonurological associated symptoms, including endometriosis, may enable a more targeted therapeutic approach.
Objective: This study investigated the prevalence, clinical correlates, and clinical sequelae associated with concurrent endometriosis in patients with IC/BPS.
Study design: Demographic, clinical, surgical, and questionnaire data from female patients (n = 533) with a diagnosis of IC/BPS were evaluated in this retrospective cohort study. Surgical history was obtained from patient electronic medical records, using Current Procedural Terminology (CPT) and International Classification of Diseases (ICD) codes. Data from participants with and without concurrent endometriosis were compared using univariate analysis, followed by binary logistic regression to identify associated variables.
Results: Of 533 participants, 108 (20.3%) reported a history of endometriosis. Those with concurrent endometriosis were younger, had a larger bladder capacity, and had a higher number of nonurological associated symptoms. Patients with concurrent endometriosis were less likely to have a history of cystectomy (the surgical removal of the bladder) and report allergies but more prone to report comorbidities such as chronic pelvic pain, chronic fatigue, fibromyalgia, migraines, and pelvic floor dysfunction. Binary logistic regression identified a positive association between endometriosis and chronic pelvic pain, and a negative association between allergies and low bladder capacity for those with concurrent endometriosis.

The Evil Twins of Chronic Pelvic Pain Syndrome: A Systematic Review and Meta-Analysis on Interstitial Cystitis/Painful Bladder Syndrome and Endometriosis.
Inzoli A, Barba M, Costa C, Carazita V, Cola A, Fantauzzi M, Passoni P, Polizzi S, Frigerio M.
Healthcare (Basel). 2024 Nov 29;12(23):2403. doi: 10.3390/healthcare12232403. PMID: 39685025.

Background: Chronic pelvic pain is a debilitating condition affecting quality of life. Endometriosis is one of the leading causes of CPP, but recent studies highlighted the role of interstitial cystitis/bladder pain syndrome (IC/PBS) in causing CPP. Only some studies addressed the coexistence of these two conditions, which seems more frequent than what is supposed, leading to diagnostic delays and unnecessary surgeries. This systematic review aimed to evaluate the estimate of the prevalence of the comorbidity of endometriosis and IC/PBS.
Methods: We performed a systematic review of the literature indexed on PubMed, Scopus, ISI Web of Science, and Cochrane using a combination of keywords and text words represented by "painful bladder syndrome", "endometriosis", "interstitial cystitis", and "bladder pain syndrome". We performed a meta-analysis of the results.
Results: The meta-analysis shows that the coexistence of endometriosis and IC/PBS in women with CPP ranged from 15.5% to 78.3%, which is higher than the prevalence of IC/PBS in the general population.
Conclusions: Prevalence data about the coexistence of endometriosis and IC/PBS are highly heterogeneous, probably due to the paucity of available data. However, in cases of endometriosis unresponsive to treatment, other reasons for CPP (such as IC/PBS) need to be ruled out.

Pain Phenotypes in Endometriosis: A Population-Based Study Using Latent Class Analysis.
Kanti FS, Allard V, Métivier AA, Lemyre M, Arendas K, Maheux-Lacroix S.
BJOG. 2024 Dec 3. doi: 10.1111/1471-0528.18021. Epub ahead of print. PMID: 39627905.

Objective: To identify pain phenotypes in patients with endometriosis and investigate their associations with demographics, clinical characteristics, comorbidities and pain-related quality of life (QoL).
Design: Cross-sectional, single-centre, population-based study.
Setting: Referral university centre in Quebec City, Canada.
Population: Patients diagnosed with endometriosis were enrolled consecutively between January 2020 and April 2024.
Methods: Latent class analysis was used to identify pain phenotypes. A three-step approach of latent class analysis, involving logistic regression models, was applied to assess the associations between pain phenotypes and demographics, clinical

characteristics, comorbidities and pain-related QoL.
Main outcome measures: Pain phenotypes; demographic, clinical and comorbidity predictors of phenotype membership; association between QoL and pain phenotypes.
Results: A total of 352 patients were included. Two pain phenotypes were identified with distinct clinical presentations: one (54% of the participants) with more severe and frequent pain symptoms and poorer QoL and the other (46% of the participants) with mild and less frequent pain symptoms. The high pain phenotype was associated with previous treatment failure, painkiller use, familial history of endometriosis, low annual family income and comorbidities, including painful bladder, fibromyalgia, migraines, lower back pain, irritable bowel syndrome, anxiety and depression or mood disorders. The presence of endometrioma was associated with the low pain phenotype. Phenotype membership was associated with distinct QoL profiles ($p < 0.001$). The mean QoL score was higher in the high pain phenotype (59; 95% CI, 56-62) than in the low pain phenotype (33; 95% CI, 29-37).
Conclusion: Patients with endometriosis can be categorised into two distinct phenotypes that correlate with QoL and patient characteristics. Validation in other populations is necessary and could aid the development of specialised or personalised interventions.

