CUTTING EDGE

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This e-newsletter - published the CPRA to keep the medical-scientific and patient communities abreast of research advances on Chronic Overlapping Pain Conditions (COPCs) - contains abstracts of studies on the epidemiology, pathophysiology and clinical management of COPCs published between April and June 2021.

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Pathophysiology Studies

Sex-stratified genome-wide association study of multisite chronic pain in UK Biobank.
Johnston KJA, Ward J, Ray PR, Adams MJ, McIntosh AM, Smith BH, Strawbridge RJ, Price TJ, Smith DJ, Nicholl BI, Bailey MES.
PLoS Genet. 2021 Apr 8;17(4):e1009428. doi: 10.1371/journal.pgen.1009428. PMID: 33830993; PMCID: PMC8031124.

Chronic pain is highly prevalent worldwide and imparts a significant socioeconomic and public health burden. Factors influencing susceptibility to, and mechanisms of, chronic pain development, are not fully understood, but sex is thought to play a significant role, and chronic pain is more prevalent in women than in men. To investigate sex differences in chronic pain, we carried out a sex-stratified genome-wide association study of Multisite Chronic Pain (MCP), a derived chronic pain phenotype, in UK Biobank on 178,556 men and 209,093 women, as well as investigating sex-specific genetic correlations with a range of psychiatric, autoimmune and anthropometric phenotypes and the relationship between sex-specific polygenic risk scores for MCP and chronic widespread pain. We also assessed whether MCP-associated genes showed expression pattern enrichment across tissues. A total of 123 SNPs at five independent loci were significantly associated with MCP in men. In women, a total of 286 genome-wide significant SNPs at ten independent loci were discovered. Meta-analysis of sex-stratified GWAS outputs revealed a further 87 independent associated SNPs. Gene-level analyses revealed sex-specific MCP associations, with 31 genes significantly associated in females, 37 genes associated in males, and a single gene, DCC, associated in both sexes. We found evidence for sex-specific pleiotropy and risk for MCP was found to be associated with chronic widespread pain in a sex-differential manner. Male and female MCP were highly genetically correlated, but at an rg of significantly less than 1 (0.92). All 37 male MCP-associated genes and all but one of 31 female MCP-associated genes were found to be expressed in the dorsal root ganglion, and there was a degree of enrichment for expression in sex-specific tissues. Overall, the findings indicate that sex differences in chronic pain exist at the SNP, gene and transcript abundance level, and highlight possible sex-specific pleiotropy for MCP. Results support the proposition of a strong central nervous-system component to chronic pain in both

sexes, additionally highlighting a potential role for the DRG and nociception.

Sex differences in brain modular organization in chronic pain.
Fauchon C, Meunier D, Rogachov A, Hemington KS, Cheng JC, Bosma RL, Osborne NR, Kim JA, Hung PS, Inman RD, Davis KD.
Pain. 2021 Apr 1;162(4):1188-1200. doi: 10.1097/j.pain.0000000000002104. PMID: 33044396.

Men and women can exhibit different pain sensitivities, and many chronic pain conditions are more prevalent in one sex. Although there is evidence of sex differences in the brain, it is not known whether there are sex differences in the organization of large-scale functional brain networks in chronic pain. Here, we used graph theory with modular analysis and machine-learning of resting-state-functional magnetic resonance imaging data from 220 participants: 155 healthy controls and 65 individuals with chronic low back pain due to ankylosing spondylitis, a form of arthritis. We found an extensive overlap in the graph partitions with the major brain intrinsic systems (ie, default mode, central, visual, and sensorimotor modules), but also sex-specific network topological characteristics in healthy people and those with chronic pain. People with chronic pain exhibited higher cross-network connectivity, and sex-specific nodal graph properties changes (ie, hub disruption), some of which were associated with the severity of the chronic pain condition. Females exhibited atypically higher functional segregation in the mid cingulate cortex and subgenual anterior cingulate cortex and lower connectivity in the network with the default mode and frontoparietal modules, whereas males exhibited stronger connectivity with the sensorimotor module. Classification models on nodal graph metrics could classify an individual's sex and whether they have chronic pain with high accuracies (77%-92%). These findings highlight the organizational abnormalities of resting-state-brain networks in people with chronic pain and provide a framework to consider sex-specific pain therapeutics.

Transitioning to chronic TMD pain: A combination of patient vulnerabilities and iatrogenesis.
Greene CS, Manfredini D.
J Oral Rehabil. 2021 May 9. doi: 10.1111/joor.13180. PMID: 33966303.

This paper describes known vulnerability factors that make individuals susceptible to developing temporomandibular disorders (TMDs), as well as those that contribute to the perpetuation of such problems. In addition, the topic of iatrogenesis is discussed as a major contributor to the negative outcomes that can be seen in this field. At the patient level, anatomical, psychosocial, and genetic factors may contribute to individual vulnerability. The anatomy and pathophysiology of muscles, joints, disc, and nerves may all be involved in predisposing to TMD symptoms, especially when the patients have pain elsewhere in the body. Amongst the psychosocial factors, some features may be elucidated by the DC/TMD axis II, whilst others (e.g., illness behavior, Munchausen syndrome, lack of acceptance of non-mechanical approaches) require careful evaluation by trained clinicians. Genetic predisposition to first onset TMDs and to chronification of symptoms has been identified for individuals with certain psychological traits, presence of comorbid conditions, and certain abnormal clinical manifestations. Regarding iatrogenesis, sins of omission may influence the clinical picture, with the main ones being misdiagnosis and undertreatment. Joint repositioning strategies, occlusal modifications, abuse of oral appliances, use of diagnostic technologies, nocebo effect, and complications with intracapsular treatments are the most frequent sins of commission that may contribute to chronification of TMDs. The patients who present with massive occlusal and jaw repositioning changes combined with persistent severe orofacial pain are not a rarity within TMD and orofacial pain centers; these patients are the most difficult ones to manage because of this horrific combination of negative factors.

Long-term evaluation of temporomandibular disorders in association with cytokine and autoantibody status in young women.
Son C, Park YK, Park JW.
Cytokine. 2021 Apr 30:155551. doi: 10.1016/j.cyto.2021.155551. PMID: 33941445.

