CUTTING EDGE

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COPCs Research Advances

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This e-newsletter - published by the CPRA to keep the medical-scientific and patient communities abreast of research advances on Chronic Overlapping Pain Conditions (COPCs) - contains abstracts of studies on the epidemiology, pathophysiology and clinical management of COPCs published between May and August 2024.

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Pathophysiology Studies

Chronic Overlapping Pain Conditions and Nociplastic Pain.
Johnston KJA, Signer R, Huckins LM.
medRxiv [Preprint]. 2024 May 8:2023.06.27.23291959. doi: 10.1101/2023.06.27.23291959. PMID: 38766033; PMCID: PMC11100847.

Chronic Overlapping Pain Conditions (COPCs) are a subset of chronic pain conditions commonly comorbid with one another and more prevalent in women and assigned female at birth (AFAB) individuals. Pain experience in these conditions may better fit with a new mechanistic pain descriptor, nociplastic pain, and nociplastic type pain may represent a shared underlying factor among COPCs. We applied GenomicSEM common-factor genome wide association study (GWAS) and multivariate transcriptome-wide association (TWAS) analyses to existing GWAS output for six COPCs in order to find genetic variation associated with nociplastic type pain, followed by genetic correlation (linkage-disequilibrium score regression), gene-set and tissue enrichment analyses. We found 24 independent single nucleotide polymorphisms (SNPs), and 127 unique genes significantly associated with nociplastic type pain, and showed nociplastic type pain to be a polygenic trait with significant SNP-heritability. We found significant genetic overlap between multisite chronic pain and nociplastic type pain, and to a smaller extent with rheumatoid arthritis and a neuropathic pain phenotype. Tissue enrichment analyses highlighted cardiac and thyroid tissue, and gene set enrichment analyses emphasized potential shared mechanisms in cognitive, personality, and metabolic traits and nociplastic type pain along with distinct pathology in migraine and headache. We use a well-powered network approach to investigate nociplastic type pain using existing COPC GWAS output, and show nociplastic type pain to be a complex, heritable trait, in addition to contributing to understanding of potential mechanisms in development of nociplastic pain.

The Influence of Pain Hypersensitivity and Psychological Factors on Pain and Disability in the

Transition from Acute to Chronic Low Back Pain: A Longitudinal Exploratory Investigation and Cluster Analysis.
Chang WJ, Jenkins LC, Humburg P, Schabrun SM.
J Pain. 2024 May 31:104584. doi: 10.1016/j.jpain.2024.104584. Epub ahead of print. PMID: 38825052.

Pain hypersensitivity is present in some people with acute low back pain (LBP) and thought to be involved in the development of chronic LBP. Early evidence suggests that pain hypersensitivity in acute LBP precedes poor long-term outcome. We aimed to examine whether the presence of pain hypersensitivity in acute LBP influenced recovery status at six months and differentiated how pain and disability changed over time. Participants with acute non-specific LBP (<6 weeks after pain onset, N=118) were included in this longitudinal study. Quantitative sensory testing including pressure and heat pain thresholds and conditioned pain modulation and questionnaires were compared at baseline and longitudinally (at three and six months) between recovered and unrecovered participants. Using k-means clustering, we identified subgroups based on baseline sensory measures alone, and in combination with psychological factors, and compared pain and disability outcomes between subgroups. Sensory measures did not differ at baseline or longitudinally between recovered (N=50) and unrecovered (N=68) participants. Subgrouping based on baseline sensory measures alone did not differentiate pain or disability outcomes at any timepoint. Participants with high psychological distress at baseline (N=19) had greater disability, but not pain, at all timepoints than those with low psychological distress, regardless of the degrees of pain sensitivity. Our findings suggest that pain hypersensitivity in acute LBP does not precede poor recovery at six months or differentiate how pain and disability change over time. High psychological distress during acute LBP is associated with unremitting and pronounced disability, while pain severity is unaffected. PERSPECTIVE: Pain hypersensitivity is thought to be involved in the transition to chronic LBP. Contradictory to prevailing hypothesis, our findings suggest pain hypersensitivity alone in acute LBP do not precede poor recovery. High psychological distress in acute LBP has stronger influence than pain hypersensitivity on long-term disability, but not pain outcomes.

Symptomatic Autonomic Dysfunction in Interstitial Cystitis/Bladder Pain Syndrome.
Ritts R, Wolff D, Namugosa M, Hsu FC, Ferrara K, Evans R, Walker SJ.
Urogynecology (Phila). 2024 Jun 27. doi: 10.1097/SPV.0000000000001536. Epub ahead of print. PMID: 38954605.

Importance: Interstitial cystitis/bladder pain syndrome (IC/BPS) is a highly prevalent condition with incompletely understood pathophysiology, especially in relation to the systemic symptoms experienced. The role of autonomic nervous system dysfunction in IC/BPS remains poorly understood.
Objective: The purpose of this study was to assess the relationship between autonomic symptom severity and clinical characteristics of patients with IC/BPS.
Study design: This is a retrospective cohort study of 122 IC/BPS patients who completed the Composite Autonomic Symptoms Score (COMPASS-31) questionnaire. Data were collected on anesthetic bladder capacity (BC), Hunner lesion (HL) status, results for validated IC/BPS symptom questionnaires (O'Leary Sant Interstitial Cystitis Symptom Index and Interstitial Cystitis Problem Index (ICSI/ICPI) and the Pelvic Pain and Urgency/Frequency (PUF) scale), and comorbid nonurologic associated syndromes. Using the first quartile of COMPASS-31 scores as the cutoff, we compared patients within the first quartile (low symptom load; n = 30), to the remainder of the patients (high symptom load; n = 92).
Results: Patients scoring ≥20.36 were significantly less likely to be HL positive (10.9% vs 26.7%; P = 0.043) and had a significantly higher BC (823.10 ± 396.07 vs 635.00 ± 335.06; P = 0.027), higher scores on the PUF questionnaire (23.80 ± 4.98 vs; 19.61 ± 5.22 P < 0.001), and a higher number of nonurologic associated syndromes (5.65 ± 2.90 vs 2.60 ± 1.89; P < 0.001).
Conclusions: Patients with IC/BPS experience widespread symptoms associated with autonomic nervous system dysfunction. A higher symptom load strongly correlates with a nonbladder-centric phenotype. These findings provide further evidence that total body nervous system dysfunction is present in patients with nonbladder centric IC/BPS.

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 Jul 31:qeae053. doi: 10.1093/sxmrev/qeae053. Epub ahead of print. 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.

Neuroinflammatory Activation in Sensory and Motor Regions of the Cortex is Related to Sensorimotor Function in Individuals with Low Back Pain Maintained by Nociplastic Mechanisms: A Preliminary Proof-of-Concept Study.
Shraim MA, Massé-Alarie H, Farrell MJ, Cavaleri R, Loggia ML, Hodges PW.
Eur J Pain. 2024 Jul 15. doi: 10.1002/ejp.2313. Epub ahead of print. PMID: 39007713.

Background: Chronic pain involves communication between neural and immune systems. Recent data suggest localization of glial (brain immune cells) activation to the sensorimotor regions of the brain cortex (S1/M1) in chronic low back pain (LBP). As glia perform diverse functions that impact neural function, activation might contribute to sensorimotor changes, particularly in LBP maintained by increased nervous system sensitivity (i.e., nociplastic pain). This preliminary proof-of-concept study aimed to: (i) compare evidence of neuroinflammatory activation in S1/M1 between individuals with and without LBP (and between nociceptive and nociplastic LBP phenotypes), and (ii) evaluate relationships between neuroinflammatory activation and sensorimotor function.
Methods: Simultaneous PET-fMRI measured neuroinflammatory activation in functionally defined S1/M1 in pain-free individuals (n = 8) and individuals with chronic LBP (n = 9; nociceptive: n = 4, nociplastic: n = 5). Regions of S1/M1 related to the back were identified using fMRI during motor tasks and thermal stimuli. Sensorimotor measures included single and paired-pulse transcranial magnetic stimulation (TMS) and quantitative sensory testing (QST). Sleep, depression, disability and pain questionnaires were administered.
Results: Neuroinflammatory activation was greater in the lower back cortical representation of S1/M1 of the nociplastic LBP group than both nociceptive LBP and pain-free groups. Neuroinflammatory activation in S1/M1 was positively correlated with sensitivity to hot (r = 0.52) and cold (r = 0.55) pain stimuli, poor sleep, depression, disability and BMI, and negatively correlated with intracortical facilitation (r = -0.41).
Conclusion: This preliminary proof-of-concept study suggests that neuroinflammation in back regions of S1/M1 in individuals with nociplastic LBP could plausibly explain some characteristic features of this LBP phenotype.
Significance statement: Neuroinflammatory activation localized to sensorimotor areas of the brain in individuals with nociplastic pain might contribute to changes in sensory and motor function and aspects of central sensitization. If cause-effect relationships are established in longitudinal studies, this may direct development of therapies that target neuroinflammatory activation.

Exploring the Bidirectional Causal Associations Between Pain and Circulating Inflammatory Proteins: A Mendelian Randomization Study.
Wang Y, Zhou W, Zhang F, Wei J, Wang S, Min K, Chen Y, Yang H, Lv X.
Clin Exp Pharmacol Physiol. 2024 Aug;51(8):e13905. doi: 10.1111/1440-1681.13905. PMID: 38965671.

Multisite chronic pain (MCP) and site-specific chronic pain (SSCP) may be influenced by circulating inflammatory proteins, but the causal relationship remains unknown. To overcome this limitation, two-sample bidirectional Mendelian randomization (MR) analysis was used to analyse data for 91 circulating inflammatory proteins, MCP and SSCP encompassing headache, back pain, shoulder pain, hip pain, knee pain, stomach abdominal pain and facial pain. The primary MR method used was inverse variance weighting, sensitivity analyses included weighted median, MR pleiotropy residual sum and outlier and the Egger intercept method. Heterogeneity was also detected using Cochrane's Q test and leave-one-out analyses. Finally, a causal relationship between 29 circulating inflammatory proteins and chronic pain was identified. Among these proteins, 14 exhibited a protective effect, including MCP (T-cell surface glycoprotein cluster of differentiation 5), headache (4E-binding protein 1 [4EBP1], cluster of differentiation 40, cluster of differentiation 6 and C-X-C motif chemokine [CXCL] 11), back pain (leukaemia inhibitory factor), shoulder pain (fibroblast growth factor [FGF]-5 and interleukin [IL]-18R1), stomach abdominal pain (tumour necrosis factor [TNF]-α), hip pain (CXCL1, IL-20 and signalling lymphocytic activation molecule 1) and knee pain (IL-7 and TNF-β). Additionally, 15 proteins were identified as risk factors for MCP and SSCP: MCP (colony-stimulating factor 1, human glial cell line-derived neurotrophic factor and IL-17C), headache (fms-related tyrosine kinase 3 ligand, IL-20 receptor subunit α [IL-20RA], neurotrophin-3 and tumour necrosis factor receptor superfamily member 9), facial pain (CXCL1), back pain (TNF), shoulder pain (IL-17C and matrix metalloproteinase-10), stomach abdominal pain (IL-20RA), hip pain (C-C motif chemokine 11/eotaxin-1 and tumour necrosis factor ligand superfamily member 12) and knee pain (4EBP1). Importantly, in the opposite direction, MCP and SSCP did not exhibit a significant causal impact on circulating inflammatory proteins. Our study identified potential causal influences of various circulating inflammatory proteins on MCP and SSCP and provided promising treatments for the clinical management of MCP and SSCP.