Prevalence of Temporomandibular Disorders in Adult Women with Endometriosis.
Marciniak T, Walewska N, Skoworodko A, Bobowik P, Kruk-Majtyka W.
J Clin Med. 2024 Dec 13;13(24):7615. doi: 10.3390/jcm13247615. PMID: 39768537; PMCID: PMC11677550.

Background/Objectives: The prevalence of endometriosis varies between 10% and 18%, while temporomandibular disorders (TMDs) concern between 29 and 34% of the general population. Both conditions share similar etiological factors and symptoms such as widespread, chronic pain. Therefore, both are qualified as Chronic Overlapping Pain Conditions. Even though TMDs and endometriosis appear to be comorbidities, up until now, no research has examined how the incidence rates compare between them. Thus, this study aimed to analyze the prevalence of TMD symptoms in women with endometriosis in the Polish population.
Methods: 163 adult women with endometriosis, aged 32.41 ± 6.76 years, completed an anonymous online survey regarding their medical history and TMD symptoms. The participants were screened for TMD symptoms using two questionnaires-3Q/TMD and TMD Pain Screener (part of the DC/TMD protocol). The history mainly consisted of a chronology of symptoms' appearance, medical consultations, and final confirmation of the diagnosis, to establish delay time.
Results: The analysis revealed that 77.3% of women with endometriosis showed TMD symptoms, and 49.08% of the whole studied population showed important pain levels. Then, the sample was divided into two groups according to the 3Q/TMD questionnaire-a TMD and an nTMD group. The results showed significantly higher pain levels in the TMD group ($r = 0.721$) compared to non-symptomatic subjects. The mean patients' delay time (T1) was 2.81 ± 4.40 years, and the mean doctors' delay (T2) was 5.32 ± 5.65 years.
Conclusions: The results provide a new insight into the relationship between endometriosis and TMD. The prevalence of the latter condition was found to be high, creating a strong recommendation for the use of TMD screening tools in this particular population.

Association Between Temporomandibular Disorders and Irritable Bowel Syndrome: A Scoping Review.
Saczuk K, Roszuk S, Wirkijowska M, Fabisiak A, Eyüboğlu TF, Özcan M, Lukomska-Szymanska M.
J Clin Med. 2024 Dec 2;13(23):7326. doi: 10.3390/jcm13237326. PMID: 39685784; PMCID: PMC11642684.

Temporomandibular disorders (TMDs) encompass various clinical conditions associated with the temporomandibular joint (TMJ) and the masticatory muscles. TMD symptoms include pain in the orofacial region, restricted or altered mandibular movement, and sounds associated with the temporomandibular joint (TMJ). This condition adversely affects quality of life, social functioning, and daily activities, and may also contribute to widespread pain syndromes and comorbidities, including irritable bowel syndrome (IBS). IBS is a common chronic functional disorder of the lower gastrointestinal tract, characterized by recurrent abdominal pain associated with impaired bowel symptoms. Previous studies indicate an association between TMD and IBS. This scoping review examined the correlation between

TMD and IBS concerning their pathology, frequency, and severity, and the potential similarities in how the nervous and endocrine systems influence them. PubMed, SCOPUS, Web of Science, and Google Scholar search engines were utilized to identify suitable studies for this article. Following the application of selection criteria, a total of 58 clinical papers met the eligibility requirements for inclusion in the systematic review. Research showed that both conditions significantly enhance the development of one another and have mutual comorbidities. Both ailments were proven to modify central nervous system processing, leading to high comorbidity in patients. Combining dental and gastroenterological treatments, including a simultaneous therapeutic approach, can significantly enhance patients' quality of life, but further research is needed for a holistic approach.

Analysis of Temporomandibular Disorders, Bruxism and Well-Being in Patients with Fibromyalgia Syndrome: A Case-Control Study.

J Oral Rehabil. 2024 Nov 18. doi: 10.1111/joor.13908. Epub ahead of print. PMID: 39558542.

Esteve M, Rosales-Leal JI.