Temporomandibular disorders (TMD) is a chronic pain disease affecting 4-60% of general population. Its suggested etiology includes mechanical overloading to related structures, psychosocial factors, and genetic vulnerability. However, its pathogenesis is yet to be fully understood, especially in cases with a higher level of pain and more associated comorbidities. Recently chronic systemic inflammation and possible autoimmunity has been indicated in several pain conditions as the underlying mechanism of chronicity but this aspect has not been rigorously investigated in TMD. This article focuses on analyzing the levels of cytokines, chemokines, autoantibodies and nonspecific inflammatory markers and comparing their levels according to pain severity and duration in 66 female TMD patients in their 20 s and investigating their association with clinical indices of TMD and comorbidities. The high pain disability group showed decreased range of jaw function and more pain on palpation of capsule areas compared to the low pain disability group. Comorbidities such as anxiety and sleep disturbance were also significantly more prevalent. The level of IL-8 and IgG were significantly higher in the high pain disability group. IL-2, -8, -13, IFN- γ, RANTES, PGE2, and thrombopoietin levels showed a significant effect on indices reflecting jaw function, generalized pain intensity, and health related quality of life. Such results imply that longer pain duration and higher pain intensity is associated with higher levels of systemic inflammation suggesting the possible role of immunologic disturbance as an underlying factor of chronic TMD pain and warranting further investigation for its consideration in diagnosis and treatment.

Dynamics of brain function in chronic pain patients assessed by microstate analysis of resting-state electroencephalography.
May ES, Ávila CG, Dinh ST, Heitmann H, Hohn VD, Nickel MM, Tiemann L, Tölle TR, Ploner M.
Pain. 2021 Apr 8. doi: 10.1097/j.pain.0000000000002281. PMID: 33863863.

Chronic pain is a highly prevalent and severely disabling disease that is associated with substantial changes of brain function. Such changes have mostly been observed when analyzing static measures of resting-state brain activity. However, brain activity varies over time and it is increasingly recognized that the temporal dynamics of brain activity provide behaviorally relevant information in different neuropsychiatric disorders. Here, we therefore investigated whether the temporal dynamics of brain function are altered in chronic pain. To this end, we applied microstate analysis to eyes-open and eyes-closed resting-state electroencephalography (EEG) data of 101 patients suffering from chronic pain and 88 age- and sex-matched healthy controls. Microstate analysis describes EEG activity as a sequence of a limited number of topographies termed microstates that remain stable for tens of milliseconds. Our results revealed that sequences of 5 microstates, labelled with the letters A to E, consistently described resting-state brain activity in both groups in the eyes-closed condition. Bayesian analysis of the temporal characteristics of microstates revealed that microstate D has a less predominant role in patients than in controls. As microstate D has been previously related to attentional networks and functions, these abnormalities might relate to dysfunctional attentional processes in chronic pain. Subgroup analyses replicated microstate D changes in patients with chronic back pain, while chronic widespread pain patients did not show microstates alterations. Together, these findings add to the understanding of the pathophysiology of chronic pain and point to changes of brain dynamics specific to certain types of chronic pain.

Pathophysiological bases of comorbidity in migraine.
Altamura C, Corbelli I, de Tommaso M, Di Lorenzo C, Di Lorenzo G, Di Renzo A, Filippi M, Jannini TB, Messina R, Parisi P, Parisi V, Pierelli F, Rainero I, Raucci U, Rubino E, Sarchielli P, Li L, Vernieri F, Vollono C, Coppola G.
Front Hum Neurosci. 2021 Apr 20;15:640574. doi: 10.3389/fnhum.2021.640574. PMID: 33958992; PMCID: PMC8093831.

Despite that it is commonly accepted that migraine is a disorder of the nervous system with a prominent genetic basis, it is comorbid with a plethora of medical conditions. Several studies have found bidirectional comorbidity between migraine and different disorders including neurological, psychiatric, cardio- and cerebrovascular, gastrointestinal, metaboloendocrine, and immunological conditions. Each of these has its own genetic load and shares some common characteristics with migraine. The bidirectional mechanisms that are likely to underlie this extensive comorbidity between migraine and other diseases are manifold. Comorbid pathologies can induce and promote thalamocortical network dysexcitability, multi-organ transient or persistent pro-inflammatory state, and disproportionate energetic needs in a variable combination, which in turn may be causative mechanisms of the activation of an ample defensive system with includes the trigeminovascular system in conjunction with the neuroendocrine hypothalamic system. This strategy is designed to maintain brain homeostasis by regulating homeostatic needs, such as normal subcortico-cortical excitability, energy balance, osmoregulation, and emotional response. In this light, the treatment of migraine should always involves a multidisciplinary approach, aimed at identifying and, if necessary, eliminating possible risk and comorbidity factors.

Plasma calcitonin gene-related peptide (CGRP) in migraine and endometriosis during the menstrual cycle.
Raffaelli B, Overeem LH, Mecklenburg J, Hofacker MD, Knoth H, Nowak CP, Neeb L, Ebert AD, Sehouli J, Mechsner S, Reuter U.
Ann Clin Transl Neurol. 2021 Jun;8(6):1251-1259. doi: 10.1002/acn3.51360. PMID: 33934575.

Objective: Migraine, endometriosis, and the comorbidity of both are frequent pain disorders of special relevance for women. The neuropeptide calcitonin gene-related peptide (CGRP) is critically involved in migraine, and circumstantial evidence suggests a role in endometriosis. We assessed CGRP levels at different times of menstrual cycle in four groups: healthy women, women with migraine or endometriosis and with the comorbidity of both. Methods: Women with episodic migraine and women with a histologically confirmed endometriosis were recruited from specialized centers. For CGRP determination with a commercial enzyme immunoassay kit, cubital vein blood samples were collected on menstrual cycle day 2 ± 2 (during menstruation) and on day 15 ± 2 (periovulatory period). The primary endpoint of the study was the absolute difference of CGRP plasma levels between the menstrual and the periovulatory phase of all study groups. Groups were compared using nonparametric test procedures. Results: A total of 124 women were included in the study. The change of CGRP plasma levels between menstruation and the periovulatory period was different between groups ($p = 0.007$). Women with comorbid migraine and endometriosis showed an increase of CGRP in the menstrual phase of +6.32 (interquartile range, IQR -3.64-13.60) compared to the periovulatory time, while healthy controls had a decrease of -10.14 (-22.54-0.91, $p = 0.004$). CGRP levels were different in the periovulatory phase among groups ($p = 0.008$), with highest values in healthy controls. Interpretation: CGRP levels change significantly during the menstrual cycle. Different patterns in women with the comorbidity point to a deviant regulation of CGRP release.

