



CUTTING EDGE

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This e-newsletter - published by the CPRA to keep the medical-scientific and patient communities abreast of research advances on Chronic Overlapping Pain Conditions (COPCs) - contains abstracts of studies on the epidemiology, pathophysiology and clinical management of COPCs published between November 2020 and April 2021.

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National Multi-Site Studies

[Phenotypic profile clustering pragmatically identifies diagnostically and mechanistically informative subgroups of chronic pain patients.](#)

Gaynor SM, Bortsov A, Bair E, Fillingim RB, Greenspan JD, Ohrbach R, Diatchenko L, Nackley A, Tchivileva IE, Whitehead W, Alonso AA, Buchheit TE, Boortz-Marx RL, Liedtke W, Park JJ, Maixner W, Smith SB.

Pain. 2020 Nov 30. doi: 10.1097/j.pain.0000000000002153.

Traditional classification and prognostic approaches for chronic pain conditions focus primarily on anatomically based clinical characteristics not based on underlying biopsychosocial factors contributing to perception of clinical pain and future pain trajectories. Using a supervised clustering approach in a cohort of temporomandibular disorder (TMD) cases and controls from the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study, we recently developed and validated a rapid algorithm (ROPA) to pragmatically classify chronic pain patients into three groups that differed in clinical pain report, biopsychosocial profiles, functional limitations, and comorbid conditions. The present aim was to examine the generalizability of this clustering procedure in two additional cohorts: a cohort of patients with chronic overlapping pain conditions (Complex Persistent Pain Conditions (CPPC) study), and a real-world clinical population of patients seeking treatment at Duke Innovative Pain Therapies (DIPT). In each cohort, we applied ROPA for cluster prediction, which requires only four input variables: pressure pain threshold (PPT) and anxiety, depression, and somatization scales. In both CPPC and DIPT, we distinguished three clusters, including one with more severe clinical characteristics and psychological distress. We observed strong concordance with observed cluster solutions, indicating the ROPA method allows for reliable subtyping of

clinical populations with minimal patient burden. The ROPA clustering algorithm represents a rapid and valid stratification tool independent of anatomic diagnosis. ROPA holds promise in classifying patients based on pathophysiological mechanisms rather than structural or anatomical diagnoses. As such, this method of classifying patients will facilitate personalized pain medicine for patients with chronic pain.

[Comparison of deep phenotyping features of UCPPS with and without Hunner lesion: A MAPP-II Research Network Study.](#)

Lai HH, Newcomb C, Harte S, Appleby D, Ackerman AL, Anger JT, Nickel JC, Gupta LV, Landis JR, Clemens JQ, MAPP Research Network
Neurourol Urodyn 2021 Mar;40(3):810-818. doi: 10.1002/nau.24623.

Objective: To use the phenotyping data from the MAPP-II Symptom Patterns Study (SPS) to compare the systemic features between urologic chronic pelvic pain syndrome (UCPPS) with Hunner lesion (HL) versus those without HL. **Methods:** We performed chart review on 385 women and 193 men with UCPPS who enrolled in the MAPP-II SPS. 223 had cystoscopy and documentation of HL status. Among them, 12.5% had HL and 87.5% did not. **Results:** UCPPS participants with HL were older, had increased nocturia, higher Interstitial Cystitis Symptom and Problem Indexes, and were more likely to report "painful urgency" compared with those without HL. On the other hand, UCPPS without HL reported more intense nonurologic pain, greater distribution of pain outside the pelvis, greater numbers of comorbid chronic overlapping pain conditions, higher fibromyalgia-like symptoms, and greater pain centralization, and were more likely to have migraine headache than those with HL. UCPPS without HL also had higher anxiety, perceived stress, and pain catastrophizing than those with HL. There were no differences in sex distribution, UCPPS symptom duration, intensity of urologic pain, distribution of genital pain, pelvic floor tenderness on pelvic examination, quality of life, depression, pain characteristics (nociceptive pain vs. neuropathic pain), mechanical hypersensitivity in the suprapubic area during quantitative sensory testing, and 3-year longitudinal pain outcome and urinary outcome between the two groups. **Conclusions:** UCPPS with HL displayed more bladder-centric symptom profiles, while UCPPS without HL displayed symptoms suggesting a more systemic pain syndrome. The MAPP-II SPS phenotyping data showed that Hunner lesion is a distinct phenotype from non-Hunner lesion.

Pathophysiology Studies

[Persistent brainstem dysfunction in Long-COVID: A hypothesis.](#)

Yong SJ.