Objectives: To analyse temporomandibular disorders (TMD), bruxism and well-being in patients with fibromyalgia and compare these outcomes with a control group.
Method: Diagnostic criteria for the assessment of TMD, bruxism and well-being were used in a clinic context including patients with fibromyalgia (n = 71) and a control group of healthy subjects (n = 151). Participants completed an online questionnaire measuring temporomandibular pain, headache attributed to TMD, jaw locking, joint sounds, headache to bruxism, potential sleep bruxism, potential awake bruxism, jaw functional limitation scale 8 (JFLS-8), generalised anxiety disorder scale 7, oral health impact profile scale 14, World Health Organization well-being index (WHO-5) and Pittsburgh sleep quality index (PSQI).
Results: TMD and bruxism were significantly associated with the type of population (χ^2 = 8.77-57.62; $p < 0.05$; ES = 0.20-0.51). Fibromyalgia patients showed higher prevalence (% values) than control group in temporomandibular pain, headache attributed to TMD, jaw locking, headache attributed to potential bruxism, sleep bruxism and awake bruxism. However, there was a greater prevalence of joint sounds in the control group compared to the fibromyalgia group. Also, fibromyalgia patients scored significantly higher ($p < 0.001$) on JFLS-8, GAD-7, OHIP-14 and PSQI with a large effect size (ES = 0.51-0.73), while WHO-5 scores were significantly lower (ES = 0.58).
Conclusion: Patients with fibromyalgia had greater prevalence than the control group in TMJ pain, headache attributed to TMD, jaw locking, headache attributed to bruxism, sleep bruxism and awake bruxism. Another main finding was that patients with fibromyalgia had greater jaw functional limitation, generalised anxiety and impact of oral health on an individual's life. In addition, fibromyalgia patients showed lower sleep quality and well-being index.

Health and Socioeconomic Well-being of Women with Endometriosis and Provoked Vestibulodynia: Longitudinal Insights from Swedish Registry Data.

Mühlrad H, Olovsson M, Linnros E, Haraldson P, Bohm-Starke N. PLoS One. 2024 Sep 3;19(9):e0307412. doi: 10.1371/journal.pone.0307412. PMID: 39226269; PMCID: PMC11371220.

Endometriosis and provoked vestibulodynia (PVD) are prevalent pain conditions among women of reproductive age, significantly impacting their quality of life and psychological well-being. However, comprehensive evidence regarding the lifelong health and socioeconomic outcomes for these individuals remains scarce. Additionally, many prior studies rely on limited and sometimes unrepresentative samples. This study aims to inform on the long-term consequences of these disorders by examining health, fertility, and employment outcomes in a cohort of women diagnosed with endometriosis and/or PVD, tracing their experiences from childhood to their 40s. Leveraging nationwide administrative data from Sweden and employing a matched case-control design, we investigate both similarities and differences between women with these diagnoses and those without. Our findings indicate that women diagnosed with endometriosis and/or PVD demonstrate elevated healthcare utilization patterns, commencing in their early teenage years and progressively increasing over time. Notably, disparities in labor market outcomes emerge in their 20s, showcasing lower labor earnings and a rise in sickness benefit receipt. Moreover, our results show a higher likelihood among these women to experience mental health disorders and concurrent chronic pain diseases, as well as infertility. While the association

between endometriosis and infertility is well-documented, this study offers novel insights into a potential similar link between PVD and infertility. Our study informs healthcare professionals and policymakers about the considerable burden of compromised health, adverse psychosocial well-being, and reduced productivity in the labor market faced by young women with these common pain conditions. These findings underscore the urgency of addressing the multifaceted challenges encountered by individuals diagnosed with endometriosis and PVD across their lifespan.

Subgroups of Pelvic Pain are Differentially Associated with Endometriosis and Inflammatory Comorbidities: A Latent Class Analysis.
Ghiasi M, Chang C, Shafrir AL, Vitonis AF, Sasamoto N, Vazquez AI, DiVasta AD, Upson K, Sieberg CB, Terry KL, Holzman CB, Missmer SA.
Pain. 2024 Sep 1;165(9):2119-2129. doi: 10.1097/j.pain.0000000000003218. Epub 2024 Apr 2. PMID: 38563996; PMCID: PMC11333181.