Epilepsy and migraine shared genetic and molecular mechanisms: Focus on therapeutic strategies.
Gotra P, Bhardwaj N, Ludhiadch A, Singh G, Munshi A. Mol Neurobiol. 2021 Apr 15. doi: 10.1007/s12035-021-02386-x. PMID: 33856647.

Epilepsy and migraine are both episodic disorders and share clinical as well as pathophysiological mechanisms. The prevalence of epilepsy in migraine patients is generally higher than normal as compared to general population and vice versa. Various environmental risk factors and genetic factors have been reported to be associated with susceptibility of these comorbid diseases. Specific genes have been implicated in the

pathogenesis of the two diseases. However, the shared genetic susceptibility has not been explored extensively. Previous studies have reported that the alterations in the genes encoding ion channel proteins are common risk factors for both the diseases. The alterations in ion channel-encoding genes CACNAIA (T666M) and SCNIA (Q1489K and L1649Q) have been found to be involved in the development of familial hemiplegic migraine (FHM) as well as generalized epilepsy and some cases of focal epilepsy as well. The fact that both these disorders are treated with anti-epileptic drugs (AEDs) strongly supports common underlying mechanisms. This review has been compiled with an aim to explore the alterations in common genes involved in various pathways regulating neuronal hyperexcitability, a common risk factor for both these conditions. The avenue for future treatment strategies targeting common genes and molecular mechanisms has also been discussed.

Frequency of irritable bowel syndrome in patients with brugada syndrome and drug-induced type 1 brugada pattern.
Sarica AS, Bor S, Orman MN, Barajas-Martinez H, Juang JJ, Antzelevitch C, Hasdemir C.
Am J Cardiol. 2021 May 22:S0002-9149(21)00363-5. doi: 10.1016/j.amjcard.2021.04.010. PMID: 34034907.

Irritable bowel syndrome (IBS) is one of the most widely recognized functional bowel disorders (FBDs) with a genetic component. SCN5A gene and SCN1B loci have been identified in population-based IBS cohorts and proposed to have a mechanistic role in the pathophysiology of IBS. These same genes have been associated with Brugada syndrome (BrS). The present study examines the hypothesis that these two inherited syndromes are linked. Prevalence of FBDs over a 12 month period were compared between probands with BrS/drug-induced type 1 Brugada pattern (DI-Type 1 BrP) (n = 148) and a control group (n = 124) matched for age, female sex, presence of arrhythmia and co-morbid conditions. SCN5A/SCN1B genes were screened in 88 patients. Prevalence of IBS was 25% in patients with BrS/DI-Type 1 BrP and 8.1% in the control group ($p = 2.34 \times 10^{-4}$). On stepwise logistic regression analysis, presence of current and/or history of migraine (OR of 2.75; 95% CI: 1.08 to 6.98; p = 0.033) was a predictor of underlying BrS/DI-Type 1 BrP among patients with FBDs. We identified 8 putative SCN5A/SCN1B variants in 7 (12.3%) patients with BrS/DI-Type 1 BrP and 1 (3.2%) patient in control group. Five out of 8 (62.5%) patients with SCN5A/SCN1B variants had FBDs. In conclusion, IBS is a common co-morbidity in patients with BrS/DI-Type 1 BrP. Presence of current and/or history of migraine are a predictor of underlying BrS/DI-Type 1 BrP among patients with FBDs. Frequent co-existence of IBS and BrS/DI-Type 1 BrP necessitates cautious use of certain drugs among the therapeutic options for IBS that are known to exacerbate the Brugada phenotype.

Brain-derived neurotrophic factor and immune cells in osteoarthritis, chronic low back pain, and chronic widespread pain patients: Association with anxiety and depression.
Dimmek DJ, Korallus C, Buyny S, Christoph G, Lichtinghagen R, Jacobs R, Nugraha B.
Medicina (Kaunas). 2021 Apr 1;57(4):327. doi: 10.3390/medicina57040327. PMID: 33915758; PMCID: PMC8065931.

Background and Objectives: Musculoskeletal dysfunction can induce several types of chronic pain syndromes. It is of particular interest to elucidate the pathomechanism of different forms of chronic pain. It is possible that patients who have developed chronic widespread pain (CWP) may endure different pathomechanisms as compared to those who suffer from local pain (osteoarthritis, OA) and regional pain (chronic low back pain, cLBP), especially with regard to pain regulation and its related biomediators. The aim of this study was to determine the differences in pathomechanisms among these patients by measuring pain-related biomediators, particularly brain-derived neurotrophic factor (BDNF). Additionally, subpopulations of immune cells were determined in parallel. Materials and Methods: Patients and healthy subjects (HSs) were recruited (age and gender-matched). BDNF was measured from serum samples of patients and HSs and the data of body composition parameters were recorded. Additionally, both patients and HSs were asked to fill in questionnaires related to pain intensity, anxiety, and depression. Results: Our results highlight that the levels of both free and total BDNF are significantly lower in pain patients compared to HSs, with *p* values of 0.041 and 0.024, respectively. The number of $CD3^-$ $CD56_{bright}$ natural killer (NK) cells shows significant differences between the groups. Comparing all chronic pain patients with HSs reveals a significantly lower number of $CD4^+$ $CD8^+$ T cells ($p = 0.031$), $CD3^-$ $CD56_{bright}$ NK cells ($p = 0.049$) and $CD20^+$ $CD3^-$ cells ($p = 0.007$). Conclusions: To conclude, it seems that a general conformity between the pathomechanisms of different chronic pain diseases exists, although there are unique findings only in specific chronic pain patients.

Epidemiology Studies

Pain trends among American adults, 2002-2018: Patterns, disparities, and correlates.
Zajacova A, Grol-Prokopczyk H, Zimmer Z.
Demography. 2021 Apr 1;58(2):711-738. doi: 10.1215/00703370-8977691. PMID: 33834222; PMCID: PMC8035485.

