

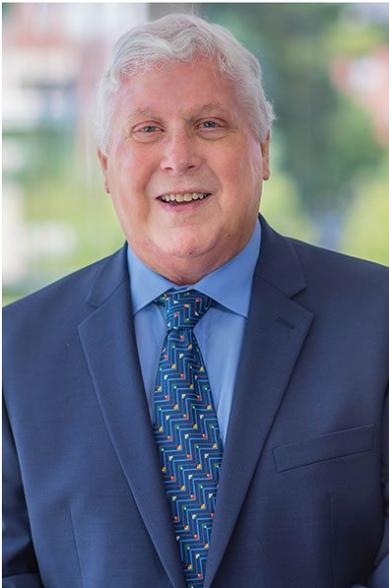


# CUTTING EDGE

a publication of  CHRONIC PAIN  
Research Alliance

COPCs Research Advances

Issue 20 - November 2020



This issue of *COPCs Research Advances* is dedicated - in loving memory - to Dr. William "Bill" Maixner, who passed away on November 2, 2020. Bill was a treasured friend, highly respected and accomplished scientist and empathic clinician. He was a visionary who pioneered the clinical concept of Chronic Overlapping Pain Conditions (COPCs) and conducted rigorous science to legitimize the biologic basis for COPCs as complex, multi-system illnesses - leading a paradigm shift in their understanding, most notably for TMJ. The transformative findings of his team's most recent COPCs research are highlighted in this newsletter issue. His passing has left an enormous void - not only in this field, but in our hearts. He is greatly missed by all of us who had the gift of calling him a friend. The significant impact of his life's work, dedication, advocacy and vision will continue to live on, forever changing the lives of those affected by these life-altering conditions.

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 August and November 2020. Prior issues are available on our website, <http://www.cpralliance.org>. To read the CPRA's White Paper, click [here](#). Please direct questions or comments to the CPRA's Director, Christin Veasley - [cveasley@cpralliance.org](mailto:cveasley@cpralliance.org). If you are not already on our mailing list would like to sign up to receive future issues of *COPCs Research Advances*, [click here](#).

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### NATIONAL MULTI-SITE STUDIES

#### [Overlap of five chronic pain conditions: Temporomandibular disorders, headache, back pain, irritable bowel syndrome, and fibromyalgia.](#)

Slade GD, Greenspan JD, Fillingim RB, Maixner W, Sharma S, Ohrbach R.  
J Oral Facial Pain Headache. 2020 Suppl;34:s15-s28. doi: 10.11607/ofph.2581.

Aims: To assess cohort retention in the OPPERA project and to compare the degree of overlap between pairs of chronic overlapping pain conditions (COPCs) using a cross-sectional analysis of data from 655 adults who completed follow-up in the OPPERA study. Methods: Subjects were classified for the absence or presence of each of the five COPCs. The extent of overlap beyond chance was quantified using odds ratios, which were calculated using binary logistic regression models. Results: While overlap was the norm, its magnitude varied according to COPC: 51% of people with headache had one or more overlapping COPCs, and this proportion increased to 90% for people with fibromyalgia. The degree of overlap between pairs of COPCs also varied considerably, with odds ratios being greatest for associations between musculoskeletal conditions (fibromyalgia, temporomandibular disorders, and low back pain) and less pronounced for overlap involving headache or IBS. Furthermore, univariate associations between some pairs of COPCs were nullified after adjusting for other COPCs. Conclusion: There was greater overlap between fibromyalgia and either temporomandibular disorders or low back pain than between other pairs of COPCs. While musculoskeletal conditions exhibited some features that could be explained by a single functional syndrome, headache and irritable bowel syndrome did not.

#### [Clinical characteristics of pain among five chronic overlapping pain conditions.](#)

Ohrbach R, Sharma S, Fillingim RB, Greenspan JD, Rosen JD, Slade GD.  
J Oral Facial Pain Headache. 2020 Suppl;34:s29-s42. doi: 10.11607/ofph.2573.

Aims: To describe the pain characteristics of five index chronic overlapping pain conditions (COPCs) and to assess each COPC separately in order to determine whether the presence of comorbid COPCs is associated with bodily pain distribution, pain intensity, pain interference, and high-impact pain of the index COPC. Methods: Data were from a convenience sample of 655 US adults, of whom 388 had one or more of the five COPCs: painful temporomandibular disorders, headache, low back pain, irritable bowel syndrome, and/or fibromyalgia. Data were collected using pain location checklists and self-report questions regarding pain attributes. The contributions of the COPCs to reported pain intensity and interference were assessed using multivariable regression models. Results/conclusion: Heat maps from a pain body manikin illustrated that very little of the body was pain free within these COPCs. All pain attributes were the most severe for fibromyalgia and the least severe for irritable bowel syndrome. Within each index COPC, pain intensity, pain interference, and the proportion of participants with high-impact pain increased with each additional comorbid COPC up to four or more COPCs (including the index COPC) ( $P < .01$ ). High-impact pain associated with an index COPC was influenced by type and number of comorbid COPCs, largely in a gradient-specific manner.

#### [Attributes germane to temporomandibular disorders and their associations with five chronic overlapping pain conditions.](#)

Sharma S, Slade GD, Fillingim RB, Greenspan JD, Rathnayaka N, Ohrbach R.

Aims: To investigate whether TMD-related characteristics are indeed specific to TMD or whether they are also associated with other chronic overlapping pain conditions (COPCs). Methods: In this cross-sectional study, 22 characteristics related broadly to TMD (eg, jaw kinesiophobia, overuse behaviors, and functional limitation) were measured in 178 painful TMD cases who were also classified according to four COPCs: headache, low back pain, irritable bowel syndrome, and fibromyalgia. Differences in mean subscale scores were compared according to individual chronic pain conditions and according to number of COPCs. Results: Headache, low back pain, irritable bowel syndrome, and fibromyalgia were each associated ( $P < .05$ ) with higher values of at least one TMD-relevant characteristic. In the multivariable analysis, TMD was independently associated with 20 of the 22 characteristics ( $P < .01$ ), and other COPCs were associated variably. A critical threshold existed between the number of COPCs and TMD characteristics: all characteristics were elevated for subjects with  $\geq 3$  COPCs ( $P \leq .01$ ). Conclusion: The overlap between COPCs and characteristics typically regarded as specific to painful TMD has implications for treatment targeted at both the local TMD condition and the broader pain disorder underlying the COPC(s). In TMD patients, the overall burden of pain from COPCs may create a shift in the pain-processing systems that underlie these TMD-relevant characteristics.

[Associations of sleep disturbance, atopy, and other health measures with chronic overlapping pain conditions.](#)

Sanders AE, Greenspan JD, Fillingim RB, Rathnayaka N, Ohrbach R, Slade GD. J Oral Facial Pain Headache. 2020 Suppl;34:s73-s84. doi: 10.11607/ofph.2577.

Aims: To quantify the contributions of atopic disorders, sleep disturbance, and other health conditions to five common pain conditions. Methods: This cross-sectional analysis used data from 655 participants in the OPPERA study. The authors investigated the individual and collective associations of five chronic overlapping pain conditions (COPCs) with medically diagnosed atopic disorders and self-reported sleep disturbance, fatigue, and symptoms of obstructive sleep apnea. Atopic disorders were allergies, allergic rhinitis, atopic dermatitis, allergic asthma, urticaria, allergic conjunctivitis, and food allergy. Logistic regression models estimated odds ratios as measures of association with temporomandibular disorders, headache, irritable bowel syndrome, low back pain, and fibromyalgia. Measures of sleep and atopy disorders were standardized to z scores to determine the relative strength of their associations with each COPC. Sociodemographic characteristics and body mass index were covariates. Random forest regression analyzed all variables simultaneously, computing importance metrics to determine which variables best differentiated pain cases from controls. Results: Fatigue and sleep disturbance were strongly associated with each COPC and with the total number of COPCs. An increase of one standard deviation in fatigue or sleep disturbance score was associated with approximately two-fold greater odds of having a COPC. In random forest models, atopic disorders contributed more than other health measures to differentiating between cases and controls of headache, whereas other COPCs were best differentiated by measures of fatigue or sleep. Conclusion: Atopic disorders, previously recognized as predictors of poor sleep, are associated with COPCs after accounting for sleep problems.

[Associations of psychologic factors with multiple chronic overlapping pain conditions.](#)

Fillingim RB, Ohrbach R, Greenspan JD, Sanders AE, Rathnayaka N, Maixner W, Slade GD.

J Oral Facial Pain Headache. 2020 Suppl;34:s85-s100. doi: 10.11607/ofph.2584.