Genetic Variations in TrkB.T1 Isoform and Their Association With Somatic and Psychological Symptoms in Individuals With IBS.
Hong H, Mocci E, Kamp K, Zhu S, Cain KC, Burr RL, Perry JA, Heitkemper MM, Weaver-Toedtman KR, Dorsey SG.

J Pain. 2024 Jul 14:104634. doi: 10.1016/j.jpain.2024.104634. Epub ahead of print. PMID: 39004388.

Irritable bowel syndrome (IBS), a disorder of gut-brain interaction, is often comorbid with somatic pain and psychological disorders. Dysregulated signaling of brain-derived neurotrophic factor (BDNF) and its receptor, tropomyosin-related kinase B (TrkB), has been implicated in somatic-psychological symptoms in individuals with IBS. We investigated the association of 10 single nucleotide polymorphisms (SNPs) in the regulatory 3' untranslated region (UTR) of NTRK2 (TrkB) kinase domain-deficient truncated isoform (TrkB.T1) and BDNF Val66Met SNP with somatic and psychological symptoms and quality of life in a cohort from the United States (U.S.) (IBS n=464; healthy controls n=156). We found that the homozygous recessive genotype (G/G) of rs2013566 in individuals with IBS is associated with worsened somatic symptoms, including headache, back pain, joint pain, muscle pain, and somatization as well as diminished sleep quality, energy level and overall quality of life. Validation using United Kingdom BioBank (UKBB) data confirmed the association of rs2013566 with increased likelihood of headache. Several SNPs (rs1627784, rs1624327, rs1147198) showed significant associations with muscle pain in our U.S. cohort. These 4 SNPs are predominantly located in H3K4Me1-enriched regions, suggesting their enhancer and/or transcription regulation potential. Our findings suggest that genetic variation within the 3'UTR region of the TrkB.T1 isoform may contribute to comorbid conditions in individuals with IBS, resulting in a spectrum of somatic and psychological symptoms impacting their quality of life. These findings advance our understanding of the genetic interaction between BDNF/TrkB pathways and somatic-psychological symptoms in IBS, highlighting the importance of further exploring this interaction for potential clinical applications. PERSPECTIVE: This study aims to understand the genetic effects on IBS-related symptoms across somatic, psychological, and quality of life domains, validated by UKBB data. The rs2013566 homozygous recessive genotype correlates with worsened somatic symptoms and reduced quality of life, emphasizing its clinical significance.

Sex Differences in Mechanisms of Pain Hypersensitivity.
Mogil JS, Parisien M, Esfahani SJ, Diatchenko L.
Neurosci Biobehav Rev. 2024 Aug;163:105749. doi: 10.1016/j.neubiorev.2024.105749. Epub 2024 Jun 3. PMID: 38838876.

The introduction of sex-as-a-biological-variable policies at funding agencies around the world has led to an explosion of very recent observations of sex differences in the biology underlying pain. This review considers evidence of sexually dimorphic mechanisms mediating pain hypersensitivity, derived from modern assays of persistent pain in rodent animal models. Three well-studied findings are described in detail: the male-specific role of spinal cord microglia, the female-specific role of calcitonin gene-related peptide (CGRP), and the female-specific role of prolactin and its receptor. Other findings of sex-specific molecular involvement in pain are subjected to pathway analyses and reveal at least one novel hypothesis: that females may preferentially use Th1 and males Th2 T cell activity to mediate chronic pain.

Chronic Stress Induces Wide-Spread Hyperalgesia: The Involvement of Spinal CCK_1 Receptors.
Li JH, Zhao SJ, Guo Y, Chen F, Traub RJ, Wei F, Cao DY.
Neuropharmacology. 2024 Jul 9;258:110067. doi: 10.1016/j.neuropharm.2024.110067. Epub ahead of print. PMID: 38992792.

Chronic primary pain (CPP) occurs in the absence of tissue injury and includes temporomandibular disorders (TMD), fibromyalgia syndrome (FMS) and irritable bowel syndrome (IBS). CPP is commonly considered a stress-related chronic pain and often presents as wide-spread pain or comorbid pain conditions in different regions of the body. However, whether prolonged stress can directly result in the development of CPP comorbidity remains unclear. In the present study, we adapted a 21 day heterotypic stress paradigm in mice and examined whether chronic stress induced wide-spread hyperalgesia, modeling comorbid CPP in the clinic. We found that chronic stress induced anxiety- and depression-like behaviors, and resulted in long-lasting wide-spread hyperalgesia over several body regions such as the orofacial area, hindpaw, thigh, upper back and abdomen in female mice. We further found that the expression of cholecystokinin $(CCK)_1$ receptors was significantly increased in the L4-L5 spinal dorsal horn of the female mice after 14 and 21 day heterotypic stress compared with the control animals. Intrathecal injection of the CCK_1 receptor antagonist CR-1505 blocked pain hypersensitivity in the subcervical body including the upper back, thigh, hindpaw and abdomen. These findings suggest that the upregulation of spinal CCK_1 receptors after chronic stress contributes to the central mechanisms underlying the development of wide-spread hyperalgesia, and may provide a potential and novel central target for clinical treatment of CPP.

Mechanisms Underlying Sex Differences in Temporomandibular Disorders and Their Comorbidity with Migraine.
Khan A, Liu S, Tao F.
Brain Sci. 2024 Jul 15;14(7):707. doi: 10.3390/brainsci14070707. PMID: 39061447; PMCID: PMC11274652.

Sexual dimorphism in temporomandibular disorders (TMDs) and their comorbidity with migraine are important phenomena observed in clinics. TMDs are the most prevalent orofacial pain conditions with jaw joint and masseter muscle dysfunction. Migraine is the predominant headache commonly associated with TMDs. Women much more often suffer from this orofacial pain than men. However, currently, there is no gender-specific therapy for such pain conditions. Understanding the pathophysiological mechanisms behind sex differences in TMDs as well as their comorbidity with migraines is essential for developing novel

approaches for gender-specific treatment of TMDs and related orofacial pain comorbidity. In this review, we summarize recent research progress regarding sex differences in TMDs, focusing on the underlying mechanisms including craniofacial anatomy, hormonal regulation, and roles of opioids, transient receptor potential channels, and endocannabinoid systems. We also discuss the mechanisms of comorbid TMDs and migraine. The information covered in this review will provide mechanistic insights into sex differences in TMDs and their comorbidity with migraine, which could aid in developing effective treatment strategies for the overlapping orofacial pain condition.

Sex Differences in Visceral Pain and Comorbidities: Clinical Outcomes, Preclinical Models, and Cellular and Molecular Mechanisms.
Tiwari N, Qiao LY.
Cells. 2024 May 14;13(10):834. doi: 10.3390/cells13100834. PMID: 38786056; PMCID: PMC11119472.

Sexual dimorphism of visceral pain has been documented in clinics and experimental animal models. Aside from hormones, emerging evidence suggests the sex-differential intrinsic neural regulation of pain generation and maintenance. According to the International Association for the Study of Pain (IASP) and the American College of Gastroenterology (ACG), up to 25% of the population have visceral pain at any one time, and in the United States 10-15 percent of adults suffer from irritable bowel syndrome (IBS). Here we examine the preclinical and clinical evidence of sex differences in visceral pain focusing on IBS, other forms of bowel dysfunction and IBS-associated comorbidities. We summarize preclinical animal models that provide a means to investigate the underlying molecular mechanisms in the sexual dimorphism of visceral pain. Neurons and nonneuronal cells (glia and immune cells) in the peripheral and central nervous systems, and the communication of gut microbiota and neural systems all contribute to sex-dependent nociception and nociplasticity in visceral painful signal processing. Emotion is another factor in pain perception and appears to have sexual dimorphism.

Pain Hypersensitivity is Dependent on Autophagy Protein Beclin 1 in Males but not Females.
Tam TH, Zhang W, Tu Y, Hicks JL, Farcas S, Kim D, Salter MW.
Cell Rep. 2024 Jun 25;43(6):114293. doi: 10.1016/j.celrep.2024.114293. Epub 2024 May 29. PMID: 38814784.

Chronic pain is associated with alterations in fundamental cellular processes. Here, we investigate whether Beclin 1, a protein essential for initiating the cellular process of autophagy, is involved in pain processing and is targetable for pain relief. We find that monoallelic deletion of Becn1 increases inflammation-induced mechanical hypersensitivity in male mice. However, in females, loss of Becn1 does not affect inflammation-induced mechanical hypersensitivity. In males, intrathecal delivery of a Beclin 1 activator, tat-beclin 1, reverses inflammation- and nerve injury-induced mechanical hypersensitivity and prevents mechanical hypersensitivity induced by brain-derived neurotrophic factor (BDNF), a mediator of inflammatory and neuropathic pain. Pain signaling pathways converge on the enhancement of N-methyl-D-aspartate receptors (NMDARs) in spinal dorsal horn neurons. The loss of Becn1 upregulates synaptic NMDAR-mediated currents in dorsal horn neurons from males but not females. We conclude that inhibition of Beclin 1 in the dorsal horn is critical in mediating inflammatory and neuropathic pain signaling pathways in males.

Clinical Studies

Deciphering Nociplastic Pain: Clinical Features, Risk Factors and Potential Mechanisms.
Kaplan CM, Kelleher E, Irani A, Schrepf A, Clauw DJ, Harte SE.
Nat Rev Neurol. 2024 Jun;20(6):347-363. doi: 10.1038/s41582-024-00966-8. Epub 2024 May 16. PMID: 38755449.

Nociplastic pain is a mechanistic term used to describe pain that arises or is sustained by altered nociception, despite the absence of tissue damage. Although nociplastic pain has distinct pathophysiology from nociceptive and neuropathic pain, these pain mechanisms often coincide within individuals, which contributes to the intractability of chronic pain. Key symptoms of nociplastic pain include pain in multiple body regions, fatigue, sleep disturbances, cognitive dysfunction, depression and anxiety. Individuals with nociplastic pain are often diffusely tender - indicative of hyperalgesia and/or allodynia - and are often more sensitive than others to non-painful sensory stimuli such as lights, odours and noises. This Review summarizes the risk factors, clinical presentation and treatment of nociplastic pain, and describes how alterations in brain function and structure, immune processing and peripheral factors might contribute to the nociplastic pain phenotype. This article concludes with a discussion of two proposed subtypes of nociplastic pain that reflect distinct neurobiological features and treatment responsivity.