Determining long-term trends in chronic pain prevalence is critical for evaluating and shaping U.S. health policies, but little research has examined such trends. This study (1) provides estimates of pain trends among U.S. adults across major population groups; (2) tests whether sociodemographic disparities in pain have widened or narrowed over time; and (3) examines socioeconomic, behavioral, psychological, and medical correlates of pain trends. Regression and decomposition analyses of joint, low back, neck, facial/jaw pain, and headache/migraine using the 2002-2018 National Health Interview Survey for adults aged 25-84 (N = 441,707) assess the trends and their correlates. We find extensive escalation of pain prevalence in all

population subgroups: overall, reports of pain in at least one site increased by 10%, representing an additional 10.5 million adults experiencing pain. Socioeconomic disparities in pain are widening over time, and psychological distress and health behaviors are among the salient correlates of the trends. This study thus comprehensively documents rising pain prevalence among Americans across the adult life span and highlights socioeconomic, behavioral, and psychological factors as important correlates of the trends. Chronic pain is an important dimension of population health, and demographic research should include it when studying health and health disparities.

Association of multimorbidity on healthcare expenditures among older United States adults with pain.
Marupuru S, Axon DR.
J Aging Health. 2021 Apr 21:8982643211011841. doi: 10.1177/08982643211011841. PMID: 33881371.

Objectives: This cross-sectional study compared the healthcare expenditures associated with multimorbidity (having ≥2 chronic conditions) versus no multimorbidity among older United States (US) adults (aged ≥ 50 years) with self-reported pain in the past 4 weeks. Methods: This research used data from the 2018 Medical Expenditure Panel Survey. Adjusted linear regression models evaluated group differences in various annual healthcare expenditures. Results: Descriptive statistics indicated multimorbidity was associated with all personal characteristics ($p < 0.05$) except gender and smoking status ($p > 0.05$). Multimorbidity had 75.8% greater annual total health expenditures ($p = 0.0083$), 40.6% greater office-based expenditures ($p = 0.0224$), 100.6% greater prescription medication costs, ($p = 0.0268$), yet 47.3% lower inpatient expenditures ($p = 0.0158$), and 56.6% lower home healthcare expenditures ($p < 0.0001$) than no multimorbidity. Discussion: This study found greater healthcare expenditures among older US adults with pain and multimorbidity, which captures the financial burden of comorbidity in this population.

Estimating and characterizing the burden of multimorbidity in the community: A comprehensive multistep analysis of two large nationwide representative surveys in France.
Coste J, Valderas JM, Carcaillon-Bentata L.
PLoS Med. 2021 Apr 26;18(4):e1003584. doi: 10.1371/journal.pmed.1003584. PMID: 33901171; PMCID: PMC8109815.

Background: Given the increasing burden of chronic conditions, multimorbidity is now a priority for healthcare and public health systems worldwide. Appropriate methodological approaches for assessing the phenomenon have not yet been established, resulting in inconsistent and incomplete descriptions. We aimed to estimate and characterize the burden of multimorbidity in the adult population in France in terms of number and type of conditions, type of underlying mechanisms, and analysis of the joint effects for identifying combinations with the most deleterious interaction effects on health status. Methods and findings: We used a multistep approach to analyze cross-sectional and longitudinal data from 2 large nationwide representative surveys: 2010/2014 waves of the Health, Health Care, and Insurance Survey (ESPS 2010-2014) and Disability Healthcare Household Survey 2008 (HSM 2008), that collected similar data on 61 chronic or recurrent conditions. Adults aged ≥25 years in either ESPS 2010 (14,875) or HSM 2008 (23,348) were considered (participation rates were 65% and 62%, respectively). Longitudinal analyses included 7,438 participants of ESPS 2010 with follow-up for mortality (97%) of whom 3,798 were reinterviewed in 2014 (52%). Mortality, activity limitation, self-reported health, difficulties in activities/instrumental activities of daily living, and Medical Outcomes Study Short-Form 12-Item Health Survey were the health status measures. Multiple regression models were used to estimate the impact of chronic or recurrent conditions and multimorbid associations (dyads, triads, and tetrads) on health status. Etiological pathways explaining associations were investigated, and joint effects and interactions between conditions on health status measures were evaluated using both additive and multiplicative scales. Forty-eight chronic or recurrent conditions had an independent impact on mortality, activity limitations, or perceived heath. Multimorbidity prevalence varied between 30% (1-year time frame) and 39% (lifetime frame), and more markedly according to sex (higher in women), age (with greatest increases in middle-aged), and socioeconomic status (higher in less educated and low-income individuals and manual workers). We identified various multimorbid combinations, mostly involving vasculometabolic and musculoskeletal conditions and mental disorders, which could be explained by direct causation, shared or associated risk factors, or less frequently, confounding or chance. Combinations with the highest health impacts included diseases with complications but also associations of conditions affecting systems involved in locomotion and sensorial functions (impact on activity limitations), and associations including mental disorders (impact on perceived health). The interaction effects of the associated conditions varied on a continuum from subadditive and additive (associations involving cardiometabolic conditions, low back pain, osteoporosis, injury sequelae, depression, and anxiety) to multiplicative and supermultiplicative (associations involving obesity, chronic obstructive pulmonary disease, migraine, and certain osteoarticular pathologies). Study limitations included self-reported information on chronic conditions and the insufficient power of some analyses. Conclusions: Multimorbidity assessments should move beyond simply counting conditions and take into account the variable impacts on health status, etiological pathways, and joint effects of associated conditions. In particular, the multimorbid combinations with substantial health impacts or shared risk factors deserve closer attention. Our findings also suggest that multimorbidity assessment and management may be beneficial already in midlife and probably earlier in disadvantaged groups.

The effects of chronic back pain on self-management, clinical and psychological outcomes among patients with type 2 diabetes.
Nicolau J, Dotres K, Rodríguez I, Sanchís P, Tamayo MI, Soler AG, Fortuny R, Masmiquel L.
Minerva Endocrinol (Torino). 2021 Apr 21. doi: 10.23736/S2724-6507.21.03408-4. Epub ahead of print. PMID: 33880893.