Aims: To characterize psychologic functioning across five chronic overlapping pain conditions (COPCs)-temporomandibular disorders, fibromyalgia, low back pain,

headache, and irritable bowel syndrome-and their overlaps. Methods: Participants were 655 adults in the OPPERA study. Psychologic variables were standardized in separate logistic regression models to compare their relative strength of association with each COPC. Random forest regression was used to explore the association of all psychologic measures with COPCs simultaneously. Linear regression analyses examined whether the count of COPCs was associated with psychologic measures. Results: In univariate and multivariable analyses, measures of somatic symptom burden showed the strongest associations with individual COPCs and with the number of COPCs. Additional psychologic variables that showed significant associations with individual COPCs and their overlap included negative mood, perceived stress, and pain catastrophizing. Conclusion: These findings highlight the importance of psychologic functioning in the assessment and management of these overlapping pain conditions.

[Commentary 1: Introduction: At the crossroads of chronic overlapping pain conditions and research diagnostic criteria: Which direction to take?](#)

LeResche L, Von Korff M.

J Oral Facial Pain Headache. 2020 Suppl;34:s3-s5. doi: 10.11607/ofph.2020.suppl.c1.

No abstract available.

[Commentary 2: Further evidence for overlaps among chronic pain conditions-but no news about causal relationships.](#)

Svensson P, Exposto F.

J Oral Facial Pain Headache. 2020 Suppl;34:s6-s8. doi: 10.11607/ofph.2020.suppl.c2.

No abstract available.

[Commentary 3: Temporomandibular disorders - Casting the net to find answers.](#)

Stohler CS.

J Oral Facial Pain Headache. 2020 Supple;34:s9-s10. doi:

10.11607/ofph.2020.suppl.c3.

No abstract available.

[Commentary 4: OPPERA-2 conundrums and challenges: Lumping versus splitting?](#)

Benoliel R.

J Oral Facial Pain Headache. 2020 Supple;34:s11. doi: 10.11607/ofph.2020.suppl.c4.

No abstract available.

[Authors' Response: When you come to the fork in the road, take it! Future research into chronic pain as a general condition.](#)

Ohrbach R, Fillingim RB, Greenspan JD, Maixner W, Sanders AE, Sharma S, Slade GD.

J Oral Facial Pain Headache. 2020 Supple;34:s12-s14. doi:

10.11607/ofph.2020.suppl.ar.

No abstract available.

## **PATHOPHYSIOLOGY STUDIES**

[Preclinical studies investigating the neural mechanisms involved in the co-morbidity of migraine and temporomandibular disorders: The role of CGRP.](#)

Akerman S, Romero-Reyes M.

Background and purpose: Temporomandibular disorders (TMD) and migraine can be co-morbid. This can be a significant factor in exacerbating and increasing the prevalence of migraine-like symptoms. However, the underlying mechanisms involved are unknown. Our objective was to investigate these neural mechanisms and the role of CGRP as a key modulator in this co-morbidity. Experimental approach: We combined experimental approaches using CGRP, which triggers a migraine-like response in patients, with that of masseteric muscle injection of complete Freund's adjuvant (CFA), to model myofascial TMD-like inflammation. Using validated electrophysiological methods to assess each of the above approaches independently or in combination, we examined their effects on the response properties of migraine-like dural-trigemino-cervical neurons. Key results: Independently, in ~2/3 of animals (rats) each approach caused delayed migraine-like activation and sensitisation of dural-trigemino-cervical neurons. The response to masseteric-CFA was attenuated by a selective CGRP receptor antagonist. The combination approach caused a migraine-like neuronal response in all animals tested, with somatosensory-evoked cranial hypersensitivity significantly exacerbated. Conclusion and implications: The data demonstrate a neuronal phenotype that translates to the exacerbated clinical co-morbid phenotype, supporting this combination approach as a relevant model to study the mechanisms involved. It provides a pathophysiological rationale for this exacerbated phenotype, strongly implicating the involvement of CGRP. The results provide support for targeting the CGRP pathway as a novel monotherapy approach for treating this co-morbid condition. This has key implications into our understanding of this co-morbid condition, as well as potentially addressing the major unmet need for novel and effective therapeutic approaches.

[Orthostatic stress testing in myalgic encephalomyelitis/chronic fatigue syndrome patients with or without concomitant fibromyalgia: Effects on pressure pain thresholds and temporal summation.](#)

Van Campen CMC, Rowe PC, Verheugt FWA, Visser FC.  
Clin Exp Rheumatol. 2020 Sep 10.

Objectives: Muscle pain and fibromyalgia (FM) are common among individuals with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). We recently demonstrated that during orthostatic stress testing, adults with ME/CFS reported increased pain. In the current study, we hypothesised that pain pressure thresholds (PPT) would decrease and temporal summation (windup) would increase after head-up tilt testing (HUT), and that the presence of co-morbid FM would be associated with greater change in both measures. Methods: We studied adult ME/CFS patients undergoing HUT. PPT and temporal summation (or windup) measurements were obtained pre- and post-HUT at the finger and shoulder. Results: 248 ME/CFS patients (164 with FM and 84 without FM), and 22 healthy controls (HC) were analysed. In HC there were no significant differences in PPT between pre- and post- HUT (finger: from 4.7(1.6) to 4.4(1.5); shoulder: from 2.8(1.0) to 2.9(1.0)). In ME/CFS patients with and without FM, a significant decrease in PPT post-HUT was found compared to HC (both  $p < 0.0001$ ). Patients with FM had a lower PPT pre- and post-HUT (finger: from 2.0(0.9) to 1.5(0.8); shoulder: from 1.2(0.5) to 1.0(0.5) compared to patients without FM (finger: from 5.0(1.6) to 3.3(1.5); shoulder: from 2.2(0.9) to 1.9(1.0) ( $p$  ranging from 0.001 to  $< 0.0001$ ). Windup in HC did not significantly change from pre- to post-HUT. In ME/CFS patients with and without FM windup was increased compared to HC pre-HUT (both  $p < 0.0001$ ), but did not significantly change post-HUT. Conclusions: Pressure pain threshold decreased in ME/CFS patients with or without fibromyalgia after head-up tilt test (HUT), but did not change post-HUT in healthy controls. Windup pre- and post-HUT was significantly higher compared to healthy controls, but did not change from pre- to post-HUT. These results demonstrate that, like exercise, orthostatic stress can negatively influence the physiology of pain perception in

ME/CFS. Furthermore, the physiology of pain perception is even more negatively influenced by concomitant fibromyalgia.

[Small fiber polyneuropathy is associated with non-bladder-centric interstitial cystitis/bladder pain syndrome patients.](#)

Overholt TL, Matthews CA, Evans RJ, Badlani G, Ahn C, Simon T, Walker SJ. Female Pelvic Med Reconstr Surg. 2020 Oct 26. doi: 10.1097/SPV.0000000000000972.

Objectives: Interstitial cystitis/bladder pain syndrome (IC/BPS) comprises at least 2 phenotypes. Bladder centric patients typically demonstrate low bladder capacity (BC), often with Hunner lesion (HL), whereas non-bladder-centric patients typically have normal cystoscopic findings and more co-occurring nonurologic symptoms/syndromes (NUS), contributing to widespread pain beyond the bladder. Small fiber polyneuropathy (SFPN) is significantly associated with fibromyalgia, a frequent IC/BPS codiagnosis and may play an etiologic role in IC/BPS. We assessed SFPN status in bladder-centric versus non-bladder-centric IC/BPS patients. Methods: Distal leg biopsies were obtained from 11 IC/BPS patients after therapeutic hydrodistention. Specimens were embedded/sectioned per standard protocol and stained for protein gene product 9.5, an intraepidermal nerve fiber marker. To determine SFPN status, intraepidermal nerve fiber density was calculated and compared with normative reference values stratified by age/sex. The SFPN prevalence and reported comorbidities were compared between low BC and/or HL-positive (bladder-centric) versus non-low BC, HL (non-bladder-centric) patients. Results: Seven patients (63.6%) were SFPN positive. Non-bladder-centric patients demonstrated significantly more SFPN (6/7, 85.7%) compared with bladder-centric patients (1/4, 25.0%;  $P = 0.027$ ). Non-bladder-centric patients also reported more comorbid NUS overall ( $1.25 \pm 0.83$  vs  $5.86 \pm 2.47$ ;  $P = 0.003$ ), including fibromyalgia ( $P = 0.010$ ), migraines ( $P = 0.035$ ), anxiety/panic disorder ( $P = 0.035$ ), allergies ( $P = 0.027$ ), and asthma ( $P = 0.035$ ). Conclusions: In this pilot study, SFPN was significantly more common in non-bladder-centric IC/BPS, that is, those patients who also reported greater prevalence of NUS, including fibromyalgia, migraines, anxiety/panic disorders, allergies, and asthma. These findings suggest that SFPN may have an etiologic role in a larger, systemic pain syndrome and should be explored further.