ACS Chem Neurosci. 2021 Feb 4. doi: 10.1021/acschemneuro.0c00793

Long-COVID is a postviral illness that can affect survivors of COVID-19, regardless of initial disease severity or age. Symptoms of long-COVID include fatigue, dyspnea, gastrointestinal and cardiac problems, cognitive impairments, myalgia, and others. While the possible causes of long-COVID include long-term tissue damage, viral persistence, and chronic inflammation, the review proposes, perhaps for the first time, that persistent brainstem dysfunction may also be involved. This hypothesis can be split into two parts. The first is the brainstem tropism and damage in COVID-19. As the brainstem has a relatively high expression of ACE2 receptor compared with other brain regions, SARS-CoV-2 may exhibit tropism therein. Evidence also exists that neuropilin-1, a co-receptor of SARS-CoV-2, may be expressed in the brainstem. Indeed, autopsy studies have found SARS-CoV-2 RNA and proteins in the brainstem. The brainstem is also highly prone to damage from pathological immune or vascular activation, which has also been observed in autopsy of COVID-19 cases. The second part concerns functions of the brainstem that overlap with symptoms of long-COVID. The brainstem contains numerous distinct nuclei and subparts that regulate the respiratory, cardiovascular, gastrointestinal, and neurological processes, which can be linked to long-COVID. As neurons do not readily regenerate, brainstem dysfunction may be long-lasting and, thus, is long-COVID. Indeed, brainstem dysfunction has been implicated in other similar disorders, such as chronic pain and migraine and myalgic encephalomyelitis or chronic fatigue syndrome.

[Diseases, disorders, and comorbidities of interoception.](#)

Bonaz B, Land RD, Oshinsky ML, Kenny PJ, Sinha R, Mayer EA. Critchley HD.
Trends Neurosci. 2021 Jan;44(1):39-51. doi: 10.1016/j.tins.2020.09.009.

Interoception, the sense of the body's internal physiological state, underpins homeostatic

reflexes, motivational states, and sensations contributing to emotional experiences. The continuous nature of interoceptive processing, coupled to behavior, is implicated in the neurobiological construction of the sense of self. Aberrant integration and control of interoceptive signals, originating in the brain and/or the periphery, can perturb the whole system. Interoceptive abnormalities are implicated in the pathophysiology of psychiatric disorders and in the symptomatic expression of developmental, neurodegenerative, and neurological disorders. Moreover, interoceptive mechanisms appear central to somatic disorders of brain-body interactions, including functional digestive disorders, chronic pain, and comorbid conditions. The present article provides an overview of disorders of interoception and suggests future directions for better understanding, diagnosis, and management of these disorders.

[Rosacea, germs, and bowels: A review on gastrointestinal comorbidities and gut-skin axis of Rosacea.](#)

Wang FY, Chi CC.

Adv Ther. 2021 Jan 28. doi: 10.1007/s12325-021-01624-x.

Rosacea is a chronic inflammatory disease with complicated pathophysiology that involves genetic and environmental elements and dysregulation of innate and adaptive immunity, neurovascular responses, microbiome colonization or infection, resulting in recurrent inflammation. Rosacea has been reported associated with various gastrointestinal diseases including inflammatory bowel disease, celiac disease, irritable bowel syndrome, gastroesophageal reflux disease, *Helicobacter pylori* (HP) infection, and small intestine bacterial overgrowth (SIBO). The link may involve common predisposing genetic, microbiota, and immunological factors, comprising the theory of the gut-skin axis. Although the evidence is still controversial, interestingly, medications for eradicating SIBO and HP provided an effective and prolonged therapeutic response in rosacea, and conventional therapy for which is usually disappointing because of frequent relapses. In this article, we review the current evidence and discuss probable mechanisms of the association between rosacea and gastrointestinal comorbidities.

[Aberrant activity within auditory network is associated with psychiatric comorbidities in interictal migraineurs without aura.](#)

Wei HL, Chen YC, Yu YS, Guo X, Zhou GP, Zhou QQ, Qu LJ, Yin X, Li J, Zhang H.

Brain Imaging Behav. 2021 Jan 21. doi: 10.1007/s11682-020-00446-9.

The present study aimed to explore associations between brain activity in the auditory cortex and clinical and psychiatric characteristics in patients with migraine without aura (MwoA) during interictal periods. Resting-state data were acquired from patients with episodic MwoA ($n = 34$) and healthy controls ($n = 30$). Independent component analysis was used to extract and calculate the resting-state auditory network. Subsequently, we analyzed the correlations between spontaneous activity in the auditory cortex and clinical and psychiatric features in interictal MwoA. Compared with healthy controls, patients with MwoA showed increased activity in the left superior temporal gyrus (STG), postcentral gyrus (PoCG) and insula. Brain activity in the left STG was positively correlated with anxiety scores, and activity in the left PoCG was negatively correlated with anxiety and depression scores. No significant differences were found in intracranial volume between the two groups. This study indicated that functional impairment and altered integration linked to the auditory cortex existed in patients with MwoA in the interictal period, suggesting that auditory-associated cortex disruption as a biomarker may be implemented for the early diagnosis and prediction of neuropsychiatric impairment in interictal MwoA patients.

[Comorbid bipolar disorder and migraine: From mechanisms to treatment.](#)

Duan J, Yang R, Lu W, Zhao L, Hu S, Hu C.