Background: Chronic back pain (CBP) in patients with type 2 diabetes (T2DM) is twice as high among age-and-gender-matched controls. The presence of both conditions impacts negatively on both quality of life and physical function, which might negatively affect mood. Methods: We aimed to determine the prevalence of CBP among patients with T2DM by using the Lattinen Index (LI) and to assess whether the presence of CBP had any influence on clinical or psychological outcomes. Results: 13.5% out of 299 patients had significant CBP. The percentage of patients with less than 150 minutes per 1 week of exercise was higher in the group of patients with significant CBP (70% vs 51.4%; p= 0.04). The proportion of patients who met criteria for food addiction was greater among subjects with CBP (47.5% vs 26.6%; p=0.009). The percentage of patients with criteria for depression was higher among the CBP group (82.5% vs 29.7%; p<0.0001), as well as the prescription of antidepressants (45% vs 17.4%; p<0.0001). However, no significant differences were seen regarding glycemic control or the frequency of complications related to T2DM. Conclusions: CBP is prevalent among subjects with T2DM and it constitutes an important limiting factor of both self-care behaviors and psychological well-being.

Comorbidities in a nationwide, heterogenous population of Veterans with interstitial cystitis/bladder pain syndrome.
Laden BF, Bresee C, De Hoedt A, Dallas KB, Scharfenberg A, Saxena R, Senechal JF, Barbour KE, Kim J, Freedland SJ, Anger JT
Urology. 2021 Apr 23:S0090-4295(21)00343-5. doi: 10.1016/j.urology.2021.04.015. PMID: 33901534.

Objective: To examine the prevalence of comorbid conditions in a nationwide population of men and women with IC/BPS utilizing a more heterogeneous sample than most studies to date. Methods: Using the Veterans Affairs Informatics and Computing Infrastructure, we identified random samples of male and female patients with and without an ICD-9/ICD-10 diagnosis of IC/BPS. Presence of comorbidities (NUAS [chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, migraines], back pain, diabetes, and smoking) and psychosocial factors (alcohol abuse, post-traumatic stress disorder, sexual trauma, and history of depression) were determined using ICD-9 and ICD-10 codes. Associations between these variables and IC/BPS status were evaluated while adjusting for the potential confounding impact of race/ethnicity, age, and gender. Results: Data was analyzed from 872 IC/BPS patients (355 [41%] men, 517 [59%] women) and 558 non-IC/BPS patients (291 [52%] men, 267 [48%] women). IC/BPS patients were more likely than non-IC/BPS patients to have a greater number of comorbidities (2.72+/-1.77 vs 1.73+/-1.30, p<0.001), experience one or more NUAS (chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, and migraines) (45% [388/872] vs. 18% [101/558]; p<0.001) and had a higher prevalence of at least one psychosocial factor (61% [529/872] v. 46% [256/558]; p<0.001). Differences in the frequencies of comorbidities between patients with and without IC/BPS were more pronounced in female patients. Conclusions: These findings validate the findings of previous comorbidity studies of IC/BPS in a more diverse population.

Temporomandibular-disorder-related pain as a predictor of severe headaches.
Ashraf J, Närhi M, Suominen AL, Zaproudina N, Saxlin T.
Community Dent Oral Epidemiol. 2021 May 7. doi: 10.1111/cdoe.12654. PMID: 33961319.

Objective: The current study aimed to investigate the association of temporomandibular disorders (TMD)-related pain with the presence of migraine or tension-type headaches (TTH) over a follow-up period of 11 years. Methods: Data sets from Finnish national health surveys, the Health 2000 Survey (baseline), and the Health 2011 Survey (follow-up) were utilized. Study participants are undergoing clinical TMD examination at baseline and answering questions related to the presence of migraine and TTH at follow-up were included in the study (n = 530). For analyses, the study sample was divided into two data sets: One with those excluded suffering from migraine at baseline (Data set I, n = 345), and the other excluding those having TTH at baseline (Data set II, n = 464). Results: Based on logistic regression modelling, no consistent association between TMD-related pain and the presence of migraine was observed, although jTMD associated with elevated estimates for migraine. However, participants with muscle-related TMD pain (mTMD) at baseline had markedly higher odds for having TTH at follow-up than participants without mTMD at baseline (OR 2.1, 95% CI 1.2-3.8). Joint-related TMD pain (jTMD) at baseline was inversely associated with the presence of TTH at follow-up (OR 0.4, 95% CI 0.1-1.3). Conclusion: Contrasting patterns of the associations of TMD-related pain with different severe headaches point towards a more thorough and systematic research approach are needed to understand the mechanisms behind these associations.

Risks of major mental disorders and irritable bowel syndrome among the offspring of parents with irritable bowel syndrome: A nationwide study.
Yeh TC, Bai YM, Tsai SJ, Chen TJ, Liang CS, Chen MH.
Int J Environ Res Public Health. 2021 Apr 28;18(9):4679. doi: 10.3390/ijerph18094679. PMID: 33924787; PMCID: PMC8124475.

Irritable bowel syndrome (IBS) is a functional bowel disorder that is highly comorbid with mental disorders. However, few studies have examined the risk of attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), bipolar disorder, major depressive disorder (MDD), and schizophrenia in the offspring of parents with IBS. We used nationally representative cross-sectional survey data to analyze cross-generational transmission patterns of both IBS and major mental disorders. Odds ratio (OR) was calculated by using logistic regression models with adjustment for potential confounding factors. Offspring of parents with IBS were more likely to develop IBS themselves (OR = 2.41, 95% confidence interval (CI), 2.09-2.78), ADHD (OR = 1.33, 95% CI, 1.08-1.62), and MDD (OR = 1.32, 95% CI, 1.04-1.68) than the controls. Data stratification by parental sex revealed that paternal IBS increased risk of ADHD (OR = 1.34, 95% CI, 1.01-

1.77) in the offspring, while maternal IBS increased the risk of MDD (OR = 1.51, 95% CI, 1.11-2.06). This is the first study to reveal parental IBS is associated with IBS, ADHD, and MDD among offspring, suggesting the necessity for early implementation of prevention strategies for at-risk children.

Dysmenorrhea symptom-based phenotypes: A replication and extension study.
Chen CX, Carpenter JS, Ofner S, LaPradd M, Fortenberry JD.
Nurs Res. 2021 Jan/Feb;70(1):24-33. doi: 10.1097/NNR.0000000000000477. PMID: 32956256; PMCID: PMC7736149.