[Genetic analysis of endometriosis and depression identifies shared loci and implicates causal links with gastric mucosa abnormality.](#)

Adewuyi EO, Mehta D, Sapkota Y, International Endogene Consortium; 23andMe Research Team; Auta A, Yoshihara K, Nyegaard M, Griffiths L, Montgomery GW, Chasman DI, Nyholt DR. Hum Genet. 2020 Sep 21. doi: 10.1007/s00439-020-02223-6.

Evidence from observational studies indicates that endometriosis and depression often co-occur. However, conflicting evidence exists, and the etiology as well as biological mechanisms underlying their comorbidity remain unknown. Utilizing genome-wide association study (GWAS) data, we comprehensively assessed the relationship between endometriosis and depression. Single nucleotide polymorphism effect concordance analysis (SECA) found a significant genetic overlap between endometriosis and depression ( $P_{F_{\text{sig-permuted}}} = 9.99 \times 10^{-4}$ ). Linkage disequilibrium score regression (LDSC) analysis estimated a positive and highly significant genetic correlation between the two traits ( $r_G = 0.27$ ,  $P = 8.85 \times 10^{-27}$ ). A meta-analysis of endometriosis and depression GWAS (sample size = 709,111), identified 20 independent genome-wide significant loci ( $P < 5 \times 10^{-8}$ ), of which eight are novel. Mendelian randomization analysis (MR) suggests a causal effect of depression on endometriosis. Combining gene-based association results across endometriosis and depression GWAS, we identified 22 genes with a genome-wide significant Fisher's

combined P value (FCP<sub>gene</sub> < 2.75 × 10<sup>-6</sup>). Genes with a nominal gene-based association (P<sub>gene</sub> < 0.05) were significantly enriched across endometriosis and depression (P<sub>binomial-test</sub> = 2.90 × 10<sup>-4</sup>). Also, genes overlapping the two traits at P<sub>gene</sub> < 0.1 (P<sub>binomial-test</sub> = 1.31 × 10<sup>-5</sup>) were significantly enriched for the biological pathways 'cell-cell adhesion', 'inositol phosphate metabolism', 'Hippo-Merlin signaling dysregulation' and 'gastric mucosa abnormality'. These results reveal a shared genetic etiology for endometriosis and depression. Indeed, additional analyses found evidence of a causal association between each of endometriosis and depression and at least one abnormal condition of gastric mucosa. Our study confirms the comorbidity of endometriosis and depression, implicates links with gastric mucosa abnormalities in their causal pathways and reveals potential therapeutic targets for further investigation.

### [Pain in endometriosis.](#)

Maddern J, Grundy L, Castro J, Brierley SM.

Front Cell Neurosci. 2020 Oct 6;14:590823. doi: 10.3389/fncel.2020.590823.

Endometriosis is a chronic and debilitating condition affecting ~10% of women. Endometriosis is characterized by infertility and chronic pelvic pain, yet treatment options remain limited. In many respects this is related to an underlying lack of knowledge of the etiology and mechanisms contributing to endometriosis-induced pain. Whilst many studies focus on retrograde menstruation, and the formation and development of lesions in the pathogenesis of endometriosis, the mechanisms underlying the associated pain remain poorly described. Here we review the recent clinical and experimental evidence of the mechanisms contributing to chronic pain in endometriosis. This includes the roles of inflammation, neurogenic inflammation, neuroangiogenesis, peripheral sensitization and central sensitization. As endometriosis patients are also known to have co-morbidities such as irritable bowel syndrome and overactive bladder syndrome, we highlight how common nerve pathways innervating the colon, bladder and female reproductive tract can contribute to co-morbidity via cross-organ sensitization.

### [Dysmenorrhea symptom-based phenotypes: A replication and extension study.](#)

Chen CX, Carpenter JS, Ofner S, LaPradd M, Fortenberry JD.

Nurs Res. 2020 Sep 16. doi: 10.1097/NNR.0000000000000477.

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 also is 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 to 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.

[A novel method to classify and subgroup patients with IBS based on gastrointestinal symptoms and psychological profiles.](#)

Black CJ, Yiannakou Y, Guthrie EA, West R, Houghton LA, Ford AC.  
Am J Gastroenterol. 2020 Oct 23. doi: 10.14309/ajg.0000000000000975.

Introduction: Conventionally, patients with irritable bowel syndrome (IBS) are subgrouped based on their predominant bowel habit. Given the relevance of psychological comorbidity to IBS symptoms, our aim was to explore an alternative approach to subgrouping by incorporating factors beyond stool form and frequency. Methods: We collected demographic, symptom, and psychological health data from 1,375 adult subjects in the community who self-identified as having IBS, identifying 2 cohorts meeting either Rome III or Rome IV criteria. In each cohort, we performed latent class analysis, a method of model-based clustering, to identify specific subgroups (clusters). For each cluster, we drew a radar plot and compared these by visual inspection, describing cluster characteristics. Results: In total, 1,080 individuals met the Rome III criteria for IBS, and 811 met the Rome IV criteria. In both cohorts, a 7-cluster model was the optimum solution, and the characteristics of the clusters were almost identical between Rome III and IV. Four clusters were defined by the pattern of gastrointestinal symptoms (loose stools and urgency or hard stools and bloating), further differentiated by the presence of abdominal pain not relieved by defecation, and by the extent of psychological comorbidity. Two clusters had below-average gastrointestinal symptoms, differentiated by the extent of psychological comorbidity. The final cluster had well-above-average gastrointestinal symptoms and high levels of psychological comorbidity. The proportion of subjects with severe IBS symptom scores, high levels of perceived stress, and high levels of gastrointestinal symptom-specific anxiety was significantly higher in clusters with high psychological comorbidity ( $P < 0.001$ ). Discussion: Latent class analysis identified 7 distinct IBS subgroups characterized by varying degrees of gastrointestinal symptoms, extraintestinal symptoms, and psychological comorbidity. Further research is needed to assess whether they might be used to direct treatment.

[Reduced heart rate variability in patients with medically unexplained physical symptoms: A meta-analysis of HF-HRV and RMSSD.](#)

Vreijling SR, Troudart Y, Brosschot JF.  
Psychosom Med. 2020 Oct 14. doi: 10.1097/PSY.0000000000000874.

Objectives: Medically unexplained physical symptoms (MUPS) and related syndromes are common and place a substantial burden on both patients and society. Chronic psychological distress and dysregulation of the autonomic nervous system may be common factors associated with MUPS, although previous studies have reported

mixed results. The aim of this meta-analysis is to provide an updated synthesis of studies investigating heart rate variability (HRV) indices associated with autonomic nervous system functioning in three common MUPS-syndromes and to explain inconsistencies in previous study findings. Method: Literature search yielded 58 studies comparing HRV indices of reduced parasympathetic activity of healthy individuals to patients with chronic fatigue syndrome (Npatients = 271), irritable bowel syndrome (Npatients = 1005), and fibromyalgia (Npatients = 534). Separate random-effects meta-analyses were conducted on studies measuring root mean square of successive differences (RMSSD) and high frequency HRV (HF-HRV). Results: Regardless of syndrome type, patients had significantly lower RMSSD ( $k = 22$ , Hedges'  $g = -0.37$  [-0.53; -0.21],  $p < .001$ ) and HF-HRV ( $k = 52$ , Hedges'  $g = -0.69$  [-1.03; -0.36],  $p < .001$ ) than healthy individuals. Sample age and publication year explained substantial variation in RMSSD, whereas controlling for confounders in statistical analyses explained variation in HF-HRV. Conclusions: Lower RMSSD and HF-HRV in patients with MUPS versus healthy controls indicates that autonomic nervous system dysregulation, particularly lower parasympathetic activity, may play a role in patients with these conditions. This conclusion may have important implications for the underlying mechanisms and treatment of MUPS and related syndromes.

#### [Contribution of central sensitization to stress-induced spreading hyperalgesia in rats with orofacial inflammation.](#)

Li J, Yang J, Wei S, Li Z, Collins AA, Zou M, Wei F, Cao D.

Mol Brain. 2020 Jul 28;13(1):106. doi: 10.1186/s13041-020-00645-x.