Prognostic Subgroups of Chronic Pain Patients Using Latent Variable Mixture Modeling within a Supervised Machine Learning Framework.
Zhao X, Dannenberg K, Repsilber D, Gerdle B, Molander P, Hesser H.
Sci Rep. 2024 May 31;14(1):12543. doi: 10.1038/s41598-024-62542-w. PMID: 38822075; PMCID: PMC11143186.

The present study combined a supervised machine learning framework with an unsupervised method, finite mixture modeling, to identify prognostically meaningful subgroups of diverse chronic pain patients undergoing interdisciplinary treatment. Questionnaire data collected at pre-treatment and 1-year follow up from 11,995 patients from the Swedish Quality Registry for Pain Rehabilitation were used. Indicators

measuring pain characteristics, psychological aspects, and social functioning and general health status were used to form subgroups, and pain interference at follow-up was used for the selection and the performance evaluation of models. A nested cross-validation procedure was used for determining the number of classes (inner cross-validation) and the prediction accuracy of the selected model among unseen cases (outer cross-validation). A four-class solution was identified as the optimal model. Identified subgroups were separable on indicators, predictive of long-term outcomes, and related to background characteristics. Results are discussed in relation to previous clustering attempts of patients with diverse chronic pain conditions. Our analytical approach, as the first to combine mixture modeling with supervised, targeted learning, provides a promising framework that can be further extended and optimized for improving accurate prognosis in pain treatment and identifying clinically meaningful subgroups among chronic pain patients.

Factors Associated with Having Previously Received a Diagnosis of Fibromyalgia, Chronic Fatigue Syndrome and Irritable Bowel Syndrome: A Cross Sectional DanFunD Study.
Tattan M, Ørnbøl E, Wellnitz KB, Hanssen DJC, Dantoft TM, Rosmalen JGM, Fink P, Petersen MW.
J Psychosom Res. 2024 Jun;181:111693. doi: 10.1016/j.jpsychores.2024.111693. Epub 2024 May 5. PMID: 38724318.

Objectives: Fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome are highly prevalent conditions and part of the functional somatic syndromes (FSS) diagnosis, that are classified under the unifying umbrella term functional somatic disorder (FSD). Multiple factors are associated with FSD symptom development; However, few studies have explored these associations in relation to the diagnosis status. This study aims to examine associations with a previously received FSS diagnosis from a physician in participants fulfilling the FSD diagnostic criteria in a population-based sample.
Methods: This research employs a comprehensive observational approach using a cross sectional design with data from the DanFunD part two cohort. Information about received FSS diagnoses was obtained from self-reported questionnaires. Participants fulfilling the FSD diagnostic criteria were identified with both self-reported questionnaires and diagnostic interviews. Validated questionnaires were used to assess the examined factors.
Results: 1704 cases fulfilled the diagnostic criteria for an FSD according to questionnaires or interviews in the DanFunD study. In participants fulfilling the diagnostic criteria, having previously received an FSS diagnosis by a physician was strongly associated with female sex, negative illness perceptions and poor health-related quality of life for questionnaire and interview-based diagnoses. Less consistent associations were observed for lower socioeconomic status, anxiety, and adverse life events.
Conclusion: Previously received FSS diagnoses showed associations with multiple factors with a particular strong association with female sex and poor health related quality of life.

How to Understand the Overlap of Long COVID, Chronic Fatigue Syndrome/Myalgic Encephalomyelitis, Fibromyalgia and Irritable Bowel Syndromes.
Goldenberg DL
Semin Arthritis Rheum. 2024 Aug;67:152455. doi: 10.1016/j.semarthrit.2024.152455. Epub 2024 May 7. PMID: 38761526.

Long COVID should be limited to patients with multiple, persistent symptoms not related to well-defined organ damage. Once redefined, a focused review of long COVID demonstrates striking similarity to chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), fibromyalgia (FM) and irritable bowel syndrome (IBS). Research in long COVID has revealed similar findings to those noted in CFS/ME and FM, characterized by central nervous system organ dysfunction. Long COVID, like CFS/ME, FM and IBS, is best understood as a bidirectional mind-body, neuroimmune illness.

The State of Synthetic Cannabinoid Medications for the Treatment of Pain.
Maglaviceanu A, Peer M, Rockel J, Bonin RP, Fitzcharles MA, Ladha KS, Bhatia A, Leroux T, Kotra L, Kapoor M, Clarke H.
CNS Drugs. 2024 Aug;38(8):597-612. doi: 10.1007/s40263-024-01098-9. Epub 2024 Jul 1. PMID: 38951463.

Synthetic cannabinoids are compounds made in the laboratory to structurally and functionally mimic phytocannabinoids from the Cannabis sativa L. plant, including delta-9-tetrahydrocannabinol (THC). Synthetic cannabinoids (SCs) can signal via the classical endogenous cannabinoid system (ECS) and the greater endocannabidiome network, highlighting their signalling complexity and far-reaching effects. Dronabinol and nabilone, which mimic THC signalling, have been approved by the Food and Drug Administration (FDA) for treating nausea associated with cancer chemotherapy and/or acquired immunodeficiency syndrome (AIDS). However, there is ongoing interest in these two drugs as potential analgesics for a variety of other clinical conditions, including neuropathic pain, spasticity-related pain, and nociplastic pain syndromes including fibromyalgia, osteoarthritis, and postoperative pain, among others. In this review, we highlight the signalling mechanisms of FDA-approved synthetic cannabinoids, discuss key clinical trials that investigate their analgesic potential, and illustrate challenges faced when bringing synthetic cannabinoids to the clinic.

Duloxetine Improves Chronic Orofacial Pain and Comorbid Depressive Symptoms in Association with Reduction of Serotonin Transporter Protein through Upregulation of Ubiquitinated Serotonin Transporter Protein.
Nakamura M, Yoshimi A, Tokura T, Kimura H, Kishi S, Miyauchi T, Iwamoto K, Ito M, Sato-Boku A, Mouri

A, Nabeshima T, Ozaki N, Noda Y.
Pain. 2024 May 1;165(5):1177-1186. doi: 10.1097/j.pain.0000000000003124. Epub 2024 Jan 11. PMID: 38227563.

Chronic orofacial pain (COP) is relieved by duloxetine (DLX) and frequently causes depressive symptoms. The aim of this study was to confirm effects of DLX on pain and depressive symptoms, and to associate with their effectiveness in platelet serotonin transporter (SERT) expression, which is a target molecule of DLX and plasma serotonin concentration in COP patients with depressive symptoms. We assessed for the severity of pain and depressive symptoms using the Visual Analog Scale (VAS) and 17-item Hamilton Depression Rating Scale (HDRS), respectively. Chronic orofacial pain patients were classified into 2 groups based on their HDRS before DLX-treatment: COP patients with (COP-D) and without (COP-ND) depressive symptoms. We found that the VAS and HDRS scores of both groups were significantly decreased after DLX treatment compared with those before DLX treatment. Upregulation of total SERT and downregulation of ubiquitinated SERT were observed before DLX treatment in both groups compared with healthy controls. After DLX treatment, there were no differences in total SERT of both groups and in ubiquitinated SERT of COP-D patients compared with healthy controls; whereas, ubiquitinated SERT of COP-ND patients remained downregulated. There were positive correlations between changes of serotonin concentrations and of VAS or HDRS scores in only COP-D patients. Our findings indicate that DLX improves not only pain but also comorbid depressive symptoms of COP-D patients. Duloxetine also reduces platelet SERT through upregulation of ubiquitinated SERT. As the result, decrease of plasma serotonin concentrations may be related to the efficacy of DLX in relieving pain and depression in COP patients.

Latent Profile Analysis of Canadian Military Veterans with Chronic Pain Identifies 5 Meaningful Classes Through Self-Report Measures.
Walton DM, Bobos P, MacDermid JC.
J Pain. 2024 Aug;25(8):104517. doi: 10.1016/j.jpain.2024.03.013. Epub 2024 Apr 10. PMID: 38609027.

The purpose of this study was to identify meaningful response patterns in self-report survey data collected from Canadian military veterans with chronic pain and to create an algorithm intended to facilitate triage and prioritization of veterans to the most appropriate interventions. An online survey was presented to former members of the Canadian military who self-identified as having chronic pain. Variables collected were related to pain, physical and mental interference, prior traumatic experiences, and indicators from each of the 7 potential drivers of the pain experience. Maximum likelihood estimation-based latent profile analysis was used to identify clinically and statistically meaningful profiles using the 7-axis variables, and classification and regression tree (CRT) analysis was then conducted to identify the most parsimonious set of indicators that could be used to accurately classify respondents into the most relevant profile group. Data from N = 322 veterans were available for analysis. The results of maximum likelihood estimation-based latent profile analysis indicated a 5-profile structure was optimal for explaining the patterns of responses within the data. These were: Mood-Dominant (13%), Localized Physical (24%), Neurosensory-Dominant (33%), Central-Dominant with complex mood and neurosensory symptoms (16%), and Trauma- and mood-dominant (14%). From CRT analysis, an algorithm requiring only 3 self-report tools (central symptoms, mood screening, bodily coherence) achieved 83% classification accuracy across the 5 profiles. The new classification algorithm requiring 16 total items may be helpful for clinicians and veterans in pain to identify the most dominant drivers of their pain experience that may be useful for prioritizing intervention strategies, targets, and relevant health care disciplines. PERSPECTIVE: This article presents the results of latent profile (cluster) analysis of responses to standardized self-report questionnaires by Canadian military veterans with chronic pain. It identified 5 clusters that appear to represent different drivers of the pain experience. The results could be useful for triaging veterans to the most appropriate pain care providers.

Effects on Temporomandibular Disorder in the Treatment of Tension-Type Headache with Acupuncture and Therapeutic Exercises. A Secondary Analysis from a Randomized Controlled Trial.
Schiller J, Büttner A, Niederer D, Bökel A, Korallus C, Sturm C, Vogt L, Gutenbrunner C, Karst M, Fink M, Egen C.
Clin Rehabil. 2024 May;38(5):623-635. doi: 10.1177/02692155241229282. Epub 2024 Feb 2. PMID: 38304940; PMCID: PMC11005303.

Objectives: To examine the effects of acupuncture and therapeutic exercise alone and in combination on temporomandibular joint symptoms in tension-type headache and to evaluate the potential interaction of existing temporomandibular dysfunction on the success of headache treatment.
Design: Pre-planned secondary analysis of a randomized controlled, non-blinded trial.
Setting: Outpatient clinic of a German university hospital.
Subjects: Ninety-six Participants with frequent episodic or chronic tension-type headache were randomized to one of four treatment groups.
Interventions: Six weeks of acupuncture or therapeutic exercise either as monotherapies or in combination, or usual care. Follow-up at 3 and 6 months.
Main measures: Subjective temporomandibular dysfunction symptoms were measured using the Functional Questionnaire Masticatory Organ, and the influence of this sum score and objective initial dental examination on the efficacy of headache treatment interventions was analyzed.
Results: Temporomandibular dysfunction score improved in all intervention groups at 3-month follow-up (usual care: 0.05 [SD 1.435]; acupuncture: -5 [SD 1.436]; therapeutic exercise: -4 [SD 1.798]; combination: -3 [SD 1.504]; *P* = 0.03). After 6 months, only acupuncture (-6 [SD 1.736]) showed a significant

improvement compared to the usual care group ($P < 0.01$). Subjective temporomandibular dysfunction symptoms had no overall influence on headache treatment.
Conclusions: Only acupuncture had long-lasting positive effects on the symptoms of temporomandibular dysfunction. Significant dental findings seem to inhibit the efficacy of acupuncture for tension-type headache.