Front Psychiatry. 2021 Jan 11;11:560138. doi: 10.3389/fpsyt.2020.560138. eCollection 2020.

Bipolar disorder (BD) is a severe psychiatric disorder characterized by recurrent episodes of manic/hypomanic or depressive symptoms and euthymic periods, with some patients suffering a gradual deterioration of illness and consequent cognitive deficits during the late stage. Migraine is a disease generally without abnormal medical examinations, neurological examinations or laboratory studies, and the diagnosis is made based on the retrospective demonstration of headache features and groupings of disease-associated symptoms. The epidemiology of comorbid BD and migraine is high and it is obligatory to find effective treatments to improve the prognosis. Recent investigations demonstrated that the close relationship between BD and migraine significantly increased the rapid cycling rates of both

BD and migraine in patients. Although the detailed mechanism is complex and largely unclear in comorbid BD and migraine, genetic factors, neurotransmitters, altered signaling pathways, disturbances of inflammatory cytokines, and mitochondrial dysfunction are risk factors of BD and migraine. Particularly these two diseases share some overlapping mechanisms according to previous studies. To this end, we call for further investigations of the potential mechanisms, and more efforts are underway to improve the treatment of people with comorbid BD and migraine. In this review, we provide an overview of the potential mechanisms in patients with BD or migraine and we further discuss the treatment strategies for comorbid BD and migraine and it is obligatory to find effective treatments to improve the prognosis. This work will provide insights for us to know more about the mechanisms of comorbid BD and migraine, provides new therapeutic targets for the treatment and give clinicians some guidance for more appropriate and beneficial treatment.

[A mouse model of endometriosis that displays vaginal, colon, cutaneous, and bladder sensory comorbidities.](#)

Castro J, Maddern J, Grundy L, Manavis J, Harrington AM, Schober G, Brierley SM. *FASEB J.* 2021 Apr;35(4):e21430. doi: 10.1096/fj.202002441R.

Endometriosis is a painful inflammatory disorder affecting ~10% of women of reproductive age. Although chronic pelvic pain (CPP) remains the main symptom of endometriosis patients, adequate treatments for CPP are lacking. Animal models that recapitulate the features and symptoms experienced by women with endometriosis are essential for investigating the etiology of endometriosis, as well as developing new treatments. In this study, we used an autologous mouse model of endometriosis to examine a combination of disease features and symptoms including: a 10 week time course of endometriotic lesion development; the chronic inflammatory environment and development of neuroangiogenesis within lesions; sensory hypersensitivity and altered pain responses to vaginal, colon, bladder, and skin stimulation in conscious animals; and spontaneous animal behavior. We found significant increases in lesion size from week 6 posttransplant. Lesions displayed endometrial glands, stroma, and underwent neuroangiogenesis. Additionally, peritoneal fluid of mice with endometriosis contained known inflammatory mediators and angiogenic factors. Compared to Sham, mice with endometriosis displayed: enhanced sensitivity to pain evoked by (i) vaginal and (ii) colorectal distension, (iii) altered bladder function and increased sensitivity to cutaneous (iv) thermal and (v) mechanical stimuli. The development of endometriosis had no effect on spontaneous behavior. This study describes a comprehensive characterization of a mouse model of endometriosis, recapitulating the clinical features and symptoms experienced by women with endometriosis. Moreover, it delivers the groundwork to investigate the etiology of endometriosis and provides a platform for the development of therapeutical interventions to manage endometriosis-associated CPP.

[The association between migraine and depression based on miRNA biomarkers and cohort studies.](#)

Chen YH, Wang H.

Curr Med Chem. 2020 Nov 16. doi: 10.2174/0929867327666201117100026.

Background: An association between migraine and Major Depression (MD) has been revealed in many clinical studies. Both diseases affect a large proportion of the global population. More understanding on the comorbidity mechanism of these two diseases can shed light on developing new therapies for both diseases. Methods: To the best of our knowledge, there have not been any researches in the literature based on microRNA (miRNA) biomarkers to investigate the relationship between MD and migraine. In this study, we discuss the association of these two diseases based on their miRNA biomarkers. In addition to miRNA biomarkers, we also demonstrate epidemiological evidence for their association based on Taiwan Biobank (TWB) data. Results: Among the 12 migraine miRNA biomarkers, 11 of them are related to MD. Only miR-181a has no direct evidence involved in the mechanism of MD. In addition to the biological biomarker evidence, the statistical analysis using the largescale epidemiologic data collected from TWB provides strong evidence on the relationship between MD and migraine. Conclusions: The evidence based on both molecular and epidemiological data reveals the significant association between MD and migraine. This result can help investigate the correlated underlying mechanism of these two diseases.

[Sex- and gender-related differences in common functional gastroenterologic disorders.](#)

Narayanan SP, Anderson B, Bharucha AE.

Mayo Clin Proc. 2021 Apr;96(4):1071-1089. doi: 10.1016/j.mayocp.2020.10.004.