Temporomandibular disorder (TMD) is commonly comorbid with fibromyalgia syndrome (FMS). The incidence of these pain conditions is prevalent in women and prone to mental stress. Chronic pain symptoms in patients with FMS and myofascial TMD (mTMD) are severe and debilitating. In the present study, we developed a new animal model to mimic the comorbidity of TMD and FMS. In ovariectomized female rats, repeated forced swim (FS) stress induced mechanical allodynia and thermal hyperalgesia in the hindpaws of the  $17\beta$ -estradiol (E2) treated rats with orofacial inflammation. Subcutaneous injection of E2, injection of complete Freund's adjuvant (CFA) into masseter muscles or FS alone did not induce somatic hyperalgesia. We also found that the somatic hyperalgesia was accompanied by upregulation of GluN1 receptor and serotonin (5-hydroxytryptamine, 5-HT)<sub>3A</sub> receptor expression in the dorsal horn of spinal cord at L4-L5 segments. Intrathecal injection of N-methyl-D-aspartic acid receptor (NMDAR) antagonist 2-amino-5-phosphonovaleric acid (APV) or 5-HT<sub>3</sub>

receptor antagonist Y-25130 blocked stress-induced wide-spreading hyperalgesia. These results suggest that NMDAR-dependent central sensitization in the spinal dorsal horn and 5-HT-dependent descending facilitation contribute to the development of wide-spreading hyperalgesia in this comorbid pain model.

#### [Evidence of localized and widespread pressure pain hypersensitivity in patients with tension-type headache: A systematic review and meta-analysis.](#)

Fernandez-de-Las-Penas C, Plaza-Manzano G, Navarro-Santana MJ, Olesen J, Jensen RH, Bendtsen L.

Cephalalgia. 2020 Sep 22;33(10):20958384. doi: 10.1177/0333102420958384.

Objective: This meta-analysis evaluates pressure pain sensitivity values in symptomatic and distant pain-free areas comparing individuals with tension-type headache to controls. Databases and data treatment: Electronic databases were searched for cross-sectional or prospective case-control studies comparing pressure pain thresholds in patients with tension-type headache to headache-free controls. Data were extracted by three reviewers. The methodological quality was assessed by the Newcastle-Ottawa Quality Assessment Scale. Meta-analyses of trigeminal, extra-

trigeminal (neck) and distant pain-free areas in tension-type headache were compared to headache-free controls. Frequency of tension-type headache and gender were taken into account. Results: Twenty studies were included. Patients with tension-type headache exhibited lower pressure pain thresholds than headache-free controls: Trigeminal (MD -49.11 kPa, 95% CI -66.05 to -32.17), cervical spine (MD -88.17 kPa, 95% CI -108.43 to -67.92) and distant pain-free areas (MD -98.43 kPa, 95% CI -136.78 to -60.09). Differences were significant for chronic, episodic, and mixed episodic and chronic tension-type headache within the trigeminal and neck (symptomatic areas), but only significant for chronic tension-type headache (MD -102.86, 95% CI -139.47 to -66.25 kPa) for distant pain-free areas. In general, women had lower pressure pain thresholds than men. The methodological quality ranged from fair (45%) to good (40%). The results showed a high heterogeneity and publication bias. Conclusion: This first meta-analysis addressing pressure pain thresholds differences in symptomatic and distant pain-free areas between patients with tension-type headache and controls found low to moderate evidence supporting the presence of pressure pain hypersensitivity in the trigeminal and neck areas in tension-type headache in comparison with headache-free controls. Sensitivity to pressure pain was widespread only in chronic, not episodic, tension-type headache (moderate evidence).

#### [Association between chronic pain and alterations in the mesolimbic dopaminergic system.](#)

Yang S, Boudier-Reveret M, Choo YJ, Chang MC.

Brain Sci. 2020 Oct 2;10(10):E701. doi: 10.3390/brainsci10100701.

Chronic pain (pain lasting for >3 months) decreases patient quality of life and even occupational abilities. It can be controlled by treatment, but often persists even after management. To properly control pain, its underlying mechanisms must be determined. This review outlines the role of the mesolimbic dopaminergic system in chronic pain. The mesolimbic system, a neural circuit, delivers dopamine from the ventral tegmental area to neural structures such as the nucleus accumbens, prefrontal cortex, anterior cingulate cortex, and amygdala. It controls executive, affective, and motivational functions. Chronic pain patients suffer from low dopamine production and delivery in this system. The volumes of structures constituting the mesolimbic system are known to be decreased in such patients. Studies on administration of dopaminergic drugs to control chronic pain, with a focus on increasing low dopamine levels in the mesolimbic system, show that it is effective in patients with Parkinson's disease, restless legs syndrome, fibromyalgia, dry mouth syndrome, lumbar radicular pain, and chronic back pain. However, very few studies have confirmed these effects, and dopaminergic drugs are not commonly used to treat the various diseases causing chronic pain. Thus, further studies are required to determine the effectiveness of such treatment for chronic pain.

#### [Abnormal subgenual anterior cingulate circuitry is unique to women but not men with chronic pain.](#)

Osborne NR, Cheng JC, Rogachov A, Kim JA, Hemington KS, Bosma RL, Inman RD, Davis KD.

Pain. 2020 Aug 5. doi: 10.1097/j.pain.0000000000002016.

The subgenual anterior cingulate cortex (sgACC) plays an important role in pain modulation. We previously demonstrated sex differences in sgACC functional connectivity (FC) in healthy individuals. Given that many chronic pain conditions show sex differences in prevalence, here we tested the hypothesis that people with chronic pain exhibit a sex-specific pattern of abnormal sgACC FC. We acquired resting-state functional magnetic resonance imaging data from 156 (82 W: 74 M) healthy participants and 38 (19 W: 19 M) people with chronic low back pain resulting from ankylosing spondylitis, a condition that predominantly affects men. We confirmed that there are sex differences in sgACC FC in our large cohort of healthy adults; women

had greater sgACC FC with the precuneus, a key node of the default mode network, and men had greater sgACC FC with the posterior insula and the operculum. Next, we identified an interaction effect between sex and pain status (healthy/chronic pain) for sgACC FC. Within the chronic pain group, women had greater sgACC FC than men to the default mode and sensorimotor networks. Compared to healthy women, women with chronic pain also had greater sgACC FC to the precuneus and lower FC to the hippocampus and frontal regions. No differences in sgACC FC were seen in men with vs without chronic pain. Our findings indicate that abnormal sgACC circuitry is unique to women but not men with ankylosing spondylitis-related chronic pain. These sex differences may impact the benefit of therapeutics that target the sgACC for chronic pain.

#### [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. 2020 Oct 8. doi: 10.1097/j.pain.0000000000002104.

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 (RS)-fMRI data from 220 participants; 155 healthy controls and 65 individuals with chronic low back pain due to ankylosing spondylitis (AS), a form of arthritis. We found an extensive overlap in the graph partitions with the major brain intrinsic systems (i.e., 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 (i.e., Hubs disruption), some of which were associated with the severity of the chronic pain condition. Females exhibited atypically higher functional segregation in the mid- and subgenual cingulate cortex and lower connectivity in the network with the default mode and fronto-parietal modules; whereas males exhibited stronger connectivity with the sensorimotor module. Classification models on nodal graph metrics could classify an individuals' sex and whether they have chronic pain with high accuracies (77-92%). These findings highlight the organizational abnormalities of RS-brain networks in people with chronic pain and provide a framework to consider sex-specific pain therapeutics.

## EPIDEMIOLOGY STUDIES

#### [Chronic pain and high-impact chronic pain among US adults. Data from the National Health and Nutrition Examination Survey.](#)

Zelaya CE, Dahlhamer JM, Lucas JW, Connor EM.

NCHS Data Brief No. 390, November 2020.

Chronic pain and chronic pain that frequently limits life or work activities, referred to in this report as high-impact chronic pain, are among the most common reasons adults seek medical care and are associated with decreased quality of life, opioid dependence, and poor mental health. This report examines chronic pain and high-impact chronic pain in the past 3 months among U.S. adults aged 18 and over by selected demographic characteristics and urbanization level. In 2019, 20.4% of adults had chronic pain and 7.4% of adults had chronic pain that frequently limited life or work activities (referred to as high impact chronic pain) in the past 3 months. Chronic pain and high-impact chronic pain both increased with age and were highest among adults aged 65 and over. Non-Hispanic white adults (23.6%) were more likely to have chronic

pain compared with non-Hispanic black (19.3%), Hispanic (13.0%), and non-Hispanic Asian (6.8%) adults. The percentage of adults with chronic pain and high-impact chronic pain increased as place of residence became more rural.

[Female gender Is associated with a higher prevalence of chronic neck pain, chronic low back pain, and migraine: Results of the Spanish National Health Survey, 2017.](#)

Palacio-Cena D, Albaladejo-Vicente R, Hernandez-Barrera V, Lima-Florencio L, Fernandez-de-Las-Penas C, Jimenez-Garcia R, Lopez-de-Andres A, de Miguel-Diez J, Perez-Farinos N.