Background: Dysmenorrhea is a prevalent pain condition among women and a risk factor for other chronic pain conditions. Individuals vary in dysmenorrhea pain severity, the number of painful sites, and co-occurring gastrointestinal symptoms. Three dysmenorrhea symptom-based phenotypes were previously identified using latent class analysis; however, there is a need to validate these in an independent sample, so they can be used in mechanistic and interventional research. There is also a need to further characterize dysmenorrhea symptom-based phenotypes in terms of demographic, clinical, and psychobehavioral characteristics so they can be used to inform precision dysmenorrhea treatment. Objectives: The study objectives were to (a) determine whether the same dysmenorrhea symptom-based phenotypes would be found in a new sample; (b) determine whether including demographic, clinical, and psychobehavioral covariates in latent class analyses would change individuals' phenotype memberships; and (c) investigate relationships between dysmenorrhea symptom-based phenotypes and demographic, clinical, and psychobehavioral characteristics. Methods: This cross-sectional survey study included 678 women (aged 14-42 years) with dysmenorrhea. Participants reported dysmenorrhea symptom severity, demographic, clinical (comorbid chronic pain and gynecological conditions), and psychobehavioral characteristics (perceived stress, anxiety, depression, sleep disturbance, and pain catastrophizing). We used latent class analysis to identify symptom-based phenotypes. We compared analyses with and without covariates (i.e., demographic, clinical, and psychobehavioral characteristics) to determine if individuals' phenotype memberships changed. We then examined associations between phenotypes and demographic, clinical, and psychobehavioral characteristics. Results: We reproduced three dysmenorrhea symptom-based phenotypes: the "mild localized pain" phenotype (characterized by mild abdominal cramps), the "severe localized pain" phenotype (characterized by severe abdominal cramps), and the "multiple severe symptoms" phenotype (characterized by severe pain at multiple locations and gastrointestinal symptoms). Analyses with and without covariates had little effect on individuals' phenotype membership. Race, comorbid chronic pain condition, endometriosis, and pain catastrophizing were significantly associated with the dysmenorrhea phenotypes. Discussion: Findings provide a foundation to further study mechanisms of dysmenorrhea symptom heterogeneity and develop dysmenorrhea precision treatments. The three dysmenorrhea symptom-based phenotypes were validated in a second sample. Demographic, clinical, and psychobehavioral factors were associated with dysmenorrhea symptom-based phenotypes.

Predictors of psychological distress in women with endometriosis: The role of multimorbidity, body image, and self-criticism.
Geller S, Levy S, Ashkeloni S, Roeh B, Sbiet E, Avitsur R.
Int J Environ Res Public Health. 2021 Mar 26;18(7):3453. doi: 10.3390/ijerph18073453. PMID: 33810403; PMCID: PMC8037734.

While large numbers of women report high levels of psychological distress associated with endometriosis, others report levels of distress that are comparable to those of healthy women. Thus, the aim of the current study was to develop an explanatory model for the effect of endometriosis on women's psychological distress. Furthermore, it sought to further investigate the role of body image, self-criticism, and pain intensity on the psychological distress associated with endometriosis and establish the effect of chronic illness load on the development of this distress. This study comprised a total of 247 women aged 20-49 (M = 31.3, SD = 6.4)-73 suffering from endometriosis only, 62 suffering from endometriosis and an additional chronical illness (ACI), and 112 healthy peers (HP)-who completed the Patient Health Questionnaire, the Generalized Anxiety Disorder-Item Scale, the Body Appreciation Scale-2, and the Self-Criticism Sub-Scale. When comparing each endometriosis group to their HP's, we found that the differences between HP and endometriosis ACI in depression and anxiety were mediated by body image (Betas = 0.17 and 0.09, respectively, p's < 0.05) and self-criticism (Betas = 0.23 and 0.26, respectively, p's < 0.05). When comparing endometriosis participants to endometriosis ACI participants, differences in depression were mediated by body image, self-criticism, and pain intensity (Betas = 0.12, 0.13, 0.13 respectively, p's < 0.05), and the differences in anxiety were mediated by self-criticism and pain intensity (Betas = 0.19, 0.08, respectively, p's < 0.05). Physicians and other health professionals are advised to detect women with endometriosis ACI who are distressed, and to offer them appropriate intervention.

Prevalence and association of lifestyle and medical-, psychiatric-, and pain-related comorbidities in patients with migraine: A cross-sectional study.
Yin JH, Lin YK, Yang CP, Liang CS, Lee JT, Lee MS, Tsai CL, Lin GY, Ho TH, Yang FC.
Headache. 2021 Apr 5. doi: 10.1111/head.14106. PMID: 33818765.

Background and objectives: Migraine has been associated with many comorbidities. However, lifestyle factors and the presence of comorbid diseases have not previously been extensively studied in the same sample. This study aimed to compare the prevalence of unhealthy lifestyle factors and comorbid diseases between patients with migraine and migraine-free controls with subgroup analyses to determine the pathophysiology and possible consequences. Methods: This cross-sectional study recruited 1257 patients with migraine between the ages of 20 and 65 years from a headache outpatient clinic in Taiwan and 496 non-

migraine controls. All participants completed questionnaires regarding demographics, migraine diagnosis, sleep, headache burden, and medical, pain, and psychiatric conditions. Participants also underwent a structured interview. The associations between comorbidities and migraine were investigated and further stratified by sex and aura. Results: Patients with migraine with aura had an unhealthier lifestyle compared with controls in the form of current smoking status (15.5% [67/431] vs. 11.5% [57/496], p = 0.013). Furthermore, medical- (e.g., thyroid disease; 7.2% [91/1257 vs. 2.8% [14/496]; p = 0.006), psychiatric- (e.g., depression; 6% [76/1257 vs. 2.6% [13/496]; p = 0.031), and pain-related (e.g., fibromyalgia; 8% [101/1257 vs. 3.2% [16/496]; p = 0.006) comorbidities were more prevalent in patients compared with controls. Subgroup analyses revealed that chronic migraine, migraine with aura, and female sex were associated with a greater number of significant comorbidities than episodic migraine, migraine without aura, and male patients with migraine, respectively. Conclusion: Individuals seeking treatment for migraine reported greater levels of smoking and medical, psychiatric, and pain conditions than non-treatment-seeking healthy controls who were recruited from the community. Understanding the relationship between migraine and comorbid diseases may improve medical care as well as the quality of life.