Functional gastrointestinal (GI) disorders (FGIDs) result from central and peripheral mechanisms, cause chronic remitting-relapsing symptoms, and are associated with comorbid conditions and impaired quality of life. This article reviews sex- and gender-based differences in the prevalence, pathophysiologic factors, clinical characteristics, and management of functional dyspepsia (FD) and irritable bowel syndrome (IBS) that together affect approximately 1 in 4 people in the United States. These conditions are more common in women. Among patients with IBS, women are more likely to have severe symptoms and coexistent anxiety or depression; constipation or bloating and diarrhea are more common in women and men, respectively, perhaps partly because defecatory disorders, which cause constipation, are more common in women. Current concepts suggest that biological disturbances (eg, persistent mucosal inflammation after acute gastroenteritis) interact with other environmental factors (eg, abuse) and psychological stressors, which influence the brain and gut to alter GI tract motility or sensation, thereby causing symptoms. By comparison to a considerable understanding of sex-based differences in the pathogenesis of visceral hypersensitivity in animal models, we know less about the contribution of these differences to FGID in humans. Slow gastric emptying and colon transit are more common in healthy women than in men, but effects of gonadal hormones on colon transit are less important than in rodents. Although increased visceral sensation partly explains symptoms, the effects of sex on visceral sensation, colonic permeability, and the gut microbiome are less prominent in humans than rodents. Whether sex or gender affects response to medications or behavioral therapy in FD or IBS is unclear because most patients in these studies are women.

[Sex differences and the endocannabinoid system in pain.](#)

Blanton HL, Barnes RC, McHann MC, Bilbrey JA, Wilkerson JL, Guindon J. *Pharmacol Biochem Behav.* 2021 Mar;202:173107. doi: 10.1016/j.pbb.2021.173107.

Cannabis use has been increasing in recent years, particularly among women, and one of the most common uses of cannabis for medical purposes is pain relief. Pain conditions and response to analgesics have been demonstrated to be influenced by sex, and evidence is emerging that this is also true with cannabinoid-mediated analgesia. In this review we evaluate the preclinical evidence supporting sex differences in cannabinoid pharmacology, as well as emerging evidence from human studies, both clinical and observational. Numerous animal studies have reported sex differences in the antinociceptive response to natural and synthetic cannabinoids that may correlate to sex differences in expression, and function, of endocannabinoid system components. Female rodents have generally been found to be more sensitive to the effects of Δ^9 -THC. This finding is likely a function of both pharmacokinetic and pharmacodynamics factors including differences in metabolism, differences in cannabinoid receptor expression, and influence of ovarian hormones including estradiol and progesterone. Preclinical evidence supporting direct interactions between sex hormones and the endocannabinoid system may translate to sex differences in response to cannabis and cannabinoid use in men and women. Further research into the role of sex in endocannabinoid system function is critical as we gain a deeper understanding of the impact of the endocannabinoid system in various disease states, including chronic pain.

[Neuronal correlates of cognitive control are altered in women with endometriosis and chronic pelvic pain.](#)

Steiner GZ, Barry RJ, Wassink K, De Blasio FM, Fogarty JS, Cave AE, Love S, Armour M. *Front Syst Neurosci.* 2020 Dec 16;14:593581. doi: 10.3389/fnsys.2020.593581. eCollection 2020.

Endometriosis is a debilitating women's health condition and is the most common cause of chronic pelvic pain. Impaired cognitive control is common in chronic pain conditions, however, it has not yet been investigated in endometriosis. The aim of this study was to explore the neuronal correlates of cognitive control in women with endometriosis. Using a cross-sectional study design with data collected at a single time-point, event-related potentials were elicited during a cued continuous performance test from 20 women with endometriosis (mean age = 28.5 ± 5.2 years) and 20 age- and gender-matched controls (mean age = 28.5 ± 5.2 years). Event-related potential components were extracted and P3 component amplitudes were derived with temporal principal components analysis. Behavioral and ERP outcomes were compared between groups and subjective pain severity was correlated with ERP component amplitudes. No significant behavioral differences were seen in task performance between the groups (all $p > 0.094$). Target P3b (all $p < 0.034$) and SW (all $p < 0.040$), and non-target early P3a (eP3a; all $p < 0.023$) and late P3a (lP3a; all $p < 0.035$) amplitudes were smaller for the

endometriosis compared to the healthy control group. Lower non-target eP3a ($p < 0.001$), IP3a ($p = 0.013$), and SW ($p = 0.019$) amplitudes were correlated with higher pain severity scores. Findings suggest that endometriosis-associated chronic pelvic pain is linked to alterations in stimulus-response processing and inhibitory control networks, but not impaired behavioral performance, due to compensatory neuroplastic changes in overlapping cognitive control and pain networks.

[Posttraumatic stress disorder and chronic pain conditions in men: A twin study.](#)

Gasperi M, Panizzon M, Goldberg J, Buchwald D, Afari N.

Psychosom Med. 2021 Feb-Mar 01;83(2):109-117. doi: 10.1097/PSY.0000000000000899.