Assessing the Effects of Distinct Biologic Therapies on Rheumatoid Arthritis Pain by Nociceptive, Neuropathic and Nociplastic Pain Components: A Randomised Feasibility Study.
Ahmed L, Biddle K, Blundell A, Koushesh S, Kiely P, Mein G, Sedgwick P, Sofat N.
Pilot Feasibility Stud. 2024 May 16;10(1):77. doi: 10.1186/s40814-024-01505-4. PMID: 38755699; PMCID: PMC11097416.

Background: Pain management is a major unmet need in people with rheumatoid arthritis (RA). Although many patients are treated with disease modifying anti-rheumatic drugs (DMARDS), including biologic therapies, many people with RA continue to experience significant pain. We aimed to determine whether performing a comprehensive pain evaluation is feasible in people with active RA receiving conventional DMARDs and biologic therapies.
Methods: The BIORA-PAIN feasibility study was an open-label, randomised trial, which recruited participants suitable for treatment with biologic therapy. The primary feasibility outcomes were recruitment, randomisation and retention of eligible participants. All participants underwent pain assessment for nociceptive, neuropathic and nociplastic pain during the 12-month study period, with quarterly assessments for VAS (Visual Analogue Scale) pain, painDETECT and QST (quantitative sensory testing). This trial was registered in clinicaltrials.gov NCT04255134.
Results: During the study period, 93 participants were screened of whom 25 were eligible: 13 were randomised to adalimumab and 12 to abatacept. Participant recruitment was lower than expected due to the COVID-19 pandemic. Pain assessments were practical in the clinical trial setting. An improvement was observed for VAS pain from baseline over 12 months, with a mean (SEM) of 3.7 (0.82) in the abatacept group and 2.3 (1.1) in the adalimumab group. There was a reduction in painDETECT and improvement in QST measures in both treatment groups during the study. Participant feedback included that some of the questionnaire-based pain assessments were lengthy and overlapped in their content. Adverse events were similar in both groups. There was one death due to COVID-19.
Conclusions: This first-ever feasibility study of a randomised controlled trial assessing distinct modalities of pain in RA met its progression criteria. This study demonstrates that it is feasible to recruit and assess participants with active RA for specific modalities of pain, including nociceptive, neuropathic and nociplastic elements. Our data suggests that it is possible to stratify people for RA based on pain features. The differences in pain outcomes between abatacept and adalimumab treated groups warrant further investigation.

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 May 23;91(5):105744. doi: 10.1016/j.jbspin.2024.105744. Epub ahead of print. 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 13512 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 3 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.

Migraine Among Women with Endometriosis: A Hospital-Based Case-Control Study in Bangladesh.
Sultana S, Chowdhury TA, Chowdhury TS, Mahmud N, Sultana R, Mahtab NT, Sharker Y, Ahmed F.
AJOG Glob Rep. 2024 Mar 30;4(2):100344. doi: 10.1016/j.xagr.2024.100344. PMID: 38655567; PMCID: PMC11036091.

Background: Endometriosis is a disease among women of reproductive age, which causes several health problems, such as dysmenorrhea, dyspareunia, and subfertility. In addition, it increases psychological stress and often results in marital disharmony. Similarly, migraine is more frequent among this group of women. Several studies have shown an association between endometriosis and migraine among groups of populations completely different from Bangladesh.

Objective: This study aimed to identify the association between endometriosis and migraine among the Bangladeshi population.
Study design: This nonrandomized case-control study was conducted with cases of endometriosis and controls without endometriosis who were confirmed by laparoscopy or laparotomy. Among the study participants, cases of migraine in 1 group of respondents who were already diagnosed as patients of migraine were identified, and the others with complaints of headaches were further confirmed by a medicine specialist. Patients were recruited from the Department of Obstetrics and Gynecology at the Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders General Hospital and Ibrahim Medical College. The study was approved by the ethical review committee of the Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders General Hospital. Multivariate logistic regression was used to identify the association between endometriosis and migraine using odds ratios and 95% confidence intervals.
Results: Of 1496 patients who underwent laparoscopy or laparotomy during the study period, the frequency of endometriosis was found to be 12.7%. A total of 190 patients with confirmed endometriosis cases and an equal number of controls without endometriosis were enrolled, maintaining the age distribution of the controls similar to that of the cases. Compared with controls, the distribution of age, body mass index, education, and marital status of the patients with endometriosis were similar. The average ages of respondents were 30.6 years in both the case and control groups. Regarding occupation, cases included more students than controls (12% vs 0%, respectively). The odds of suffering from dysmenorrhea and dyspareunia among the cases were 3.3 (95% confidence interval, 2.66-4.15; *P*<.001) and 9.5 (95% confidence interval, 5.3-17.9; *P*<.001) times higher than that of controls, respectively. In addition, the odds of menstrual irregularity was 60% lower among the cases than among controls (odds ratio, 0.4; 95% confidence interval, 0.24-0.64; *P*<.001). No significant difference was observed in having primary subfertility and secondary subfertility among the 2 groups of respondents. Univariate regression analysis showed that patients with endometriosis have 6.13 times higher odds (95% confidence interval, 2.50-18.40; *P*<.001) of having a migraine and 2.00 times higher odds (95% confidence interval, 1.2-3.2;*P*=.01) of having a headache than controls. Furthermore, the age- and body mass index-adjusted multivariate model showed that patients with endometriosis have 5.4 times higher odds of having migraine than patients without endometriosis (95% confidence interval, 2.11-16.4; *P*<.001). In addition, the higher the age of reproductive-age women, the higher the odds of having migraine. A 1-year increase in age increases the odds of having migraine by 23% (odds ratio, 1.23; 95% confidence interval, 1.13-1.16; *P*<.001).
Conclusion: Our results support the association between endometriosis and migraine among the Bangladeshi population, which is similar to relevant studies conducted in other geographic locations. The groups of physicians who treat patients suffering from the 2 diseases, endometriosis and migraine, should keep this interrelationship in mind to ensure a better quality of life for the patient.

Functional Somatic Syndromes are Associated with Varied Postoperative Outcomes and Increased Opioid Use After Spine Surgery: A Systematic Review.
Masood R, LeRoy TE, Moverman MA, Feldman MW, Rogerson A, Salzler MJ.
Global Spine J. 2024 Jun;14(5):1601-1608. doi: 10.1177/21925682231217706. Epub 2023 Nov 21. PMID: 38124313.

Study design: Systematic Review.
Objective: To perform a systematic review assessing the relationship between functional somatic syndromes (FSSs) and clinical outcomes after spine surgery.
Methods: A systematic review of online databases (PubMed and Web of Science) through December 2021 was conducted via PRISMA guidelines to identify all studies investigating the impact of at least one FSS (fibromyalgia, irritable bowel syndrome (IBS), chronic headaches/migraines, interstitial cystitis, chronic fatigue syndrome, multiple chemical sensitivity) on outcomes after spine surgery. Outcomes of interest included patient reported outcome measures (PROMs), postoperative opioid use, cost of care, complications, and readmission rates.
Results: A total of 207 records were identified. Seven studies (n = 40,011 patients) met inclusion criteria with a mean MINORS score of 16.6 out of 24. Four studies (n = 21,086) reported postoperative opioid use; fibromyalgia was a strong risk factor for long-term opioid use after surgery whereas the association with chronic migraines remains unclear. Two studies (n = 233) reported postoperative patient reported outcome measures (PROMs) with mixed results suggesting a possible association between fibromyalgia and less favorable PROMs. One study (n = 18,692) reported higher postoperative complications in patients with fibromyalgia.
Conclusion: Patients with fibromyalgia and possibly migraines are at higher risk for prolonged postoperative opioid use and less favorable PROMs after spine surgery. There is limited research on the relationship between other Functional somatic syndromes (FSSs) and outcomes following spine surgery. Growing evidence suggests the variation in outcomes after spine procedures may be attributed to non-identifiable organic patient factors such as FSSs.

Increased Risk of 90-Day Complications in Patients with Fibromyalgia Undergoing Total Shoulder Arthroplasty.
Sanchez JG, Rancu AL, Diatta FH, Jonnalagadda A, Dhodapkar MM, Knoedler L, Kauke-Navarro M, Grauer JN.
J Am Acad Orthop Surg Glob Res Rev. 2024 May 9;8(5):e24.00102. doi: 10.5435/JAAOSGlobal-D-24-00102. PMID: 38722914; PMCID: PMC11081627.

Introduction: Anatomic and reverse total shoulder arthroplasties (TSAs) are effective treatment options for end-stage glenohumeral osteoarthritis. Those undergoing TSA may also have fibromyalgia, a

musculoskeletal condition. However, the association of fibromyalgia with shorter and longer term outcomes after TSA has not been well characterized.
Methods: Patients undergoing TSA for osteoarthritis indications were identified in the PearlDiver M165 database from January 2016 to October 2022. Exclusion criteria included age younger than 18 years, shoulder infection, neoplasm, or trauma within 90 days before surgery, and inactivity in the database within 90 days of surgery. Patients with fibromyalgia were matched in a 1:4 ratio to patients without based on age, sex, and Elixhauser Comorbidity Index. Ninety-day adverse events were compared using univariable and multivariable analyses. Five-year revision-free survival was compared using the log-rank test.
Results: Of 163,565 TSA patients, fibromyalgia was identified for 9,035 (5.52%). After matching, cohorts of 30,770 non-fibromyalgia patients and 7,738 patients with fibromyalgia were identified. Multivariable analyses demonstrated patients with fibromyalgia were at independently increased odds ratios (ORs) for the following 90-day complications (decreasing OR order): urinary tract infection (OR = 4.49), wound dehiscence (OR = 3.63), pneumonia (OR = 3.46), emergency department visit (OR = 3.45), sepsis (OR = 3.15), surgical site infection (OR = 2.82), cardiac events (OR = 2.72), acute kidney injury (OR = 2.65), deep vein thrombosis (OR = 2.48), hematoma (OR = 2.03), and pulmonary embolism (OR = 2.01) ($P < 0.05$ for each). These individual complications contributed to the increased odds of aggregated minor adverse events (OR = 3.68), all adverse events (OR = 3.48), and severe adverse events (OR = 2.68) ($P < 0.05$ for each). No statistically significant difference was observed in 5-year revision-free survival between groups.
Discussion: This study found TSA patients with fibromyalgia to be at increased risk of adverse events within 90 days of surgery. Proper surgical planning and patient counseling are crucial to this population. Nonetheless, it was reassuring that those with fibromyalgia had similar 5-year revision-free survival compared with those without.