Pain Med. 2020 Nov 8;pnaa368. doi: 10.1093/pm/pnaa368.

Objectives: To assess the prevalence of chronic neck pain (CNP), chronic low back pain (CLBP), and migraine headache (MH) in the Spanish population and to identify sociodemographic and health-related variables associated with CNP, CLBP, and MH. Design: Observational study. Setting: Spain. Subjects: A total of 22,511 persons 18 years of age or older (10,304 males and 12,207 females) who participated in the 2017 Spanish National Health Survey. Methods: Stratified three-stage sampling was applied. CNP, CLBP, and MH were the dependent variables. The analysis was conducted separately by gender. Sociodemographic features, self-perceived health status, lifestyle habits, comorbidities, and pain features were analyzed by using logistic regression models. Results: Females reported a higher prevalence of CNP, CLBP, and MH ( $P < 0.001$ ) than males. For both sexes, anxiety and/or depression and poor self-rated health were associated with a significantly increased prevalence of CNP, CLBP, and MH. For CNP and CLBP, the identified associated factors were older age and limitations to usual activity. For CNP and MH, the most common associated factor was comorbid respiratory disease. Conclusions: Our study identified several factors associated with CNP, CLBP, and MH in Spanish female and male adults, with potential implications for health care providers.

[Developing an actionable patient taxonomy to understand and characterize high-cost Medicare patients.](#)

Zhang Y, Grinspan Z, Khullar D, Unruh MA, Shenkman E, Cohen A, Kaushal R. Healthc (Amst). 2020 Mar;8(1):100406. doi: 10.1016/j.hjdsi.2019.100406.

Background: Improving care for high-cost patients requires a better understanding of their characteristics and the ability to effectively target interventions. We developed an actionable taxonomy with clinically meaningful patient categories for high-cost Medicare patients—those in the top 10% of total costs. Methods: A cross-sectional study of a Medicare fee-for-service (FFS) patient cohort in the New York metropolitan area. We merged claims and neighborhood social determinants of health data to map patients into actionable categories. Results: Among 428,024 Medicare FFS patients, we mapped the 42,802 high-cost patients into ten overlapping categories, including: multiple chronic conditions, seriously ill, frail, serious mental illness, single condition with high pharmacy cost, chronic pain, end-stage renal disease (ESRD), single high-cost chronic condition, opioid use disorder, and socially vulnerable. Most high-cost patients had multiple chronic conditions (97.4%), followed by serious illness (53.7%) and frailty (48.9%). Patients with ESRD, who were seriously ill, and who were frail were more likely to be high-cost compared to patients in other categories. 72.7% of high-cost patients fell into multiple categories. Conclusions: High-cost patients are highly heterogeneous. A patient taxonomy incorporating medical, behavioral, and social characteristics may help providers better understand their characteristics and health needs. Implications: Mapping high-cost patients into clinically meaningful and actionable categories that incorporate medical, behavioral, and social factors could help health systems target interventions. Integrated approaches, including medical care, behavioral health, and social services may be needed to effectively and efficiently care for high-cost patients.

[Sex-modified effects of depression, low back pain, and comorbidities on pain after total knee arthroplasty for osteoarthritis.](#)

Perruccio AV, Fitzpatrick J, Power JD, Gandhi R, Rampersaud YR, Mahomed NN, Davey JR, Syed K, Veillette C, Badley EM.

Arthritis Care Res (Hoboken). 2020 Aug;72(8):1074-1080. doi: 10.1002/acr.24002.

Objective: The influence of sex on post-total knee arthroplasty (TKA) outcomes has been variable in the literature. Though sex is often reported as an averaged effect, we undertook this study to investigate whether sex modified the influence of presurgery characteristics on post-TKA knee pain. Methods: This was a prospective study with data derived from 477 TKA osteoarthritis patients (279 women, 198 men). Questionnaires were completed presurgery and at 3 months postsurgery. The association between 3-month post-TKA knee pain and presurgery covariates (body mass index, comorbidity count, symptomatic joint count, low back pain, knee pain, and depressive symptoms) was assessed by linear regression. Sex-specific effects were evaluated using interactions. Results: Women had significantly worse presurgery knee pain, joint count, and depressive symptoms, and worse postsurgery knee pain, than men. With simple covariate adjustment, no sex effect on pain was found. However, sex was found to moderate the effects of comorbidities (worse for women [P = 0.013]), presence of low back pain (worse for men [P = 0.003]), and depressive symptoms (worse for men [P < 0.001]) on postsurgery pain. Worse presurgery pain was associated with worse postsurgery pain similarly for women and men. Conclusion: The influence of some patient factors on early post-TKA pain cannot be assumed to be the same for women and men; average effects may mask underlying associations. Results suggest a need to consider sex differences in understanding TKA outcomes, which may have important implications for prognostic tool development in TKA.

[Increased risk of migraine in patients with temporomandibular disorder: A longitudinal follow-up study using a national health screening cohort.](#)

Byun S, Min C, Yoo D, Yang B, Choi H.

Diagnostics (Basel). 2020 Sep 20;10(9):724. doi: 10.3390/diagnostics10090724.

Background: The aim of this study was to investigate the association between temporomandibular disorder (TMD) and migraine through a longitudinal follow-up study using population data from a national health screening cohort. Methods: This cohort study used data from the Korean National Health Insurance Service-Health Screening Cohort from 2002 to 2015. Of the 514,866 participants, 3884 TMD patients were matched at a 1:4 ratio with 15,536 control participants. Crude models and models adjusted for obesity, smoking, alcohol consumption, systolic blood pressure, diastolic blood pressure, fasting blood glucose, total cholesterol, and Charlson Comorbidity Index (CCI) scores were calculated. Chi-squared test, Kaplan-Meier analysis, and two-tailed log-rank test were used for statistical analysis. Stratified Cox proportional hazard models were used to assess hazard ratios (HR) and 95% confidence intervals (CIs) for migraine in both control groups. Results: The adjusted HR for migraine was 2.10 (95% CI: 1.81-2.44) in the TMD group compared to the control group, which was consistent in subgroup analyses according to age, sex, and Kaplan-Meier analysis. Conclusions: This study demonstrated that TMD patients have a higher risk of migraine. These results suggest that dentists can decrease the risk of migraine in TMD patients by managing TMD properly.

[Central sensitization in migraine is related to restless legs syndrome.](#)

Suzuki K, Suzuki S, Haruyama Y, Okamura M, Shiina T, Fujita H, Kobashi G, Sairenchi T, Uchiyama K, Hirata K.

J Neurol. 2020 Nov 4. doi: 10.1007/s00415-020-10295-7.

Objective: We hypothesized that, in migraine patients, central sensitization (CS) could be associated with comorbid restless legs syndrome (RLS). Methods: We conducted a

case-control study including 186 migraine patients and 186 age- and sex-matched healthy controls. Symptoms related to CS syndrome were assessed by the Central Sensitization Inventory (CSI). Individuals with CSI Part A (CSI-A) scores  $\geq 40$  were defined as having CS. For patients with migraine, the Brief Pain Inventory (BPI) and Patient Health Questionnaire (PHQ)-9 were administered. In the patient group, RLS and migraine were diagnosed through face-to-face interviews. Results: Among migraine patients, 26 (14.0%) suffered from chronic migraine. The mean disease duration was  $23.7 \pm 11.8$  years. Migraine patients showed a higher rate of CS (21.0% vs. 8.6%) than healthy controls, with an adjusted odds ratio (AOR) of 3.039 (95% confidence interval (CI) 1.560-5.992;  $p = 0.001$ ). Migraine patients in the CS group had higher rates of smoking, chronic migraine and RLS and higher BPI and PHQ-9 scores than migraine patients in the non-CS group. The use of acute and preventive treatment for migraine did not significantly differ between the CS and non-CS groups. Multivariable analysis identified the presence of RLS (AOR, 28.471; 95% CI 6.438-125.918;  $p < 0.001$ ) and the BPI pain interference score (AOR, 1.398; 95% CI 1.061-1.843;  $p = 0.017$ ) as the significant determinants of CS among migraine patients. Conclusion: Migraine patients were 3 times more likely to have CS than healthy controls. Our study results showed an association between RLS and CS in migraine patients.

### [Endometriosis and migraine headache risk: A meta-analysis.](#)

Jenabi E, Khazaei S.

Women Health. 2020 Sep;60(8):939-945. doi: 10.1080/03630242.2020.1779905.