Chronic pelvic pain is heterogeneous with potentially clinically informative subgroups. We aimed to identify subgroups of pelvic pain based on symptom patterns and investigate their associations with inflammatory and chronic pain-related comorbidities. Latent class analysis (LCA) identified subgroups of participants (n = 1255) from the Adolescence to Adulthood (A2A) cohort. Six participant characteristics were included in the LCA: severity, frequency, and impact on daily activities of both menstruation-associated (cyclic) and non-menstruation-associated (acyclic) pelvic pain. Three-step LCA quantified associations between LC subgroups, demographic and clinical variables, and 18 comorbidities (10 with prevalence ≥10%). Five subgroups were identified: none or minimal (23%), moderate cyclic only (28%), severe cyclic only (20%), moderate or severe acyclic plus moderate cyclic (9%), and severe acyclic plus severe cyclic (21%). Endometriosis prevalence within these 5 LCA-pelvic pain-defined subgroups ranged in size from 4% in "none or minimal pelvic pain" to 24%, 72%, 70%, and 94%, respectively, in the 4 pain subgroups, with statistically significant odds of membership only for the latter 3 subgroups. Migraines were associated with significant odds of membership in all 4 pelvic pain subgroups relative to those with no pelvic pain (adjusted odds ratios = 2.92-7.78), whereas back, joint, or leg pain each had significantly greater odds of membership in the latter 3 subgroups. Asthma or allergies had three times the odds of membership in the most severe pain group. Subgroups with elevated levels of cyclic or acyclic pain are associated with greater frequency of chronic overlapping pain conditions, suggesting an important role for central inflammatory and immunological mechanisms.

Veterans with Chronic Pain: Examining Gender Differences in Pain Type, Overlap, and the Impact of Post-traumatic Stress Disorder.
Hadlandsmyth K, Driscoll MA, Johnson NL, Mares JG, Mengeling MA, Thomas EBK, Norman SB, Lund BC.
Eur J Pain. 2024 Sep;28(8):1311-1319. doi: 10.1002/ejp.2258. Epub 2024 Mar 7. PMID: 38450917.

Background: Women are more likely to experience multiple overlapping pain conditions (MOPCs) relative to men. Post-traumatic stress disorder can negatively impact the severity and trajectory of chronic pain and its treatment. Specific associations between gender, post-traumatic stress disorder (PTSD), and MOPCs require further examination.
Methods: A cohort of all Veterans in 2021 who met criteria for one or more of 12 chronic pain types was created using national Veterans Health Administration administrative data. MOPCs were defined as the number of pain types for which each patient met criteria. Multivariable logistic regression models estimated gender differences in frequency for each of the 12 pain subtypes, after controlling for demographics and comorbidities. Negative binomial regression was used to estimate gender differences in the count of MOPCs and to explore moderation effects between gender and PTSD.
Results: The cohort included 1,936,859 Veterans with chronic pain in 2021, which included 12.5% women. Among those with chronic pain, women Veterans had higher rates of MOPCs (mean = 2.3) relative to men (mean = 1.9): aIRR = 1.31, 95% CI: 1.30-1.32. PTSD also served as an independent risk factor for MOPCs in adjusted analysis (aIRR = 1.23, 95% CI: 1.23-1.24). The interaction term between gender and PTSD was not significant (p = 0.87). Independent of PTSD, depressive disorders also served as a strong risk factor for MOPCs (aIRR = 1.37, 95% CI: 1.36-1.37).
Conclusions: Individuals with MOPCs and PTSD may have complex treatment needs. They may benefit from highly coordinated trauma-sensitive care and integrated

interventions that simultaneously address pain and PTSD.
Significance: Women were significantly more likely than men to experience MOPCs. PTSD was also significantly, independently, associated with MOPCs. Patients, particularly women, may benefit from tailored interventions that address both trauma and MOPCs.

Risk Factors for Temporomandibular Disorders: A Systematic Review of Cohort Studies.
Da-Cas CD, Valesan LF, Nascimento LPD, Denardin ACS, Januzzi E, Fernandes G, Stuginski-Barbosa J, Mendes de Souza BDM.
Oral Surg Oral Med Oral Pathol Oral Radiol. 2024 Oct;138(4):502-515. doi: 10.1016/j.oooo.2024.06.007. Epub 2024 Jun 19. PMID: 39079850.

Objective: A systematic review was performed to synthesize and identify risk factors involved in TMD onset.
Study design: Electronic searches were conducted in PubMed, Web of Science, Scopus, Embase, PsyInfo and Lilacs databases, as well as in three gray literature databases (Google Scholar, ProQuest and Open grey). The studies were blindly assessed by two reviewers and selected by a pre-defined eligibility criterion. Risk of bias of included studies was assessed using the Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies. Grading of Recommendations Assessment, Development and Evaluation (GRADE) was evaluated for most related factors.
Results: Twenty-one cohort studies were included. Significant factors were female gender, symptoms of depression and anxiety, perceived stress, sleep quality, symptoms of obstructive sleep apnea and presence of any comorbidity, such as Irritable Bowel Syndrome, lower back pain, headache frequency, tension-type headache, migraine and mixed headache. Moreover, high estrogen and low testosterone levels in utero, greater pain perception, jaw mobility pain, pain during palpation, orofacial anomalies, as well as extrinsic and intrinsic injuries were also significant.
Conclusions: Several factors seems to be involved in TMD onset, however, more studies with standardized methodology are necessary to confirm these findings.