The Impact of the Microbiota-Gut-Brain Axis on Endometriosis-Associated Symptoms: Mechanisms and Opportunities for Personalised Management Strategies.
Hearn-Yeates F, Horne AW, O'Mahony S, Saunders PTK.
Reprod Fertil. 2024 May 1;5(2):e230085. doi: 10.1530/RAF-23-0085. Epub ahead of print. PMID: 38739749; PMCID: PMC11227073.

Endometriosis is a chronic inflammatory condition affecting one in 10 women and those assigned female at birth, defined by the presence of endometrial-like tissue outside the uterus. It is commonly associated with pain, infertility, and mood disorders, and often comorbid with other chronic pain conditions, such as irritable bowel syndrome. Recent research has identified a key role for the microbiota-gut-brain axis in health and a range of inflammatory and neurological disorders, prompting an exploration of its potential mechanistic role in endometriosis. Increased awareness of the impact of the gut microbiota within the patient community, combined with the often-detrimental side effects of current therapies, has motivated many to utilise self-management strategies, such as dietary modification and supplements, despite a lack of robust clinical evidence. Current research has characterised the gut microbiota in endometriosis patients and animal models. However, small cohorts and differing methodology has resulted in little consensus in the data. In this narrative review, we summarise research studies that have investigated the role of gut microbiota and their metabolic products in the development and progression of endometriosis lesions, before summarising insights from research into co-morbid conditions and discussing the reported impact of self-management strategies on symptoms of endometriosis. Finally, we suggest ways in which this promising field of research could be expanded to explore the role of specific bacteria, improve access to 'microbial' phenotyping, and to develop personalised patient advice for reduction of symptoms such as chronic pain and bloating.

The Role and Applications of Artificial Intelligence in the Treatment of Chronic Pain.
Meier TA, Refahi MS, Hearne G, Restifo DS, Munoz-Acuna R, Rosen GL, Woloszynek S.
Curr Pain Headache Rep. 2024 Jun 1. doi: 10.1007/s11916-024-01264-0. Epub ahead of print. PMID: 38822995.

Purpose of review: This review aims to explore the interface between artificial intelligence (AI) and chronic pain, seeking to identify areas of focus for enhancing current treatments and yielding novel therapies.
Recent findings: In the United States, the prevalence of chronic pain is estimated to be upwards of 40%. Its impact extends to increased healthcare costs, reduced economic productivity, and strain on healthcare resources. Addressing this condition is particularly challenging due to its complexity and the significant variability in how patients respond to treatment. Current options often struggle to provide long-term relief, with their benefits rarely outweighing the risks, such as dependency or other side effects. Currently, AI has impacted four key areas of chronic pain treatment and research: (1) predicting outcomes based on clinical information; (2) extracting features from text, specifically clinical notes; (3) modeling 'omic data to identify meaningful patient subgroups with potential for personalized treatments and improved understanding of disease processes; and (4) disentangling complex neuronal signals responsible for pain, which current therapies attempt to modulate. As AI advances, leveraging state-of-the-art architectures will be essential for improving chronic pain treatment. Current efforts aim to extract meaningful representations from complex data, paving the way for personalized medicine. The identification of unique patient subgroups should reveal targets for tailored chronic pain treatments. Moreover, enhancing current treatment approaches is achievable by gaining a more profound understanding of patient physiology and responses. This can be realized by leveraging AI on the increasing volume of data linked to chronic pain.

Methods for Pragmatic Randomized Clinical Trials of Pain Therapies: IMMPACT Statement.
Hohenschurz-Schmidt D, Cherkin D, Rice ASC, Dworkin RH, Turk DC, McDermott MP, Bair MJ, DeBar LL, Edwards RR, Evans SR, Farrar JT, Kerns RD, Rowbotham MC, Wasan AD, Cowan P, Ferguson M, Freeman R, Gewandter JS, Gilron I, Grol-Prokopczyk H, Iyengar S, Kamp C, Karp BI, Kleykamp BA,

Loeser JD, Mackey S, Malamut R, McNicol E, Patel KV, Schmader K, Simon L, Steiner DJ, Veasley C, Vollert J.
Pain. 2024 May 3. doi: 10.1097/j.pain.0000000000003249. Epub ahead of print. PMID: 38723171.

Pragmatic, randomized, controlled trials hold the potential to directly inform clinical decision making and health policy regarding the treatment of people experiencing pain. Pragmatic trials are designed to replicate or are embedded within routine clinical care and are increasingly valued to bridge the gap between trial research and clinical practice, especially in multidimensional conditions, such as pain and in nonpharmacological intervention research. To maximize the potential of pragmatic trials in pain research, the careful consideration of each methodological decision is required. Trials aligned with routine practice pose several challenges, such as determining and enrolling appropriate study participants, deciding on the appropriate level of flexibility in treatment delivery, integrating information on concomitant treatments and adherence, and choosing comparator conditions and outcome measures. Ensuring data quality in real-world clinical settings is another challenging goal. Furthermore, current trials in the field would benefit from analysis methods that allow for a differentiated understanding of effects across patient subgroups and improved reporting of methods and context, which is required to assess the generalizability of findings. At the same time, a range of novel methodological approaches provide opportunities for enhanced efficiency and relevance of pragmatic trials to stakeholders and clinical decision making. In this study, best-practice considerations for these and other concerns in pragmatic trials of pain treatments are offered and a number of promising solutions discussed. The basis of these recommendations was an Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) meeting organized by the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks.

Nociplastic Pain and Pain-Motivated Drinking in Alcohol Use Disorder.
Hall OT, Rausch J, Entrup P, Lagisetty P, Bryan C, Black L, Moreno J, Gorka S, Phan KL, Clauw DJ.
J Pain. 2024 Jun;25(6):104467. doi: 10.1016/j.jpain.2024.01.332. Epub 2024 Jan 12. PMID: 38219852.

Heavy chronic alcohol use may produce pain amplification through neurochemical and neuroplastic changes at multiple levels of the nervous system. Similar changes are thought to underlie nociplastic pain. The American College of Rheumatology Fibromyalgia Survey has been used as a surrogate for nociplastic pain, including among individuals with alcohol use disorder (AUD). However, studies linking nociplastic pain to pain-motivated drinking are lacking. The present study aimed to determine if nociplastic pain is associated with pain-motivated drinking in AUD. To achieve this aim, a new scale-the Pain-Motivated Drinking Scale (PMDS)-was developed to measure how often participants were motivated by pain to drink alcohol. Measurement properties of this new scale were determined, including its factor structure, internal consistency reliability, and construct validity. In this cross-sectional observational study, participants with AUD (n = 138) were consecutively recruited from the patient pool at an academic addiction treatment facility. Seventy-two percent (95, 72.0%) reported they drank alcohol "to get relief from physical pain" at least some of the time, and over forty-two percent (56, 42.4%) reported pain relief motivated their drinking at least half of the time. PMDS had a single-factor structure, strong internal consistency reliability, and construct validity. A multiple hierarchical linear regression was run to determine if nociplastic pain was associated with pain-motivated drinking. Nociplastic pain was associated with PMDS even after controlling for potential confounders and pain severity. These findings suggest nociplastic pain is uniquely associated with pain-motivated drinking in AUD. PERSPECTIVE: Nociplastic pain is independently associated with pain-motivated drinking in alcohol use disorder (AUD). The Pain-Motivated Drinking Scale (PMDS) is a new scale to measure how often people drink to cope with pain. PMDS has promising psychometric properties. Nociplastic pain may be uniquely associated with pain-motivated drinking in AUD.

A Study on Irritable Bowel Syndrome, Temporomandibular Disorder, and Restless Leg Syndrome in Chinese Patients with Fibromyalgia.
Tang KT, Chen DY, Chen YH.
Int J Rheum Dis. 2024 May;27(5):e15149. doi: 10.1111/1756-185X.15149. PMID: 38751222.

No abstract available.

Investigating Migraine Phenotype and Dynamics in Women with Endometriosis: An Observational Pilot Study.
Merki-Feld G, Dietrich H, Imesch P, Gantenbein AR, Sandor P, Schankin CJ.
Acta Neurol Belg. 2024 Jun 15. doi: 10.1007/s13760-024-02484-2. Epub ahead of print. PMID: 38878131.

Introduction: Migraine and endometriosis are chronic disabling pain conditions. There is evidence for a shared genetic background. Migraine phenotype and course in patients with the comorbidity are insufficient investigated. Both conditions can be treated with progestins.
Methods: For this observational study we included women with migraine and endometriosis, visiting our clinic from 2015 to 2021. We collected available information from charts and complemented these data by a structured phone interview to collect more specific information on migraine and the course of both diseases.
Results: From 344 patients fulfilling the inclusion criteria, 94 suffered from both, endometriosis and migraine. Migraine with aura was reported by 41% of the patients and was associated with earlier onset of migraine (age < 17 years (OR 6.54) and with a history of medication overuse headache (OR 9.9, CI 1.6-59.4). Present monthly migraine frequency (1.5 ± 2.6) was significantly lower than five years before the interview (2.9 ± 4.64). There was a correlation between medication overuse headache and use of analgesics more than 3 days/months for dysmenorrhoea ($p < 0.03$). ASRM endometriosis score was not associated with migraine characteristics.

Conclusions: We conclude that the comorbidity of endometriosis is highly linked to migraine with aura. Migraine onset in these patients was earlier. Further studies are needed to explore, if the observed decrease in migraine frequency can be attributed to recent endometriosis surgery and to understand if early diagnosis and treatment of both conditions may contribute to improve the course of both conditions.

Impact of Migraine and Fibromyalgia on Temporomandibular Disorder: A Retrospective Study on Pain, Psychological Factors and Quality of Life.
Yakkaphan P, Lambru G, Renton T.
J Oral Rehabil. 2024 Jul 4. doi: 10.1111/joor.13789. Epub ahead of print. PMID: 38965737.

Objectives: This study assessed the impact of migraine and fibromyalgia (FM) in TMD patients, focusing on pain, anxiety, depression, and quality of life (QoL). Additionally, we investigated how these variables relate to the total number of comorbidities to gain insights into their interactions.
Methods: A retrospective data collection was conducted during January 2016 to December 2022, involving 409 adult TMD patients. TMD patients were categorised into four groups: those without comorbidity (TMD-only) and those with comorbid migraine and/or fibromyalgia (TMD + MG, TMD + FM and TMD + MG + FM). Quantitative variables were compared among them. Linear regression was used to analyse the associations between these variables.
Results: Most of study population were women (79%) with a mean age of 44.43 years. TMD + MG patients reported longer pain duration, higher pain scores and greater pain interference compared with TMD-only patients. Similarly, TMD + FM patients had higher pain intensity than patients with TMD only. Both the TMD + MG and TMD + FM groups had higher levels of anxiety, depression, and health impairment compared with patients with TMD only. Patients with all three pain conditions (TMD + MG + FM) experienced the longest pain duration, highest pain intensity, psychological distress, and impaired QoL. The result showed positive associations between pain outcomes, psychological measures, pain's impact on QoL, and the number of comorbidities and a negative association between overall health states and the number of comorbidities.
Conclusions: These findings underscore the importance of considering the presence of comorbidities and addressing physical and psychological aspects in the management of TMD patients.