There is high prevalence of both migraine and endometriosis; however, the association between both is controversial. This systematic review evaluated the association between endometriosis and the risk of migraine headache. A search was done of the following international electronic bibliographic databases including: PubMed, Web of Science, and Scopus to May 2020. Heterogeneity among studies was determined by Q-test and  $I^2$  statistic. Publication bias was assessed by Begg's and Egger's tests. The results were reported using the odds ratio (OR) estimate with its 95% confidence interval (CI) using a random-effects model. The search identified 802 articles with 287,174 participants. There was a significant association between endometriosis and the risk of migraine headache (OR = 1.56; 95% CI: 1.21, 1.90). Based on the Newcastle Ottawa Statement Manual (NOS) scale, all studies had high quality. The findings showed that endometriosis was significantly associated with an increased risk of migraine headache. Future research should be focused on measures that could help to reduce the risk of migraine headache among women with endometriosis.

### [Impact of pain and non-pain co-morbidities on opioid use in women with endometriosis.](#)

Lamvu G, Soliman AM, Johns B, Vora JB, Estes SJ.

J Comp Eff Res. 2020 Nov 3. doi: 10.2217/ce-2020-0181.

Aim: To evaluate impact of co-morbidities on opioid use in endometriosis. Patients & Methods: This was a retrospective analysis of data obtained from the Symphony Health database (July 2015-June 2018), which contains medical and pharmacy claims information on 79,947 women with endometriosis. Relative risk (RR) of postdiagnosis opioid use and supply duration associated with baseline co-morbidities were determined. Results: Women with endometriosis using opioids at baseline were 61% more likely to receive opioids postdiagnosis (RR: 1.61; 95% CI: 1.59-1.63). Risk of prolonged opioid supply postdiagnosis was highest for those with prolonged supply at baseline (RR: 21.14; 20.14-22.19), and was 1.32 (1.26-1.38) for patients with  $\geq 1$  co-morbidity, 1.37 (1.31-1.43) for pain co-morbidities and 1.07 (1.04-1.11) for psychiatric co-morbidities. Conclusion: Risk of opioid use after endometriosis diagnosis was greater in patients who used opioids before diagnosis. Risk of prolonged opioid use

was greater if co-morbidities existed before diagnosis.

[Prevalence of autoimmune disorders among bladder pain syndrome patients' relatives.](#)

Kujala MM, Tammela TL, Poyhonen A, Forsell T, Pasanen S, Paananen I, Horte A, Leppilahti M, Sairanen J.

Scand J Urol. 2020 Sep 23;1-6. doi: 10.1080/21681805.2020.1821766.

Purpose: Possible genetic background and autoimmune etiology of Bladder Pain Syndrome (BPS, formerly Interstitial Cystitis, IC) has been suggested. We studied whether familial clustering of BPS, other autoimmune diseases or fibromyalgia exist among BPS patients' genetically close relatives; possibly reflecting some common predisposing genetic background of these diseases. Materials and methods: Altogether 420 first- or second-degree relatives of 94 BPS patients fulfilling the NIDDK criteria were asked to fill in a survey on the self-reported diagnosis of urinary tract diseases, fibromyalgia and 23 autoimmune diseases, together with filling the O'Leary-Sant symptom score. The ones with high symptom scores were interviewed and, if necessary, referred to a further clinical consultation. The prevalence of other diseases was compared to previously published prevalence percentages. Results: 334 (80%) of 420 family members returned the questionnaire. Only one of the relatives fulfilled the NIDDK criteria, and one sibling pair among the original BPS patients was found. Asthma, ulcerative colitis, fibromyalgia, iritis and rheumatoid arthritis were more common in the study population than in the reference populations. The reported prevalence of atopic dermatitis and rhinoconjunctivitis causing allergies were lower. In addition, the results show that the O'Leary-Sant symptom score is not reliable in screening for new BPS cases. Conclusions: Our study suggests that in BPS patients' families, fibromyalgia and autoimmune diseases including asthma, and especially the non-allergic form of asthma, may be over-represented.

[Endometriosis and irritable bowel syndrome: A systematic review and meta-analysis.](#)

Chiapparino F, Cipriani S, Ricci E, Mauri PA, Esposito G, Barretta M, Vercellini P, Parazzini F.

Arch Gynecol Obstet. 2020 Sep 19. doi: 10.1007/s00404-020-05797-8.

Purpose: Irritable bowel disease and endometriosis are two common diseases characterized by chronic inflammation state and recurrent abdominal pain. As a consequence of sharing of symptoms and chronic inflammation, endometriosis and IBS may coexist and be misdiagnosed and this leads to delays in diagnosis, mismanagement, and unnecessary testing. In recent years, some studies have found higher risk of IBS in women with endometriosis, compared to women without endometriosis. To provide a general overview, we performed a systematic review and a meta-analysis on published data on this issue. Methods: By a systematic literature search selection process, 11 studies were identified for the current study: 2 prospective and 2 retrospective cohort studies, 4 case-control studies, 1 cross-sectional study and 2 clinical series. Results: When we meta-analysed data about the prevalence of IBS in women with endometriosis, the overall OR (95%CI), compared to women without endometriosis was 3.26 (1.97-5.39) with no statistically significant heterogeneity. All three studies considering the incidence of IBS in women with a previous diagnosis of endometriosis showed about twofold greater risk among women with endometriosis than women without. Likewise, in the random effects model of the meta-analysis, the overall OR of history of IBS in women with endometriosis was 3.10 (95% CI 2.06-4.67), with no heterogeneity between three studies considered. Conclusion: This meta-analysis provides epidemiological evidence of a link between endometriosis and IBS, highlighting two or more times higher risk of IBS in women with endometriosis compared to women without the condition.

[Migraine: Results of the American Migraine Prevalence and Prevention \(AMPP\) Study.](#)

Background: Migraine is typically divided into 2 headache frequency denominated categories, episodic migraine (EM) and chronic migraine (CM). Characterizing more narrow headache day frequency groups may be of value for better understanding the broad range of migraine experience and making treatment decisions. Objective: To characterize the impact and burden of migraine in 4 monthly headache day (MHD) categories. Methods: Respondents to the American Migraine Prevalence and Prevention Study 2005 survey who met criteria for migraine were categorized into low frequency episodic migraine (LFEM) 0-3, moderate frequency episodic migraine (MFEM) 4-7, high frequency episodic migraine (HFEM) 8-14, and CM with  $\geq 15$  headache days per month. Data including sociodemographics, headache features and symptomology, comorbidities, cutaneous allodynia, and severe migraine-related disability were compared among groups. We combined the low- and medium-frequency EM groups (L/MFEM) and compared them with the HFEM group in 1 set of models and compared the HFEM and CM groups in a second set of models. Binary logistic regression, linear regression, and ordered logistic regression were used depending upon the variable type and adjusted for sociodemographics. Results: Among 11,603 eligible respondents with migraine, 67.7% (7860/11,603) were categorized with LFEM, 17.7% (2051/11,603) with MFEM, 7.8% (898/11,603) with HFEM, and 6.8% (794/11,603) with CM. The mean age was 46 (SD 13.7), 80.2% (9301/11,603) were female, and 90.0% (10,187/11,323) were White, 6.9% were Black (784/11,323), and 3.1% (352/11,323) were identified as Other race(s). Individuals with HFEM differed from L/MFEM on a wide range of sociodemographic variables in the categories of headache features, disability, and comorbidities while few differences were found when modeling HFEM vs CM. In comparison with L/MFEM and HFEM, the HFEM group was more likely to have severe disability ( $P < .001$  OR = 1.74 [1.42, 2.15]), chronic pain ( $P \leq .007$  OR = 1.35 [1.09, 1.69]), arthritis ( $P = .001$  OR = 1.44 [1.15, 1.80]), high cholesterol ( $P = .005$ , OR = 1.37 [1.10, 1.70]), ulcers ( $P = .016$ , OR = 1.44 [1.07, 1.93]), and depression (Patient Health Questionnaire [PHQ-9]) ( $P < .001$  OR = 1.50 [1.22, 1.84]). Conclusion: While rates of migraine symptoms, headache impact and disability, and comorbidities generally increased with increases in MHD frequency, respondents with HFEM and CM were remarkably similar on a broad range of variables including sociodemographics, disability/impact, and comorbidities. There were many more significant differences between the HFEM and L/MFEM groups on the same variables. Future work should use empirical strategies to identify naturally occurring groups and possibly reconsider the boundary between CM and HFEM.

#### [Prevalence of temporomandibular disorder in adult patients with chronic pain.](#)

Stalnacke C, Ganzer N, Liv P, Wanman A, Lovgren A.  
Scand J Pain. 2020 Sep 24.