Objective: Posttraumatic stress disorder (PTSD) is highly comorbid with chronic pain conditions that often co-occur such as migraine headaches, temporomandibular disorder, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, chronic prostatitis/chronic pelvic pain syndrome, and tension headaches. Using a genetically informative sample, the current study evaluated the genetic and environmental factors contributing to the co-occurrence of PTSD and chronic pain conditions. Methods: Data from 4680 male twins in the Vietnam Era Twin Registry were examined. Biometric modeling was used to estimate genetic and environmental variance components and genetic and environmental correlations between PTSD and multiple chronic pain conditions. Results: Heritabilities were estimated at 43% (95% confidence interval [CI] = 15%-63%) for PTSD and 34% (95% CI = 27%-41%) for the combined history of any one or more pain condition. Specific pain condition heritabilities ranged from 15% (95% CI = 0%-48%) for tension headaches to 41% (95% CI = 27%-54%) for migraine headaches. Environmental influences accounted for the remaining variance in pain conditions. The genetic correlation between PTSD and combined history of any one or more pain condition was $r_g = 0.61$ (95% CI = 0.46-0.89) and ranged for individual pain conditions from $r_g = 0.44$ (95% CI = 0.24-0.77) for migraine headache to $r_g = 0.75$ (95% CI = 0.52-1.00) for tension headaches. Conclusions: PTSD and chronic pain conditions are highly comorbid, and this relationship can be explained by both genetic and environmental overlap. The precise mechanisms underlying these relationships are likely diverse and multifactorial.

Epidemiology Studies

[The prevalence of psychiatric and chronic pain comorbidities in fibromyalgia: An ACTION systematic review.](#)

Kleykamp B, Ferguson MC, McNicol E, Bixho I, Arnold LM, Edwards RR, Fillingim R, Grol-Prokopczyk H, Turk DC, Dworkin RH.

Semin Arthritis Rheum. 2020 Dec 29;51(1):166-174. doi: 10.1016/j.semarthrit.2020.10.006.

Fibromyalgia (FM) is a chronic widespread pain condition that overlaps with multiple comorbid health conditions and contributes to considerable patient distress. The aim of this review was to provide a systematic overview of psychiatric and chronic pain comorbidities among patients diagnosed with FM and to inform the development of recommendations for the design of clinical trials. Thirty-one, cross-sectional, clinical epidemiology studies that evaluated patients diagnosed with FM were included for review. None of the reviewed studies reported on the incidence of these comorbidities. Sample size-weighted prevalence estimates were calculated when prevalence data were reported in 2 or more studies for the same comorbid condition. The most prevalent comorbidity across all studies reviewed was depression/major depressive disorder (MDD) with over half of the patients included having this diagnosis in their lifetime (weighted prevalence up to 63%). In addition, nearly one-third of FM patients examined had current or lifetime bipolar disorder, panic disorder, or post-traumatic stress disorder. Less common psychiatric disorders reported included generalized anxiety disorder, obsessive compulsive disorder, and specific phobias (agoraphobia, social phobia). There were fewer studies that examined chronic pain comorbidities among FM patients, but when evaluated, prevalence was also high ranging from 39% to 76% (i.e., chronic tension-type or migraine headache, irritable bowel syndrome, myofascial pain syndrome, and temporomandibular disorders). The results of the review suggest that depression and chronic pain conditions involving head/jaw pain and IBS were elevated among FM patients compared to other conditions in the clinic-based studies. In contrast, anxiety-related disorders were much less common. Addressing the presence of these comorbid health conditions in clinical trials of treatments for FM would increase the generalizability and real-world applicability of FM research.

[A systematic review of the association between fibromyalgia and functional gastrointestinal disorders.](#)

Erdrich S, Hawrelak JA, Myers SP, Harnett JE.
Therap Adv Gastroenterol. 2020 Dec 8;13:1756284820977402. doi:
10.1177/1756284820977402. eCollection 2020.

Background: Fibromyalgia and functional gastrointestinal disorders (FGID) including irritable bowel syndrome (IBS) are common conditions presenting in clinical settings and are more prevalent in women. While the relationship between IBS and fibromyalgia has been demonstrated, a review of the prevalence of the broader group of FGID in adults with fibromyalgia has not been undertaken. The aim of this review was to systematically review the published literature, identifying the comorbidity of FGID in people with fibromyalgia, and to discuss the clinical implications, limitations of current research and areas of interest for future research. Methods: Medline, Embase, CINAHL and Web of Science were searched during June 2019. Results were screened for original research articles meeting established criteria for identification of FGID in adults diagnosed with fibromyalgia. Results: A total of 14 studies involving 1340 adults with fibromyalgia, 363 healthy controls and 441 adults with other pathologies were included in this review. Only 1 of the 14 studies included surveyed the full range of FGID. Functional gut disorders were matched to Rome II criteria for reporting and comparison. In addition to increased abdominal pain and functional bloating or gas, IBS of mixed-pattern and constipation-types appear to be more prevalent than diarrhea-predominant IBS in adults with fibromyalgia. Conclusion: This review confirms previous reports that IBS is common in people living with fibromyalgia and suggests that IBS-mixed and constipation types predominate. An association with a range of FGID other than IBS is suggested, but data are limited. Research exploring the association between fibromyalgia and functional gastrointestinal dysfunction beyond IBS are warranted.