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.
Clin J Pain. 2024 Jul 17. doi: 10.1097/AJP.0000000000001234. Epub ahead of print. PMID: 39016267.

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 finetune decision-making. Additionally, the study aimed to characterize a 'probable' versus 'no or possible' nociplastic pain mechanism using biopsychosocial variables and compare both groups in their one-year post-TKA response.
Methods: A secondary analysis of baseline data of a longitudinal prospective study involving 197 KOA patients awaiting total knee arthroplasty in Belgium and the Netherlands was performed. Two approaches, one considering four and the other three 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 one-year postoperative pain. Also, a sensitivity analysis, comparing exclusively 'probable' versus 'no' nociplastic pain mechanism groups, was performed.
Results: Thirty (15.22% - approach four pain locations) and 46 (23.35% - approach three 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, were younger, exhibited worse results on various preoperative pain-related and psychological variables, and had more pain one-year post-TKA compared to the other group.
Discussion: This study proposed additional criteria to finetune the grading system for nociplastic pain (except for discrete/regional/multifocal/widespread pain) and characterized a subgroup of KOA patients with 'probable' nociplastic pain. Future research is warranted for further validation.

Epidemiology Studies

Prevalence and Sociodemographic Correlates of Chronic Pain Among a Nationally Representative Sample of Older Adults.
LaRowe LR, Miaskowski C, Miller A, Mayfield A, Keefe FJ, Smith AK, Cooper BA, Wei LJ, Ritchie CS.
J Pain. 2024 Jun 25:104614. doi: 10.1016/j.jpain.2024.104614. Epub ahead of print. PMID: 38936750.

Subgroup analyses conducted among U.S. national survey data have estimated that 27-34% 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 three 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 (e.g., gender, race/ethnicity, socioeconomic status). Results indicated that 37.8% of older adults reported chronic pain. Compared to White older adults, Black (OR = 0.6, 95% CI: 0.4-0.8) and Asian (OR = 0.2, 95% CI: 0.1-0.8) 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 = 0.6, 95% CI: 0.4-0.8). 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 sub-groups 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. Findings underscore the high prevalence of chronic pain and highlight disparities in chronic pain prevalence rates among this historically understudied population.

Chronic Overlapping Pain Conditions Increase the Risk of Long COVID Features, Regardless of Acute COVID Status.
Bergmans RS, Clauw DJ, Flint C, Harris H, Lederman S, Schrepf
Pain. 2024 May 1;165(5):1112-1120. doi: 10.1097/j.pain.0000000000003110. Epub 2023 Nov 9. PMID: 38112577; PMCID: PMC11017744.

Chronic overlapping pain conditions (COPCs) refer to conditions that have similar central nervous system pathophysiologic mechanisms driving widespread pain as well as common comorbid symptoms such as fatigue and problems with sleep, memory, and mood. If COPCs predict the onset of long COVID, this could offer a valuable orientation for long COVID-related research and clinical care. This retrospective cohort study aimed to determine whether having a COPC predicts the onset of long COVID features using US electronic health records and 1:1 propensity score matching without replacement. The study cohorts included (1) people with acute COVID (n = 1,038,402), (2) people with acute influenza (n = 262,092), and (3) a noninfected cohort comprising people with a routine healthcare encounter (n = 1,081,593). Having a COPC increased the risk of long COVID features in all 3 study cohorts. Among those with COVID, having a pre-existing COPC increased the risk by 1.47 (95% CI = 1.46, 1.47). In the influenza cohort, COPCs increased the risk by 1.39 (95% CI = 1.38, 1.40). In the noninfected cohort, COPCs increased the risk by 1.57 (95% CI = 1.56, 1.59). These findings reinforce the likelihood that nociplastic mechanisms play a prominent role in long COVID. Recognizing that this ubiquitous nonspecific syndrome occurs frequently in the population can inform precision medicine therapies that avoid the pitfalls of viewing long COVID exclusively in the framework of postinfectious disease.

Prevalence and Epidemiological Characteristics of Chronic Pain in the Spanish Population. Results from the Pain Barometer.
Dueñas M, De Sola H, Salazar A, Esquivia A, Rubio S, Failde I.
Eur J Pain. 2024 Jul 24. doi: 10.1002/ejp.4705. Epub ahead of print. PMID: 39046161.

Background: Chronic pain (CP) is a public health problem worldwide.
Aim: To update the prevalence of CP and compare the clinical and social characteristics of people with CP with those with non-chronic continuous pain and a group without pain.
Methods: An observational cross-sectional study was carried out in a representative sample of 7058 adults from the Spanish population. Sociodemographic data, the presence of CP and non-chronic continuous pain, characteristics of pain, limitations on activities of daily living (ADL), the presence and level of anxiety and depression (HADS), quality of life (SF-12v2) and social support (DUKE) were collected. Descriptive and bivariate analyses were performed.
Results: The prevalence of CP was 25.9% (95% CI;24.8-26.9) and that of non-chronic continuous pain was 7.7% (95% CI;7.1-8.3). Women presented a higher prevalence of both CP (30.5% vs. 21.3%) and non-chronic continuous pain (8.8% vs. 6.6%). CP was more common in the group between 55 and 75 years old (30.6%, 95% CI = 28.6-32.6%), non-chronic continuous pain affected most the population between 18 and 34 years old (11.2%, 95% CI = 9.6-12.7%). The median duration of CP was 4 years. The lumbar was the most frequent pain site (58.1%), and 27.1% did not know the cause. A greater frequency of limitations on ADL, more anxiety and depression, and worse quality of life were shown among the subjects with CP.
Conclusion: CP affects one in four Spanish people and impairs the mental, physical and social health. Differences exist by sex and age in its frequency. Identifying subjects with non-chronic continuous pain is fundamental to prevent their pain from becoming chronic.
Significance statement: Indicating the main aspects where this work adds significantly to existing knowledge in the field, and if appropriate to clinical practice. Due to its high prevalence and impact on quality of life, chronic pain has become one of the main health problems nowadays. Attention must be paid to it both from a clinical and social perspective, trying to raise awareness among the population of its possible causes and consequences. In routine clinical practice, greater consideration is given to groups of people with a higher prevalence of chronic pain, such as women and people with middle age, and with no chronic pain to prevent the appearance of chronic pain.

Association of Latent Class Analysis-Derived Multimorbidity Clusters with Adverse Health Outcomes in Patients with Multiple Long-Term Conditions: Comparative Results Across Three UK Cohorts.
Krauth SJ, Steell L, Ahmed S, McIntosh E, Dibben GO, Hanlon P, Lewsey J, Nicholl BI, McAllister DA, Smith SM, Evans R, Ahmed Z, Dean S, Greaves C, Barber S, Doherty P, Gardiner N, Ibbotson T, Jolly K, Ormandy P, Simpson SA, Taylor RS, Singh SJ, Mair FS, Jani BD; PERFORM research team.
EClinicalMedicine. 2024 Jun 28;74:102703. doi: 10.1016/j.eclinm.2024.102703. PMID: 39045545; PMCID: PMC11261399.

Background: It remains unclear how to meaningfully classify people living with multimorbidity (multiple long-term conditions (MLTCs)), beyond counting the number of conditions. This paper aims to identify clusters of MLTCs in different age groups and associated risks of adverse health outcomes and service use.
Methods: Latent class analysis was used to identify MLTCs clusters in different age groups in three cohorts: Secure Anonymised Information Linkage Databank (SAIL) (n = 1,825,289), UK Biobank (n = 502,363), and the UK Household Longitudinal Study (UKHLS) (n = 49,186). Incidence rate ratios (IRR) for MLTC clusters were computed for: all-cause mortality, hospitalisations, and general practice (GP) use over 10 years, using <2 MLTCs as reference. Information on health outcomes and service use were extracted for a ten year follow up period (between 01st Jan 2010 and 31st Dec 2019 for UK Biobank and UKHLS, and between 01st Jan 2011 and 31st Dec 2020 for SAIL).
Findings: Clustering MLTCs produced largely similar results across different age groups and cohorts. MLTC clusters had distinct associations with health outcomes and service use after accounting for LTC counts, in fully adjusted models. The largest associations with mortality, hospitalisations and GP use in SAIL were observed for the "*Pain+*" cluster in the age-group 18-36 years (mortality IRR = 4.47, hospitalisation IRR = 1.84; GP use IRR = 2.87) and the "*Hypertension, Diabetes & Heart disease*" cluster in the age-group 37-54 years (mortality IRR = 4.52, hospitalisation IRR = 1.53, GP use IRR = 2.36). In UK Biobank, the "*Cancer, Thyroid disease & Rheumatoid arthritis*" cluster in the age group 37-54 years had the largest association with mortality (IRR = 2.47). Cardiometabolic clusters across all age groups, pain/mental health clusters in younger groups, and cancer and pulmonary related clusters in older age groups had higher risk for all outcomes. In UKHLS, MLTC clusters were not significantly associated with higher risk of adverse outcomes, except for the hospitalisation in the age-group 18-36 years.
Interpretation: Personalising care around MLTC clusters that have higher risk of adverse outcomes may have important implications for practice (in relation to secondary prevention), policy (with allocation of health care resources), and research (intervention development and targeting), for people living with MLTCs.

Comorbidity and Sex Differences in Functional Disorders and Internalizing Disorders.
Thomas NS, Gillespie NA, Kendler KS, Oldehinkel AJ, Rosmalen JGM, van Loo HM.
Gen Hosp Psychiatry. 2024 Jul 26;90:91-98. doi: 10.1016/j.genhosppsych.2024.07.013. Epub ahead of print. PMID: 39079424.

Objective: In the current exploratory study we estimate comorbidity rates between FDs [fibromyalgia (FM), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and irritable bowel syndrome (IBS)]-and IDs-[major depressive disorder (MDD) and generalized anxiety disorder (GAD)] by using self-reported diagnostic criteria.
Method: We analyzed data from 107,849 participants (mean age = 49.3 (SD = 13.0), 58.6% women) of the Lifelines Cohort Study. Lifelines is a prospective population-based cohort study in the northeast of the Netherlands. Current IDs were assessed using the Mini-International Neuropsychiatric Interview. Current FM, ME/CFS, and IBS were assessed according to the 2010 American College of Rheumatology criteria, the 1994 Centers for Disease Control and Prevention criteria and the ROME IV criteria, respectively. We estimated tetrachoric correlations between diagnoses and tested for sex differences. Additionally, we estimated the ratio of observed-to-expected frequency for combinations of diagnoses.
Results: FDs and IDs are highly comorbid (odds ratios: 3.2-12.6) with associations stronger among men. Participants with at least three disorders/diagnoses were more prevalent than expected by chance.
Conclusion: Studies that aim to explain sex differences and the comorbidity of specific combinations of IDs and FDs will be an important contribution to understanding the etiology of these conditions.