High attention-deficit/hyperactivity disorder scale scores among patients with persistent chronic nonspecific low back pain.
Kasahara S, Niwa SI, Matsudaira K, Sato N, Oka H, Fujii T, Konno SI, Kikuchi SI, Yamada Y.
Pain Physician. 2021 May;24(3):E299-E307. PMID: 33988951.

Background: Associations between attention-deficit/hyperactivity disorder (ADHD) and chronic pain disorders, such as fibromyalgia, have been reported. However, associations between persistent chronic nonspecific low back pain (CNLBP) and ADHD have not yet been investigated. Objectives: This study aimed to investigate the positive rates of possible ADHD, as assessed by self-reported ADHD scales, in patients with persistent CNLBP, using data from self-reported questionnaires completed by patients and their families. This study also aimed to compare the self-reported scores obtained from existing standardized data for healthy individuals, and to examine whether the ADHD scale scores of patients with persistent CNLBP are associated with pain variables. Study design: Cross-sectional study. Setting: The specialized pain clinic at our university hospital. Methods: This cross-sectional study included 60 consecutive patients with persistent CNLBP who were diagnosed with a possible somatic symptom disorder and were referred to a psychiatrist in our pain clinic. The Conners' Adult ADHD Rating Scales (CAARS) self-report (CAARS-S) and observer-rated (CAARS-O) questionnaires were utilized. We investigated the CAARS scores, and the association between the CAARS subscale scores and pain variables (pain duration and pain Numeric Rating Scale) in patients with persistent CNLBP. Results: Of the 60 patients, 19 (31.7%) were positive on both CAARS-S and CAARS-O questionnaires (T-score > 65). The ADHD indices, which comprised subscales of the CAARS estimating the necessity of treatment for ADHD, were significantly higher in both male and female patients with persistent CNLBP than in the Japanese standardized sample (P < 0.005). CAARS-S hyperactivity/restlessness, CAARS-O hyperactivity/restlessness, and the Diagnostic and Statistical Manual of Mental Disorders, fourth edition hyperactive-impulsive symptom subscale scores also correlated with the pain intensity (P < 0.05). Limitations: In this study, ADHD tendency was evaluated using only a self-reported questionnaire. Hence in the future, accurate and precise assessments of ADHD symptoms using structured clinical interviews conducted by ADHD experts are warranted. Additionally, the study only included patients with persistent CNLBP. Therefore in the future, it will be valuable to investigate ADHD scale scores (e.g., CAARS) among patients with CNLBP and nonspecific low back pain with larger sample sizes. Conclusions: Our findings revealed that the subscale scores on an ADHD scale were considerably high in patients with persistent CNLBP. As a previous study of our clinical experience indicates that persistent CNLBP can be substantially relieved by administering ADHD medications, ADHD screening is warranted in the treatment of persistent CNLBP.

Clinical Studies

Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain.
London: National Institute for Health and Care Excellence (UK); 2021 Apr 7. PMID: 33939353.

This guideline covers assessing all chronic pain (chronic primary pain, chronic secondary pain, or both) and managing chronic primary pain in people aged 16 years and over. Chronic primary pain is pain with no clear underlying cause, or pain (or its impact) that is out of proportion to any observable injury or disease. This guideline should be used alongside NICE guidelines for other chronic pain conditions, including the NICE guidelines on headaches, low back pain and sciatica, rheumatoid arthritis, osteoarthritis, spondyloarthritis, endometriosis, neuropathic pain and irritable bowel syndrome. See a visual summary setting out how to use NICE guidelines for assessing and managing chronic primary and chronic secondary pain. The recommendations in this guideline were developed before the COVID-19 pandemic. This guideline was commissioned by NICE and developed in partnership with the Royal College of Physicians (RCP). Who is it for?: Healthcare professionals; Commissioners and providers of services; People with chronic primary pain and chronic secondary pain, their families and carers.

Clinical, psychological, and sensory characteristics associated with headache attributed to temporomandibular disorder in people with chronic myogenous temporomandibular disorder and primary headaches.
Tchivileva IE, Ohrbach R, Fillingim RB, Lin FC, Lim PF, Arbes SJ Jr, Slade GD.
J Headache Pain. 2021 May 22;22(1):42. doi: 10.1186/s10194-021-01255-1. PMID: 34022805; PMCID:

PMC8141151.

Background: Headache attributed to Temporomandibular Disorder (HATMD) is a secondary headache that may have features resulting in diagnostic overlap with primary headaches, namely, tension-type (TTH) or migraine. This cross-sectional study of people with both chronic myogenous TMD and primary headaches evaluated characteristics associated with HATMD. Methods: From a clinical trial of adults, baseline data were used from a subset with diagnoses of both TMD myalgia according to the Diagnostic Criteria for TMD (DC/TMD) and TTH or migraine according to the International Classification of Headache Disorders, 3rd edition. HATMD was classified based on the DC/TMD. Questionnaires and examinations evaluated 42 characteristics of facial pain, headache, general health, psychological distress, and experimental pain sensitivity. Univariate regression models quantified the associations of each characteristic with HATMD (present versus absent), headache type (TTH versus migraine), and their interaction in a factorial design. Multivariable lasso regression identified the most important predictors of HATMD. Results: Of 185 participants, 114 (61.6%) had HATMD, while the numbers with TTH (n = 98, 53.0%) and migraine (n = 87, 47.0%) were similar. HATMD was more likely among migraineurs (61/87 = 70.1%) than participants with TTH (53/98 = 54.1%; odds ratio = 2.0; 95%CL = 1.1, 3.7). In univariate analyses, characteristics associated with HATMD included pain-free jaw opening and examination-evoked pain in masticatory muscles and temporomandibular joints (TMJ) as well as frequency and impact of headache, but not frequency or impact of facial pain. Lowered blood pressure but not psychological or sensory characteristics was associated with HATMD. Multiple characteristics of facial pain, headache, general health, and psychological distress differed between TTH or migraine groups. Few interactions were observed, demonstrating that most characteristics' associations with HATMD were consistent in TTH and migraine groups. The lasso model identified headache frequency and examination-evoked muscle pain as the most important predictors of HATMD. Conclusions: HATMD is highly prevalent among patients with chronic myogenous TMD and headaches and often presents as migraine. In contrast to primary headaches, HATMD is associated with higher headache frequency and examination-evoked masticatory muscle pain, but with surprisingly few measures of facial pain, general health, and psychological distress. A better understanding of HATMD is necessary for developing targeted strategies for its management.