[Change and onset-type differences in the prevalence of comorbidities in people with multiple sclerosis.](#)

Lo LMP, Taylor BV, Winzenberg T, Palmer AJ, Blizzard L, van der Mei I.
J Neurol. 2021 Feb;268(2):602-612. doi: 10.1007/s00415-020-10194-x.

Background: Little is known about the change in prevalence of comorbidities during the disease course of people with multiple sclerosis (MS) and whether the prevalences vary by MS onset type. Objective: To calculate the change in prevalence of comorbidities between symptom onset and the time of study, to compare the prevalences of comorbidities with those in the Australian population at the time of study and to examine onset-type differences. Methods: Comorbidity data from 1518 participants of the Australian MS Longitudinal Study and Australian population comparator data (2014-2015 National Health Survey) were used. The change in prevalence between time points and prevalence ratios (PR) at the time of study (crude, age and sex adjusted, and stratified by onset type) was calculated. Results: Comorbidities were common, and those with the largest increases in prevalence between MS symptom onset and the time of study were depression (+ 26.9%), anxiety (+ 23.1%), hypertension (+ 21.9%), elevated cholesterol (+ 16.3%), osteoarthritis (+ 17.1%), eye diseases (+ 11.6%), osteoporosis (+ 10.9%) and cancer (+ 10.3%). Compared to the general population and after age and sex adjustment, participants had a significantly higher prevalence for 14/19 comorbidities at the time of study. The associations were strongest for anaemia, cancer (both PR > 4.00), anxiety, depression, migraine (all PR > 3.00), psoriasis and epilepsy (both PR > 2.00). No significant differences were seen by onset type. Conclusion: Comorbidities are common at MS symptom onset and increase with MS duration. Having MS may thus contribute to accrual of comorbidities. This emphasises the importance of optimal screening for and management of comorbidities in early MS and throughout the disease course.

[Prevalence and risk factors of dry eye in 79,866 participants of the population-based Lifelines cohort study in the Netherlands.](#)

Vehof J, Snieder H, Jansonius N, Hammond CJ.
Ocul Surf. 2021 Jan;19:83-93. doi: 10.1016/j.jtos.2020.04.005.

Purpose: To investigate the prevalence of dry eye among all adult age categories and to discover independent risk factors by investigating a wide range of etiological categories. Methods: A cross-sectional association study including 79,866 voluntary participants aged 20-94 years of the population-based Lifelines Cohort Study in the Netherlands. Results: Overall, 9.1% of participants had dry eye disease as measured by the Women's Health Study dry eye

questionnaire. Prevalence of dry eye symptoms were particularly prevalent in 20-30 years olds. Dry eye was associated with comorbidities in almost all body systems, including musculoskeletal, gastro-intestinal, ophthalmic, autoimmune, psychiatric, pain, functional, dermatological and atopic disorders. Numerous independent risk factors were discovered or confirmed, with strong associations for female sex, contact lens use, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, eye surgery including cataract and laser refractive surgery, keratoconus, osteoarthritis, connective tissue diseases, atherosclerosis, Graves' disease, autistic disorder, depression, 'burnout', Crohn's disease, sarcoid, lichen planus, rosacea, liver cirrhosis, sleep apnea, sinusitis, thyroid function, and air pollution (NO₂). High blood pressure and high BMI were strongly associated with less dry eye, as was current smoking, while ex-smokers had more dry eye. No clear link between dry eye and lipid or blood glucose levels was found. Conclusions: This study on dry eye confirmed but also refuted many risk factors from smaller epidemiological studies, and discovered numerous new risk factors in multiple etiological categories. The finding that dry eye symptoms are particularly common in young adults is concerning, and warrants further study.

[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. 2021 Feb 1;116(2):372-381. 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.

[The effect of novel coronavirus disease-2019 \(COVID-19\) on fibromyalgia syndrome.](#)

Saliffi F, Giorgi V, Sirotti S, Bongiovanni S, Farah S, Bazzichi L, Marotto D, Atzeni F, Rizzi M, Batticciotto A, Lombardi G, Galli M, Sarzi-Puttini P.

Clin Exp Rheumatol. 2020 Nov 16.