Who Are the People with Chronic Severe Back Pain Not Receiving Pain Treatment?
Feldman DE, Nahin RL.
J Pain. 2024 Jul 20:104637. doi: 10.1016/j.jpain.2024.104637. Epub ahead of print. PMID: 39033901.

There are substantial access to care barriers for persons with chronic pain. Little is known about persons who do not receive treatment for chronic severe back pain as most studies rely on clinical samples. We sought to explore demographic, socioeconomic and clinical characteristics of U.S. adults with chronic severe back pain who had not received pain care in the preceding 3 months. In this cross-sectional study, we used data from the 2019 National Health Interview Survey and identified persons who did/did not receive treatment (including self-management strategies) in the last three months for their chronic severe back pain. We used bivariate and multivariable analyses to explore factors associated with not receiving pain treatment. Almost 21% of persons with chronic severe back pain did not receive treatment in the past three months. The following were independently associated with not having treatment in the preceding 3 months: male sex (OR = 1.40; 95% CI 1.11-1.76), living near or below the poverty level (OR 1.92; 95% CI 1.33-2.77), having less than a high-school education (OR, 2.37; 95% CI 1.52-3.68), not having insurance coverage (OR 1.77; 95% CI 1.21-2.59), living in the South (OR 2.05; 95% CI 1.40-3.00), having heart disease (OR 1.47; 95% CI 1.11-1.93). Being a single parent, having depression and multiple comorbid painful health conditions were associated with having treatment. Our conclusions are that one-fifth of persons with chronic severe back pain did not receive treatment for at least three months and socioeconomic factors were highly associated with not receiving treatment. PERSPECTIVE: In a nationally representative sample of persons with chronic severe back pain, one-fifth did not receive treatment for at least three months. Socioeconomic factors were highly associated with not receiving treatment. There is a need to implement solutions to reduce barriers to care.

Health Resource Utilization and Cost Impact of Integrative Medicine Services for Newly Diagnosed Chronic Pain Patients.
Whetten J, Medina L, Krabbenhoft C, Will V, Reising M, Maska BK, Phillips JK.
J Integr Complement Med. 2024 Jul 8. doi: 10.1089/jicm.2024.0093. Epub ahead of print. PMID: 38976483.

Background: Integrative medicine (IM) is the healing-oriented practice of medicine that emphasizes the relationship between practitioner and patient. It considers the whole person, their environment, lifestyle, and social and cultural factors. It is evidence based and makes use of all appropriate therapies, conventional and complimentary. *Objective:* To evaluate the impact of IM services on health outcomes and care costs of chronic pain management patients compared with standard care.
Methods: This article uses University of New Mexico hospital billing data from 10/2016 to 09/2019 to identify patients with nervous system or musculoskeletal pain. A total of 1,304 patients were matched using propensity scores into IM services (treatment: 652) and standard care (control: 652) cohorts for difference-in-differences analysis. The patients were matched based on age, sex, race, zip code, insurance type, ICD-10s, prescriptions, health care events, and medical claim costs.
Results: Patients who used IM services had better health outcomes and lower costs at 3-month, 6-month, and 12-month follow-up. At the 12-month follow-up, the IM group showed a 19% decrease in utilization of inpatient care, a 37% decrease in Emergency Department utilization, and an 11.3% reduction in claim costs compared with the control group.
Conclusion: Patients who utilize IM services as part of chronic pain management have overall lower health care costs and better health outcomes. Unfortunately, in the health system studied, less than 3% of patients utilize these services. Promotion of and education about IM services should be aimed at both patients and their providers.

Associations of Socioeconomic and Lifestyle Characteristics, Psychological Symptoms, Multimorbidity, and Multisite Pain with Sciatica – A 15-Year Longitudinal Study.
Anttila S, Määttä J, Heikkala E, Arokoski J, Karppinen J, Oura P.
Spine J. 2024 May;24(5):842-850. doi: 10.1016/j.spinee.2023.12.013. Epub 2024 Jan 9. PMID: 38211903.

Background and context: Sciatica is defined as pain radiating from the low back to the leg, usually below the knee. It is a disabling condition that causes a major burden to health care and society. Previous evidence of the multifactorial etiology of sciatica comes mostly from cross-sectional studies. Larger, longitudinal studies with a multidimensional set of variables are needed.
Purpose: To examine how socioeconomic and lifestyle characteristics, psychological symptoms, multimorbidity, and multisite pain are associated with sciatica.
Study design: A longitudinal study of the Northern Finland Birth Cohort 1966.
Patient sample: In total 6,683 working-aged members of the Northern Finland Birth Cohort 1966.
Outcome measures: Self-reported sciatic pain status over a 15-year study period.
Methods: We conducted a 15-year longitudinal study from the age of 31 to 46. We used multivariable generalized estimation equations analysis to examine how socioeconomic characteristics (low education, unemployment, and living alone), lifestyle characteristics (overweight, obesity, current smoking, and physical inactivity), psychological symptoms (depression, anxiety), multimorbidity, and multisite pain were associated with sciatica.
Results: At the age of 31, 21.1% of the study population reported sciatic pain and at the age of 46, 36.7%. Multisite pain was clearly the strongest factor associated with sciatica (odds ratio [OR] 2.61, 95% confidence interval [CI] 2.34–2.92). In descending order of effect size, older age, low education, psychological symptoms, multimorbidity, overweight, obesity, physical inactivity and current smoking were positively associated with sciatica. Their ORs varied between 1.17 and 2.18. Living alone was negatively associated with sciatica (OR 0.81, 95% CI 0.72–0.90).
Conclusions: Multisite pain had the strongest association with sciatica. The effect sizes of the other factors were clearly smaller. To our knowledge this is the first study to evaluate the association of multisite pain with sciatica. This finding may have considerable implications for clinical work treating patients with sciatica.

Prevalence of Chronic and Multisite Pain in Adolescents and Young Adults with ADHD: A Comparative Study Between Clinical and General Population Samples (The Hunt Study).
Mundal I, Schei J, Lydersen S, Thomsen PH, Nøvik TS, Kvitland LR.
Eur Child Adolesc Psychiatry. 2024 May;33(5):1433-1442. doi: 10.1007/s00787-023-02249-x. Epub 2023 Jun 29. PMID: 37386203; PMCID: PMC11098922.

Attention-deficit/hyperactivity disorder (ADHD) and chronic pain are prevalent and associated. We examined the prevalence and distribution of chronic pain in adolescents and young adults with ADHD using 9-years longitudinal data (from T1:2009-2011 to T3:2018-2019) with three time points from a clinical health survey compared to two age-matched reference population-based samples. Mixed-effect logistic regression and binary linear regression were used to estimate the probability for chronic and multisite pain at each time point and to compare the prevalence of chronic pain with the reference populations. The prevalence of chronic and multisite pain was high in those with ADHD, especially in female young adults, with highly prevalent chronic pain at 9 years of follow-up (75.9%) compared to 45.7% in females in the reference population. The probability of having pain was only statistically significant for chronic pain in males at 3 years of follow-up (41.9%, p = 0.021). Those with ADHD were at higher risk of reporting single-site and multisite pain compared to the general population at all measurement points. Longitudinal studies should be tailored to further understand the complex sex differences of comorbid chronic pain and ADHD in adolescents, exploring predictive factors of pain assessing long-term associations with bodyweight,

psychiatric comorbidities, and possible mechanisms of stimulant use effects on pain.

Seventeen-Year National Pain Prevalence Trends Among U.S. Military Veterans.
Taylor KA, Kapos FP, Sharpe JA, Kosinski AS, Rhon DI, Goode AP.
J Pain. 2024 May;25(5):104420. doi: 10.1016/j.jpain.2023.11.003. Epub 2023 Nov 10. PMID: 37952861; PMCID: PMC11184511.

U.S. military veterans experience higher pain prevalence than nonveterans. However, it is unclear how the disparities in pain prevalence have changed over time because previous trend studies are limited to veterans using the Veterans Health Administration. This repeated cross-sectional study aimed to characterize pain prevalence trends in the overall population of U.S. veterans compared to nonveterans, using nationally representative data. We analyzed 17 years of data from the National Health Interview Survey (2002-2018), with a mean annual unweighted sample of 29,802 U.S. adults (total unweighted n = 506,639) and mean annual weighted population of 229.7 million noninstitutionalized adults. The weighted proportion of veterans ranged from 11.48% in 2002 (highest) to 8.41% in 2017 (lowest). We found that veterans experience a similar or higher prevalence of pain than nonveterans across the study period, except for severe headaches or migraine and facial pain. Pain prevalence among veterans increased over time, with a higher rate of increase compared to nonveterans for all pain variables. From 2002 to 2018, there was an absolute increase (95% confidence interval) in pain prevalence among veterans (severe headache or migraine: 2.0% [1.6-2.4%]; facial pain: 1.9% [1.4-2.4%]; neck pain: 4.7% [4.1-5.2%]; joint pain: 11.4% [10.8-11.9%]; low back pain: 10.3% [9.5-11.1%]; any pain: 10.0% [9.6-10.4%]; and multiple pains: 9.9% [9.2-10.6%]). The continued pain prevalence increase among veterans may have implications for health care utilization, highlighting the need for improved pain prevention and care programs for this population with a disproportionate pain burden.
PERSPECTIVE: This article uses routinely-collected cross-sectional data that are nationally representative of U.S. adults to present changes in pain prevalence among military veterans compared to nonveterans. The findings underscore the need for improved prevention and pain care programs for veterans, who experienced a widening disproportionate pain burden from 2002 to 2018.

Prevalence of Fibromyalgia and Widespread Pain in Psoriatic Arthritis: Association with Disease Severity Assessment in a Large US Registry.
Mease P, Reed G, Ogdie A, Pappas DA, Kremer JM.
2024 May 12. doi: 10.1002/acr.25358. Epub ahead of print. PMID: 38736168.

Background: The classic conception of pain etiology in rheumatologic disease is nociceptive pain - tissue injury and inflammation signaling through peripheral and central nerve fibers. But this can be mixed with other pain etiologies, including nociplastic, augmented pain experience due to central sensitization. The pain of fibromyalgia (FM) is nociplastic, occurs in 10-30% of rheumatologic disease patients, and its presence can influence disease severity assessment.
Objectives: 1) Ascertain the prevalence of FM and Widespread Pain (WP) in the CorEvitas psoriatic arthritis (PsA) registry as assessed by the Widespread Pain Index (WPI) and Symptom Severity Scale (SSS) questionnaires. 2) Characterize the demographic and clinical factors associated with FM and WP. 3) Ascertain the association of FM and WP on the Clinical Disease Activity in Psoriatic Arthritis (cDAPSA) score and other disease activity measures.
Methods: PsA registry patients completing the WPI/SSS questionnaires since May 2020, at their most recent visit recorded in the registry, were analyzed.
Results: The analysis included 1823 PsA patients; 11.1% fulfilled FM definition and 20.6% fulfilled WP definition. Several factors were associated with FM definition including female sex, depression/anxiety, impaired function, increased body mass index (BMI), and increased number of comorbidities. cDAPSA, patient pain and global, and tender joint count were twice as severe in patients with FM compared to those without.
Conclusion: Fibromyalgia prevalence is elevated in PsA and is associated with elevated disease measures, confounding reliable disease assessment for treat-to-target goals. Identification of fibromyalgia as an influential contextual factor in disease assessment is recommended.