Objectives Chronic pain patients often suffer in multiple locations. In health care, examinations of bodily pain usually do not include questions about temporomandibular disorders (TMD); hence TMD symptoms and potential comorbidities are not regularly assessed. Therefore, the primary aim was to evaluate the prevalence of TMD in patients referred to a pain rehabilitation clinic, and the secondary aim was to evaluate possible factors associated with TMD symptoms. Methods Consecutive chronic pain patients referred to the Pain Rehabilitation Clinic at the Umeå University Hospital in Sweden were included. TMD symptoms were assessed using three valid screening questions - 3Q/TMD. Pain sites, emotional distress, kinesiophobia, and demographics were obtained from the Swedish Quality Registry for Pain Rehabilitation. Results In total, 188 (144 women) chronic pain patients (mean age 41.8 years) were included. Of these, 123 (96 women) answered affirmatively to at least one of the 3Q/TMD. The relative risk of TMD symptoms among the patients with chronic pain, in comparison to the general population, was 7.1 (95% CI 5.9-8.4). Age was the only independent

variable associated with TMD among the patients ( $p = 0.018$ ). Conclusions The prevalence of TMD symptoms was higher in a chronic pain population compared to the general population. The 3Q/TMD questionnaire could be a suitable screening tool at pain rehabilitation clinics to identify patients for further examination of involvement of pain in the trigeminal region. Our results reinforce the clinical importance of paying attention to concurrent widespread pain and local TMD symptoms.

### [Temporomandibular disorder, body pain and systemic diseases: Assessing their associations in adolescents.](#)

do Vale Braido GV, Campi LB, Jordani PC, Fernandes G, de Godoi Goncalves A. J Appl Oral Sci. 2020 Sep 7;28:e20190608. doi: 10.1590/1678-7757-2019-0608.

Painful temporomandibular disorders (TMD) in children and adolescents may impact negatively the individual's life. The presence of comorbidities associated with TMD tends to increase the persistence of pain and to facilitate its chronification. Objective: To investigate the presence of other painful conditions and systemic diseases and their association with painful TMD. Methodology: In this cross-sectional study, 690 adolescents aged between 12-14 years old were evaluated through questionnaires and clinical examinations. Results: Painful TMD was found in 16.2% of the sample, with a significant association with bronchitis (OR= 2.5;  $p=0.003$ ) and asthma (OR=3.1;  $p=0.013$ ), reported by the parents/legal guardians of the participants. Adolescents with regional and widespread pain were 2.7 (95% CI: 1.65-4.55) and 3.6 (95% CI: 1.29-10.14) more likely to also present painful TMD. Painful TMD was associated with a higher number of body pain sites in the last 12 months (4.26 vs. 2.90;  $p<0.001$ ), as well as a higher number of systemic diseases (1.48 vs. 1.18;  $p=0.048$ ), when compared to adolescents without painful TMD. Conclusion: The findings of this study point out the importance of considering the presence of comorbid conditions in the diagnosis and management of painful TMD in adolescents. A multidisciplinary approach would contribute to better control of painful TMD and decrease its chronification risk.

### [The association between burning mouth syndrome and urologic chronic pelvic pain syndrome: A case-control study.](#)

Crocetto F, Coppola N, Barone B, Leuci S, Imbimbo C, Mignogna MD. J Oral Pathol Med. 2020 Aug 14. doi: 10.1111/jop.13097.

Background: The overlap between some painful conditions is widespread. The aim of this study was to evaluate the overlap between burning mouth syndrome (BMS) and urological chronic pelvic pain syndrome (UCPPS) in an outpatient clinic of a university hospital. Methods: A controlled clinical study was performed. BMS patients and healthy controls were enrolled in the study. Patients were screened through laboratory test and a complete urological examination. Two validated questionnaires were submitted to all the patients: National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) and International Prostatic Symptom Score (IPSS). Results: A total of 50 BMS patients and 50 healthy controls were enrolled in the study. Statistically significant differences between the two groups regarding the items of the IPSS questionnaire of Incomplete Emptying ( $U = 750, P < .001$ ), Intermittency ( $U = 768.5, P < .001$ ), QoL ( $U = 848, P < .002$ ), and Total Symptom score ( $U = 1040, P = .05$ ) were found. Moreover, the responses of NIH-CPSI showed statistically significant differences regarding Pain subscale ( $U = 714, P < .001$ ), QoL Impact subscale ( $U = 1016.500, P = .05$ ), and NIH-CPSI total score ( $U = 953.500, P = .002$ ). Conclusion: To the best of our knowledge, the reported data demonstrate for the first time an association between BMS and UCPPS. Further studies with a larger sample are needed to confirm the co-occurrence of urological symptoms in patients with burning mouth syndrome.

### [Functional gastrointestinal disorders are increased in joint hypermobility-related disorders with concomitant postural orthostatic tachycardia syndrome.](#)

Tai FWD, Palsson OS, Lam CY, Whitehead WE, Sperber AD, Tornblom H, Simren M, Aziz I.

Neurogastroenterol Motil. 2020 Aug 16;e13975. doi: 10.1111/nmo.13975.

**Background:** Individuals with hypermobility spectrum disorders/hypermobility Ehlers-Danlos syndrome (HSD/hEDS) frequently fulfill criteria for Rome IV functional gastrointestinal disorders (FGIDs). Postural orthostatic tachycardia syndrome (POTS) is also commonly reported in HSD/hEDS and may impact on co-morbidity with and severity of FGIDs, although this remains to be studied. We determined the impact of concomitant POTS and HSD/hEDS on their association with Rome IV FGIDs. **Methods:** With the help of the charity organization Ehlers-Danlos Support UK, an online cross-sectional health survey was completed by individuals with HSD/hEDS. The survey enquired for (a) self-reported doctor diagnosis of POTS, chronic fatigue syndrome, and fibromyalgia, (b) the presence and symptom frequency of Rome IV FGIDs, and (c) anxiety and depression scores. **Key results:** Of 616 subjects with HSD/hEDS, 37.5% reported a doctor diagnosis of POTS. POTS-positive individuals were significantly younger than POTS-negative subjects (37 vs 40 years,  $P = 0.002$ ), more likely to report chronic fatigue syndrome (44% vs 31%,  $P < 0.0001$ ), and showed a trend toward increased prevalence of fibromyalgia (44% vs 37%,  $P = 0.06$ ) and higher depression score ( $P = 0.07$ ). POTS-positive subjects were also more likely to fulfill criteria for Rome IV FGIDs across various organ domains and experienced both upper and lower gastrointestinal symptoms significantly more frequently. The increased associations for FGIDs and GI symptom frequency remained unchanged in HSD/hEDS subjects with POTS following adjustments for age, chronic fatigue syndrome, fibromyalgia, and depression scores. **Conclusions and inferences:** The high FGID burden in HSD/hEDS is further amplified in the presence of POTS. Future studies should elucidate the mechanism by which POTS arises in HSD/hEDS and is associated with increased GI symptoms.

## CLINICAL STUDIES

### [Lasmiditan in patients with common migraine comorbidities: A post hoc efficacy and safety analysis of two phase 3 randomized clinical trials.](#)

Clemow DB, Baygani SK, Hauck PM, Hultman CB.

Curr Med Res Opin. 2020 Oct 6;1-16. doi: 10.1080/03007995.2020.1808780.

**Objective:** Determine whether common migraine comorbidities affect the efficacy and safety of lasmiditan, a 5-HT<sub>1F</sub> receptor agonist approved in the United States for the acute treatment of migraine. **Methods:** In SPARTAN and SAMURAI (double-blind Phase 3 clinical trials), patients with migraine were randomized to oral lasmiditan 50 mg (SPARTAN only), 100mg, 200 mg, or placebo. Lasmiditan increased the proportion of pain-free and most bothersome symptom (MBS)-free patients at 2 h after dose compared with placebo. Most common treatment-emergent adverse events (TEAEs) were dizziness, paraesthesia, somnolence, fatigue, nausea, muscular weakness, and hypoesthesia. Based upon literature review of common migraine comorbidities, Anxiety, Allergy, Bronchial, Cardiac, Depression, Fatigue, Gastrointestinal, Hormonal, Musculoskeletal/Pain, Neurological, Obesity, Sleep, and Vascular Comorbidity Groups were created. Using pooled results, efficacy and TEAEs were assessed to compare patients with or without a given common migraine comorbidity. To compare treatment groups,  $p$ -values were calculated for treatment-by-subgroup interaction, based on logistic regression with treatment-by-comorbidity condition status (Yes/No) as the interaction term; study, treatment group, and comorbidity condition status (Yes/No) were covariates. Differential treatment effect based upon comorbidity status was also examined. Trial registration at clinicaltrials.gov: SAMURAI ([NCT02439320](#)) and SPARTAN ([NCT02605174](#)). **Results:**

Across all the Comorbidity Groups, with the potential exception of fatigue, treatment-by-subgroup interaction analyses did not provide evidence of a lasmiditan-driven lasmiditan versus placebo differential treatment effect dependent on Yes versus No comorbidity subgroup for either efficacy or TEAE assessments. Conclusions: The efficacy and safety of lasmiditan for treatment of individual migraine attacks appear to be independent of comorbid conditions.