Objectives: Fibromyalgia syndrome (FM) is a complex disease that is mainly characterised by chronic widespread pain, fatigue and sleep disturbances and may be precipitated or worsened by many stressors. The aim of this study was to observe the behaviour of FM symptoms during the course of coronavirus disease 2019 (COVID-19). Methods: Patients who had been diagnosed as having FM for ≥ 3 months were recruited between February and May 2020. The collected data were age, sex, educational level and marital status; height and weight; and the scores of the revised Fibromyalgia Impact Questionnaire (FIQR), the modified Fibromyalgia Assessment Status 2019 (FASmod), and the Polysymptomatic Distress Scale (PDS). The patients were divided into those with or without concomitant COVID-19 infection. Results: Eight hundred and ninety-seven (93%) of the 965 patients (881 women [91.3%] and 84 men [8.7%]) were followed up on an outpatient basis because of FM and 68 (7.0%) were either followed up as out-patients or hospitalised because of COVID-19. There was no difference in the sociodemographic data of the two groups, but there were statistically significant between-group differences in the results of the clinimetric tests. The major differences between the

score of the items (those with the greatest disease impact) were the following related symptoms: sleep quality (FIQR15), fatigue/energy (FIQR13), pain (FIQR12), stiffness (FIQR14). Conclusions: The mean total and subdomain scores of all the tests were significantly higher in the patients with COVID-19, which suggests that global FM symptoms are more severe in patients with infection. Further studies of the post-COVID19 patients are being carried out in order to discover whether the worsened symptomatology continues because of their hypersensitized state.

[Osteoporosis and the risk of temporomandibular disorder in chronic obstructive pulmonary disease.](#)

Lee KC, Wu YT, Chien WC, Chung CH, Shen CH, Chen LC, Shieh YS.

J Bone Miner Metab. 2021 Mar;39(2):201-211. doi: 10.1007/s00774-020-01134-w.

Introduction: Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality worldwide. The coexistence of COPD and temporomandibular disorder (TMD) has been noted, and dysfunctional mastication resulting from TMD can worsen individuals' nutritional status. This association between COPD and TMD has been rarely discussed in previous studies. Therefore, this study aimed to determine whether osteoporosis increases the risk of TMD in COPD and whether anti-osteoporosis medications can prevent TMD. Materials and methods: This retrospective nationwide population-based study utilized the Taiwan National Health Insurance Research Database. We enrolled 52,652 COPD patients between 2000 and 2015: 13,163 with osteoporosis and 39,489 without osteoporosis. Groups of COPD patients with and without osteoporosis were age- and sex-matched. A multivariable Cox proportional hazards regression model was used to evaluate the risk of TMD development in COPD patients with and without osteoporosis over 15 years. Results: There was a higher risk of TMD occurrence in COPD patients with osteoporosis than in those without osteoporosis (adjusted hazard ratio 2.564, $P < 0.001$) after adjusting for demographic variables and associative comorbidities. Osteoporosis, hypertension, vertebral compression fracture, and nonpsychotic mental disorders were risk factors contributing to TMD development in patients with COPD. Anti-osteoporosis medications were associated with the prevention of TMD development concomitant with osteoporosis and COPD (adjusted hazard ratio 0.617, $P = 0.004$). Conclusions: Patients with COPD and osteoporosis are at a higher risk of developing TMD, and anti-osteoporosis medications can prevent the development of TMD in this context.

[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 Dec;32(12):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 characterization of interstitial cystitis/bladder pain syndrome in women based on the](#)

[presence or absence of Hunner lesions and glomerulations.](#)

Watanabe D, Akiyama Y, Niimi A, Nomiya A, Yamada Y, Sato Y, Nakamura M, Kawai T, Yamada D, Suzuki M, Igawa Y, Kume H, Homma Y.

Low Urin Tract Symptoms. 2021 Jan;13(1):139-143. doi: 10.1111/luts.12344.

Objectives: To compare the clinical characteristics of three groups of female patients with interstitial cystitis/bladder pain syndrome (IC/BPS) classified according to the presence or absence of Hunner lesions (HL) and glomerulations. **Methods:** The clinical records of 100 female patients with IC/BPS who underwent their first bladder hydrodistension at our institution were retrospectively reviewed. They were divided into patients having (HL-IC; n = 57) or lacking (BPS; n = 43) HL. BPS patients were further classified as those with (29) and without (14) glomerulations. Among these three subtypes, demographics, comorbidities, symptom parameters including a visual analog scale for pain scores, O'Leary and Sant Symptom and Problem (OSS/OSPI) Indices, frequency volume chart variables, and bladder capacity at hydrodistension were compared. **Results:** HL-IC patients were older and had higher OSS/OSPI scores, greater daytime frequency and nocturia, reduced maximum and average voided volumes, and smaller bladder capacity at hydrodistension compared with BPS patients. Pain intensity and illness duration were comparable among the three groups. HL-IC patients had autoimmune disorders as comorbidities more often, but had psychiatric disorders and irritable bowel syndrome less often compared with BPS patients. No discernible differences in clinical characteristics of symptom severity and comorbid disorders were evident between BPS patients with and without glomerulations. **Conclusions:** The presence of HL is associated with distinctive clinical characteristics, while glomerulations are not in female patients with IC/BPS. The presence of HL, but not glomerulations, is a robust phenotypic feature of IC/BPS in women.