Trajetories of Chronic Multimorbidity Patterns in Older Patients: MTOP Study.
Lleal M, Baré M, Herranz S, Orús J, Comet R, Jordana R, Baré M.
BMC Geriatr. 2024 May 30;24(1):475. doi: 10.1186/s12877-024-04925-2. PMID: 38816787; PMCID: PMC11137950.

Background: Multimorbidity is associated with negative results and poses difficulties in clinical management. New methodological approaches are emerging based on the hypothesis that chronic conditions are non-randomly associated forming multimorbidity patterns. However, there are few longitudinal studies of these patterns, which could allow for better preventive strategies and healthcare planning. The objective of the MTOP (Multimorbidity Trajectories in Older Patients) study is to identify patterns of chronic multimorbidity in a cohort of older patients and their progression and trajectories in the previous 10 years.
Methods: A retrospective, observational study with a cohort of 3988 patients aged > 65 was conducted, including suspected and confirmed COVID-19 patients in the reference area of Parc Taulí University Hospital. Real-world data on socio-demographic and diagnostic variables were retrieved. Multimorbidity patterns of chronic conditions were identified with fuzzy c-means cluster analysis. Trajectories of each patient were established along three time points (baseline, 5 years before, 10 years before). Descriptive statistics were performed together with a stratification by sex and age group.

Results: 3988 patients aged over 65 were included (58.9% females). Patients with ≥ 2 chronic conditions changed from 73.6 to 98.3% in the 10-year range of the study. Six clusters of chronic multimorbidity were identified 10 years before baseline, whereas five clusters were identified at both 5 years before and at baseline. Three clusters were consistently identified in all time points (Metabolic and vascular disease, Musculoskeletal and chronic pain syndrome, Unspecific); three clusters were only present at the earliest time point (Male-predominant diseases, Minor conditions and sensory impairment, Lipid metabolism disorders) and two clusters emerged 5 years before baseline and remained (Heart diseases and Neurocognitive). Sex and age stratification showed different distribution in cluster prevalence and trajectories.
Conclusions: In a cohort of older patients, we were able to identify multimorbidity patterns of chronic conditions and describe their individual trajectories in the previous 10 years. Our results suggest that taking these trajectories into consideration might improve decisions in clinical management and healthcare planning.

Clinical Outcomes, Medical Costs, and Medication Usage Patterns of Different Somatic Symptom Disorders and Functional Somatic Syndromes: A Population-Based Study in Taiwan.
Wu CS, Chen TT, Liao SC, Huang WC, Huang WL.
Psychol Med. 2024 May;54(7):1452-1460. doi: 10.1017/S0033291723003355. Epub 2023 Nov 20. PMID: 37981870.

Background: Somatic symptom disorders (SSD) and functional somatic syndromes (FSS) are often regarded as similar diagnostic constructs; however, whether they exhibit similar clinical outcomes, medical costs, and medication usage patterns has not been examined in nationwide data. Therefore, this study focused on analyzing SSD and four types of FSS (fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, functional dyspepsia).
Methods: This population-based matched cohort study utilized Taiwan's National Health Insurance (NHI) claims database to investigate the impact of SSD/FSS. The study included 2 615 477 newly diagnosed patients with SSD/FSS and matched comparisons from the NHI beneficiary registry. Healthcare utilization, mortality, medical expenditure, and medication usage were assessed as outcome measures. Statistical analysis involved Cox regression models for hazard ratios, generalized linear models for comparing differences, and adjustment for covariates.
Results: All SSD/FSS showed significantly higher adjusted hazard ratios for psychiatric hospitalization and all-cause hospitalization compared to the control group. All SSD/FSS exhibited significantly higher adjusted hazard ratios for suicide, and SSD was particularly high. All-cause mortality was significantly higher in all SSD/FSS. Medical costs were significantly higher for all SSD/FSS compared to controls. The usage duration of all psychiatric medications and analgesics was significantly higher in SSD/FSS compared to the control group.
Conclusions: All SSD/FSS shared similar clinical outcomes and medical costs. The high hazard ratio for suicide in SSD deserves clinical attention.

36-40% of Routine Care Patients With Osteoarthritis or Rheumatoid Arthritis Screen Positive for Anxiety, Depression, and/or Fibromyalgia on a Single MDHAQ.
Schmukler J, Malfait AM, Block JA, Pincus T.
ACR Open Rheumatol. 2024 Jul 16. doi: 10.1002/acr2.11711. Epub ahead of print. PMID: 39011669.

Objective: Osteoarthritis (OA) and rheumatoid arthritis (RA) are associated with similar patient disease burdens and a high prevalence of comorbid anxiety (ANX), depression (DEP), and fibromyalgia (FM). Nonetheless, these comorbidities are infrequently assessed in routine care, in part because multiple questionnaires are not feasibly completed by patients. We analyzed the prevalence of ANX, DEP, and FM in patients with OA versus patients with RA seen in routine care using indices within a single Multidimensional Health Assessment Questionnaire (MDHAQ) and associations with \ Routine Assessment of Patient Index Data 3 (RAPID3) and its component function, pain, and patient global scores.
Methods: A retrospective analysis of MDHAQ data in unselected patients with OA or RA receiving routine care at one setting included four indices within an MDHAQ: MDHAQ ANX screen, MDHAQ DEP screen, Fibromyalgia Assessment Screening Tool, and RAPID3. The prevalence of each comorbidity and associations with RAPID3 and components were analyzed in unadjusted and age-adjusted (Mantel-Haenszel) odds ratios (ORs) and 95% confidence intervals.
Results: Overall, 40.4% of 361 patients with OA and 36.3% of 488 patients with RA screened positive for ANX, DEP, and/or FM (8.1% and 7% for all three, respectively). RAPID3 and each component were elevated significantly in patients with any positive screen result for ANX, DEP, and/or FM in both diagnoses (ORs of 2.6-35.8).
Conclusion: FM, DEP, and/or ANX rates were 40.4% in patients with OA and 36.3% in patients with RA, associated with significantly poorer patient status measures. Each of these three common comorbidities of patient distress may be feasibly screened for on a single MDHAQ in routine care.

Risk Factors Associated with Symptoms of Temporomandibular Disorders Among Women with Hypermobile Ehlers-Danlos Syndrome: Questionnaire-Based Study in Finland and Sweden.
Yekkalam N, Novo M, Tyrberg MJ, Sipilä K.
J Oral Rehabil. 2024 Aug;51(8):1390-1400. doi: 10.1111/joor.13706. Epub 2024 Apr 25. PMID: 38661350.

Background: Generalized joint hypermobility as a characteristic feature of Ehlers-Danlos syndromes (EDS) is among the factors contributing to temporomandibular disorders (TMD).
Objective: To evaluate the prevalence of TMD symptoms and their risk factors among women born in

Sweden or Finland who were 27- to 78-year-olds with diagnosed hypermobile EDS (hEDS).
Methods: A cohort of women with confirmed hEDS (n = 185) was constructed from the members of the National EDS Associations in both countries. Based on questionnaire data, frequency of independent variables in terms of socio-demographic, general health and oral health-related factors, comorbid symptoms and psychological distress for self-reported TMD symptoms as the dependent variables, were calculated first. Prevalence ratios (PR) and their 95% confidence interval (95% CI) were estimated for the association between independent and dependent variables.
Results: Nearly all participants reported TMD symptoms (98%) with TMD pain (95%), TMJ clicking (90%) and jaw fatigue (80%) as the most common symptoms and TMJ crepitation (63%) and luxation (44%) as the least common symptoms. Risk factors for TMD among 27- to 50-year-olds participants were Finland as a country of birth, living alone and self-reported worst pain in the body (not the joints). The respective risk factors among the 51- to 78-year-olds were Finland as a country of birth, family history of EDS, tinnitus and regularly taking contraceptives.
Conclusions: Among adult women with confirmed hEDS, socio-demographic and health-related factors and comorbid symptoms were significantly associated with TMD but with differences regarding age group. Therefore, management of TMD requires a multidisciplinary approach among the affected.

Genital Pain and the Spectrum of Bladder-Related Symptoms: Findings from the Prevention of Lower Urinary Tract Symptoms Research Consortium RISE FOR HEALTH Study, USA.
Harlow BL, McGwin G Jr, Sutcliffe S, Fitzgerald CM, Lowder JL, Newman DK, Meister M, Camenga DR, Stapleton A, Chary V, Lukacz ES.
Int Urogynecol J. 2024 Jul 13. doi: 10.1007/s00192-024-05868-3. Epub ahead of print. PMID: 39002046.

Introduction and hypothesis: Women with vulvovaginal or genital pain more commonly experience interstitial cystitis/bladder pain syndrome (IC/BPS) and urinary tract infections. However, the relationship between genital pain and bladder health is lacking.
Methods: Women in the Prevention of Lower Urinary Tract Symptoms Consortium's RISE FOR HEALTH population-based study answered questions about bladder health globally, and across nine bladder health domains of holding, efficacy, social-occupation, physical activity, intimacy, travel, emotion, perception, and freedom. Bladder function was assessed across six indices including urinary frequency, sensation, continence, comfort, emptying, and dysbiosis (e.g., urinary tract infections). Participants were grouped by no pain beyond transitory events (i.e., minor headaches, toothaches, or sprains), nongenital-related pain only, and any genital pain using a validated pain diagram. Mean adjusted scores and indices were compared using general linear modelling.
Results: Of 1,973 eligible women, 250 (12.7%) reported genital pain, 609 (30.9%) reported nongenital pain only, and 1,114 (56.5%) reported no pain. Women with any genital pain had lower (worse) adjusted mean scores across all bladder health scales (BHS; BHS global adjusted mean 47.5; 95% CI 40.8-54.1), compared with those with nongenital pain only (53.7; 95% CI 47.6-59.8), and no pain (59.3; 95% CI 53.3-65.4). Similarly, adjusted mean total Bladder Functional Index scores were lower for those with genital pain (63.1; 95% CI 58.4-67.9) compared with nongenital pain (72.1; 95% CI 67.7-76.5) and no pain (77.4; 95% CI 73.0-81.8).
Conclusions: Heightened awareness of the relationship between genital pain and bladder health should prompt clinicians caring for women with genital pain to assess bladder health and function.

safe and effective therapies for COPCs.

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