Resistant and Refractory Migraine - Two Different Entities with Different Comorbidities? Results From the REFINE Study.
Rosignoli C, Ornello R, Caponnetto V, Onofri A, Avaltroni S, Braschinsky M, Šved O, Gil-Gouveia R, Lampl C, Paungarttner J, Martelletti P, Wells-Gatnik WD, Martins IP, Mitsikostas D, Apostolakopoulou L, Nabaei G, Ozge A, Narin DB, Pozo-Rosich P, Muñoz-Vendrell A, Prudenzano MP, Gentile M, Ryliskiene K, Vainauskiene J, Del Rio MS, Vernieri F, Iaccarino G, Waliszewska-Prosol M, Budrewicz S, Carnovali M, Katsarava Z, Sacco S.
J Headache Pain. 2024 Dec 3;25(1):212. doi: 10.1186/s10194-024-01910-3. PMID: 39627727; PMCID: PMC11613769.

Background: Resistant and refractory migraine are commonly encountered in specialized headache centers. Several comorbidities, mostly psychiatric conditions, have been linked to migraine worsening; however, there is little knowledge of the comorbidity profile of individuals with resistant and refractory migraine.
Methods: REFINE is a prospective observational multicenter international study involving individuals with migraine from 15 headache centers. Participants were categorized into three groups based on the European Headache Federation criteria: non-resistant and non-refractory (NRNRM), resistant (ResM), and refractory (RefM). We explored the prevalence of 20 comorbidities at baseline in the three groups.
Results: Of the 689 included patients (82.8% women), 262 (38.0%) had ResM, 73 (10.4%) had RefM and 354 (51.4%) NRNRM. A higher prevalence of psychiatric comorbidities, trigger points, temporomandibular joint disorders, thyroiditis, and cerebrovascular diseases was observed in the RefM group, followed by ResM and NRNRM. Multiple comorbidities were more common in the RefM group, followed by the ResM group and by the NRNRM group (41.6% vs. 24.5% vs. 14.1% respectively; $p < 0.001$). At the sensitivity analysis, exploring participants with chronic migraine, significant differences among the NRNRM, ResM, and RefM groups were found in the prevalence of anxiety ($p < 0.001$), asthma and rhinitis ($p = 0.013$), bipolar and other psychiatric disorders ($p = 0.049$), cerebrovascular diseases ($p < 0.001$), depression ($p < 0.001$), obesity ($p = 0.002$), thyroiditis ($p < 0.001$), and trigger points ($p = 0.008$).
Conclusion: REFINE data indicate that individuals with ResM and RefM have a higher burden of comorbidities than those with NRNRM. It can be postulated that those comorbidities may have an impact on the progression of migraine from a form that is easy

to treat to a form that is resistant or refractory to treatments. Longitudinal studies are needed to understand the direction of the association between ResM or RefM and those comorbidities and if proper treatment of comorbidities might help overcome treatment resistance or refractoriness.

CPRA WEBSITE | DONATE | CPRA WHITE PAPER | JOIN THIS MAILING LIST

The Chronic Pain Research Alliance is an initiative of The TMJ Association, Ltd.
A NON-PROFIT 501(c)(3) Tax Exempt Organization.

About the Chronic Pain Research Alliance

The Chronic Pain Research Alliance (CPRA) is the only research-led collaborative advocacy initiative dedicated to improving the lives of those affected by multiple pain conditions, termed Chronic Overlapping Pain Conditions (COPCs). These include temporomandibular disorders, fibromyalgia, irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, migraine and tension-type headache, endometriosis, vulvodynia, myalgic encephalomyelitis/chronic fatigue syndrome and chronic low back pain.

The CPRA envisions and is working towards a future where people with COPCs receive a timely diagnosis, followed by whole-person, team-based and patient-centered medical care, including the use of safe and effective approved treatments, that is informed by the latest and most rigorous scientific evidence.

Your support is vital to the CPRA's existence. Please consider making a contribution today! One-hundred percent of your tax-deductible gift will be used to further CPRA's mission and will specifically support initiatives to: 1) promote a rigorous, standardized and collaborative scientific research effort on COPCs; 2) translate research findings into educational initiatives for clinicians and patients; and 3) advance biopharmaceutical industry efforts to research and develop safe and effective therapies for COPCs.