Fibromyalgia as a heterogeneous condition: Subgroups of patients based on physical symptoms and cognitive-affective variables related to pain.
Martinez MP, Sanchez AI, Prados G, Lami MJ, Villar B, Miro E.
Span J Psychol. 2021 May 18;24:e33. doi: 10.1017/SJP.2021.30.

Fibromyalgia (FM) is a chronic syndrome characterized by heterogeneous clinical manifestations, and knowing this variability can help to develop tailored treatments. To understand better the heterogeneity of FM the present cross-sectional study analyzed the role of several physical symptoms (pain, fatigue and poor sleep quality) and cognitive-affective variables related to pain (pain catastrophizing, pain vigilance, self-efficacy in pain management, and pain acceptance) in the configuration of clinical profiles. A sample of 161 women with FM fulfilled an interview and several self-report measures to explore physical symptoms, cognitive-affective variables, disability and psychopathology. To establish FM groups a hierarchical cluster analysis was performed. The findings revealed three clusters that differed in the grouping variables, Wilks' λ = .17, $F(14, 304) = 31.50$, $p < .001$, $\eta p2 = .59$. Group 1 (n = 72) was characterized by high physical and psychological affectation, Group 2 (n = 19) by low physical affectation and high pain self-efficacy, and Group 3 (n = 70) by moderate physical affectation and low pain catastrophizing. The external validation of the clusters was confirmed, Wilks' λ = .72, $F(4, 314) = 14.09$, $p < .001$, $\eta p2 = .15$, showing Group 1 the highest levels of FM impact and psychopathological distress. Considering the distinctive clinical characteristics of each subgroup therapeutic strategies addressed to the specific needs of each group were suggested. Assessing FM profiles may be key for a better understanding and approach of this syndrome.

Phenotype of cluster headache: Clinical variability, persisting pain between attacks, and comorbidities-An observational cohort study in 825 patients.
Göbel CH, Karstedt S, Heinze A, Koch B, Göbel H.
Pain Ther. 2021 May 4. doi: 10.1007/s40122-021-00267-8. Epub ahead of print. PMID: 33945123.

Introduction: Cluster headaches can occur with considerable clinical variability. The inter- and intra-individual variability could contribute to the fact that the clinical headache phenotype is not captured by too strict diagnostic criteria, and that the diagnosis and the effective therapy are thereby delayed. The aim of the study was to analyze the severity and extent of the clinical symptoms of episodic and chronic cluster headaches with regard to their variability and to compare them with the requirements of the International Classification of Headache Disorders 3rd edition (ICHD-3) diagnostic criteria. Methods: The study was carried out as a cross-sectional analysis of 825 patients who had been diagnosed with cluster headaches by their physician. Using an online questionnaire, standardized questions on sociodemographic variables, clinical features of the cluster headache according to ICHD-3, and accompanying clinical symptoms were recorded. Results: The majority of patients with cluster headaches have clinical features that are mapped by the diagnostic criteria of ICHD-3. However, due to the variability of the symptoms, there is a significant proportion of clinical phenotypes that are not captured by the ICHD-3 criteria for cluster headaches. In addition, change in the side of the pain between the cluster episodes, pain location, as well as persisting pain between the attacks is not addressed in the ICHD-3 criteria. In the foreground of the comorbidities are psychological consequences in the form of depression, sleep disorders, and anxiety. Conclusions: The variability of the phenotype of cluster headaches can preclude some patients from receiving an appropriate diagnosis and effective therapy if the diagnostic criteria applied are too strict. The occurrence of persisting pain between attacks should also be diagnostically evaluated due to its high prevalence and severity as well as psychological strain. When treating

patients with cluster headaches, accompanying psychological illnesses should carefully be taken into account.

Effects of fremanezumab in patients with chronic migraine and comorbid depression: Subgroup analysis of the randomized HALO CM study.
Lipton RB, Cohen JM, Galic M, Seminerio MJ, Yeung PP, Aycardi E, Bigal ME, Bibeau K, Buse DC. Headache. 2021 Apr;61(4):662-672. doi: 10.1111/head.14097. PMID: 33891348.

Objective: To evaluate the efficacy of fremanezumab in patients with chronic migraine (CM) and moderate to severe depression. Background: Fremanezumab, a fully humanized monoclonal antibody that selectively targets calcitonin gene-related peptide, has been approved for the preventive treatment of migraine in adults. CM and depression are highly comorbid. Methods: The 12-week, Phase 3 HALO trial randomized patients with CM to fremanezumab quarterly (675 mg/placebo/placebo), fremanezumab monthly (675/225/225 mg), or placebo. Post hoc analyses evaluated the effects of fremanezumab in patients with moderate to severe depression (baseline 9-item Patient Health Questionnaire sum score ≥10) on monthly number of headache days of at least moderate severity; monthly migraine days; Patient Global Impression of Change (PGIC); 6-item Headache Impact Test (HIT-6) scores; and depression. Results: For the 219/1121 (19.5%) patients with moderate to severe depression at baseline, fremanezumab was associated with a significant reduction in monthly number of headache days of at least moderate severity for active treatment versus placebo (least-squares mean change ± standard error for quarterly dosing: -5.3 ± 0.77; for monthly dosing: -5.5 ± 0.72; and for placebo: -2.2 ± 0.81; both $p < 0.001$). More patients achieved a ≥50% reduction in headache days of at least moderate severity with fremanezumab (quarterly: 31/78 [39.7%]; monthly: 39/96 [40.6%]) than placebo (9/67 [13.4%]; both $p < 0.001$). Compared with placebo, fremanezumab improved PGIC and HIT-6 scores. Conclusions: Fremanezumab demonstrated efficacy in the preventive treatment of CM and reduced headache impact in patients with comorbid depression.