[Pressure point thresholds and ME/CFS comorbidity as indicators of patient's response to manual physiotherapy in fibromyalgia.](#)

Falaguera-Vera FJ, Garcia-Escudero M, Bonastre-Ferez J, Zacaes M, Oltra E. Int J Environ Res Public Health. 2020 Oct 31;17(21):E8044. doi: 10.3390/ijerph17218044.

Current pharmacological treatments of Fibromyalgia (FM) are merely symptom palliative, as clinical trials have so far failed to provide overall benefits without associated harms. Polypharmacy often leads to patient's health deterioration and chronic drug use to an eventual lack of patient's response. Emerging evidence supports that physiotherapy treatments based on mechanical triggers improve FM symptoms and therefore could be used for therapeutic purposes by themselves or in combination with current pharmacological treatments, as part of integrative medicine programs. However, a paucity of studies rigorously and systematically evaluating this possibility exists. This study uses scores from validated standardized questionnaires, algometer pressure point threshold (PPT) readings and responses from a custom self-developed questionnaire to determine the impact of a pressure-controlled custom manual protocol on FM hyperalgesia/allodynia, fatigue and patient's quality of life. The results show that patient's baseline sensitivity to pain inversely correlates with treatment response in FM. Moreover, post-stratification analysis unexpectedly reveals that patients presenting comorbid ME/CFS do not seem to respond to the applied therapy as those presenting FM only. Therefore, pre-treatment PPTs and ME/CFS comorbidity may serve as indicators to predict patient's response to physiotherapy programs based on mechanical triggers. Further exploration of these findings is granted. In addition, the study of gene expression profiles in the blood collection generated by this study should help unveil the molecular mechanisms behind patient's differential response to manual therapy.

[Common factors in the presentation and management of chronic temporomandibular disorders and chronic overlapping pain disorders.](#)

McCloy K, Peck C. Oral Pathol Med. 2020 Jul;49(6):454-460. doi: 10.1111/jop.13079.

The International Association for the Study of Pain has released a new classification scheme for chronic pain. This classification scheme describes chronic pain as either a symptom of a disease (chronic secondary pain) or the disease itself (chronic primary pain). Chronic temporomandibular disorders have many similarities to other proposed chronic overlapping pain disorders, but are classified and managed by dental practitioners as a localized pain condition of the orofacial region. We review the literature to describe the similarities between chronic temporomandibular disorders and chronic overlapping pain disorders, and discuss how this evolving concept may affect the way that dentists approach the diagnosis and management of chronic temporomandibular disorders.

[When to consider "mixed pain"? The right questions can make a difference!](#)

Freyenhagen R, Rey R, Argoff C. Curr Med Res Opin. 2020 Oct 21;1-10. doi: 10.1080/03007995.2020.1832058.

The term "mixed pain" is increasingly applied for specific clinical scenarios, such as low back pain, cancer pain and postsurgical pain, in which there "is a complex overlap

of the different known pain types (nociceptive, neuropathic, nociplastic) in any combination, acting simultaneously and/or concurrently to cause pain in the same body area." Whether mixed pain is the manifestation of neuropathic and nociceptive mechanisms operating simultaneously or concurrently, or the result of an entirely independent pathophysiological mechanism - distinct from nociceptive, nociplastic and neuropathic pain - is currently unknown. At present, the diagnosis of mixed pain is made based on clinical judgement following detailed history-taking and thorough physical examination, rather than by formal confirmation following explicit screening or diagnostic criteria; this lack of formalized screening or diagnostic tools for mixed pain is problematic for physicians in primary care, who encounter patients with probable mixed pain states in their daily practice. This article outlines a methodical approach to clinical evaluation of patients presenting with acute, subacute or chronic pain, and to possibly identifying those who have mixed pain. The authors propose the use of nine simple key questions, which will provide the practicing clinician a framework for identifying the predominant pain mechanisms operating within the patient. A methodical, fairly rapid, and comprehensive assessment of a patient in chronic pain - particularly one suffering from pain with both nociceptive and neuropathic components - allows validation of their experience of chronic pain as a specific disease and, importantly, allows the institution of targeted treatment.

### [Orofacial motor functions and temporomandibular disorders in patients with Sjögren's Syndrome.](#)

Zanin MC, Garcia DM, Rocha EM, de Felicio CM.

Arthritis Care Res (Hoboken). 2020 Aug;72(8):1057-1065. doi: 10.1002/acr.24001.

Objective: Sjögren's syndrome (SS) induces difficulty in chewing and swallowing due to low salivary flow. However, these symptoms may be associated with other factors, such as orofacial myofunctional disorders and temporomandibular disorder (TMD), which have not been comprehensively assessed in this population. The aims of this study were to investigate orofacial muscles and functions as well as the presence of TMD in patients with SS compared with a group without SS and to analyze whether the patients' experience of limitations in orofacial functioning is associated with the orofacial functional status and muscle pain related to TMD. Methods: Women with SS based on the 2002 American-European Consensus Group criteria and volunteers paired by age and sex were compared. The examinations included the orofacial myofunctional evaluation with scores (OMES) protocol, tongue and lip strength measures, and electromyography of the masticatory muscles. TMD investigations included clinical examination, self-report of symptoms, and assessment according to the Jaw Functional Limitation Scale. Results: Patients with SS present with impaired muscle and orofacial functions based on lower scores of all categories of OMES ( $P < 0.0001$ ), tongue strength ( $P = 0.0003-0.0004$ ), and masticatory muscle activity ( $P = 0.0002-0.007$ ), as well as worse TMD signs and symptoms ( $P < 0.05$ ) and jaw functional limitation ( $P < 0.0001-0.0003$ ). Conclusion: Patients' experiences with limitation in mastication and swallowing were associated with orofacial myofunctional status and muscle pain related to TMD. Those disorders should be monitored along with disease control and must be addressed in the clinical evaluation to prevent nutritional and metabolic comorbidities in patients with SS.

### [Smartphone based behavioral therapy for pain in multiple sclerosis \(MS\) patients: A feasibility acceptability randomized controlled study for the treatment of comorbid migraine and MS pain.](#)

Minen MT, Schaubhut KB, Morio K.

Mult Scler Relat Disord. 2020 Sep 8;46:102489. doi: 10.1016/j.msard.2020.102489.

Background: Multiple Sclerosis (MS) and Migraine are comorbid neurologic conditions. Migraine prevalence is three times higher in the MS clinic population compared to the general population, and patients with MS and migraine are more symptomatic than

patients with MS without migraine. Objective: We sought to conduct a pilot feasibility and acceptability study of the RELAXaHEAD app in MS-Migraine patients and to assess whether there was any change in migraine disability and MS pain-related disability. Methods: Randomized controlled study of patients with MS-migraine ages 18-80 years with 4+ headache days/ month who were willing to engage in smartphone based behavioral therapy. Half received the RELAXaHEAD app with progressive muscle relaxation (PMR) and the other half received the app without the PMR. Data was collected for 90 days on measures of recruitment, retention, engagement, and adherence to RELAXaHEAD. Preliminary data was also collected on migraine disability (MIDAS) and MS pain (PES). Results: Sixty-two subjects with MS-migraine were enrolled in the study (34 in PMR arm, 28 in monitored usual care arm). On average, during the 90 days, participants played the PMR on average 1.8 times per week, and for 12.9 min on days it was played. Forty-one percent (14/34) of the participants played the PMR two or more times weekly on average. Data was entered into the daily diaries, on average, 49% (44/90) of the days. There were major challenges in reaching subjects in follow-up for the efficacy data, and there was no significant change in migraine disability (MIDAS) scores or MS Pain (PES) scores from baseline to the endpoints. During the six-month follow-up, most patients felt either positively or neutral about the relaxation therapy. Conclusion: There was interest in scalable accessible forms of behavioral therapy to treat migraine and MS-related pain in patients with MS and comorbid migraine. Similar to prior studies, a significant minority were willing to practice the PMR at least twice weekly. In the societal shift from telephone to more text and internet-based interactions, follow up was challenging, but those reached indicated that they appreciated the PMR and would recommend it to others. Future work should focus on engagement and efficacy.

## About the Chronic Pain Research Alliance

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

The CPRA envisions and is working towards a future where individuals with COPCs will receive a timely diagnosis, followed by comprehensive medical care, which includes the use of safe and effective approved treatments, informed by the latest and most rigorous scientific evidence.

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