[Risk of rheumatoid arthritis in patients with endometriosis: A nationwide population-based cohort study.](#)

Chen SF, Yang YC, Hsu CY, Shen YC.

J Womens Health (Larchmt). 2020 Nov 18. doi: 10.1089/jwh.2020.8431.

Background: Abnormalities in the immune system of endometriosis has been demonstrated and may reflect the chronic inflammatory response or the autoimmune reaction to the presence of ectopic endometrial tissue. Rheumatoid arthritis (RA) is a chronic inflammatory joint disease of an autoimmune nature. The study aimed to investigate the risk of incident RA in patients with endometriosis. **Materials and Methods:** A total of 17,913 patients with endometriosis and 17,913 unaffected controls matched by age, index year, and Charlson Comorbidity Index (CCI) score were enrolled between 2000 and 2012. Patients were followed until the end of 2013 using Taiwan's National Health Insurance Research Database, at which time participants who developed RA were identified. Cox regression analysis was used to calculate the hazard ratio (HR) with a 95% confidence interval (CI) of RA incidence rate between patients with endometriosis and unaffected controls. **Results:** Patients with endometriosis were associated with an increased risk of incident RA compared with unaffected controls after adjusting for age, CCI score, and hormonal and surgical treatments (3.56 vs. 1.30 per 10,000 person-years, HR: 3.71, 95% CI: 2.91-5.73). Among these adjusted variables, hormonal and surgical treatments were treated as time-dependent covariates. Stratification analyses also revealed similar risk associations linking endometriosis to subsequent RA in all stratified age and CCI score subgroups (adjusted HR all >1, although not all were significant) **Conclusions:** Patients with endometriosis was associated with an increased risk of incident RA. Additional prospective studies that take into account genetic vulnerability and environmental exposures are warranted to confirm this relationship.

[Comorbid irritable bowel syndrome symptoms and headache have greater association with anxiety than depression: Annual health check-up survey results.](#)

Kawashima K, Fukuba N, Uemura Y, Ota K, Kazumori H, Sonoyama H, Oka A, Tada Y, Mishima Y, Oshima N, Yuki T, Katsube T, Kinoshita Y, Ishihara S.

Medicine (Baltimore). 2020 Nov 20;99(47):e23059. doi: 10.1097/MD.00000000000023059.

High rates of co-existing irritable bowel syndrome (IBS) and headache have been reported in western countries. We investigated that comorbidity in individuals in Japan, along with anxiety and depression in subjects with and without IBS symptoms and/or headache. This cross-sectional study was performed from April 2012 to January 2013 at the Matsue Seikyo General Hospital Health Check Center. Questionnaires concerning symptoms related to IBS (Rome III) and headache, as well as anxiety/depression score were sent to individuals

scheduled to undergo an annual health check-up, then returned during the visit and analyzed in a blinded manner. A total of 2885 individuals returned completed questionnaires and were enrolled, of whom 218 (7.6%) met the IBS criteria. The rates of co-existing headache in subjects with and without IBS symptoms were 44.0% (96/218) and 22.9% (611/2667), respectively, indicating a significantly higher rate of co-existing headache in subjects with as compared to without IBS (odds ratio [OR] 2.65, $P < .001$). Furthermore, the percentage of subjects with anxiety along with comorbid IBS symptoms and headache was significantly greater as compared to those with IBS (OR 3.01, $P = .001$) or headache (OR 2.41, $P < .001$) alone. Unlike anxiety, the percentage of subjects with depression was not significantly different among the IBS/non-headache, non-IBS/headache, and IBS/headache groups. Subjects with IBS symptoms had a higher rate of co-existing headache as compared to those without IBS. Furthermore, those with comorbid IBS symptoms and headache had a greater association with anxiety than with depression, as compared to those with only IBS or headache.

[Overlap between irritable bowel syndrome diagnosis and endometriosis in adolescents.](#)

DiVasta AD, Zimmerman LA, Vitonis AF, Fadayomi AB, Missmer SA.

Clin Gastroenterol Hepatol. 2021 Mar;19(3):528-537.e1. doi: 10.1016/j.cgh.2020.03.014.

Background & aims: Gastroenterologic symptoms often are reported by adults with endometriosis, leading to unnecessary diagnostic tests or complicated treatment. We investigated associations between endometriosis and irritable bowel syndrome (IBS) in adolescents and whether concurrent pain disorders affect these. **Methods:** We collected data from within The Women's Health Study: Adolescence to Adulthood, which is a US longitudinal study of premenopausal females with and without endometriosis. Our study cohort included participants younger than 21 years enrolled from 2012 to 2018. Participants completed an extensive health questionnaire. Those with IBS based on a self-reported diagnosis or meeting Rome IV diagnostic criteria were considered cases and those without IBS were controls. Subjects without concurrent gastrointestinal disorders or missing pain data ($n = 323$) were included in the analyses. We calculated adjusted odds ratios using unconditional logistic regression. **Results:** More adolescents with endometriosis (54 of 224; 24%) had comorbid IBS compared with adolescents without endometriosis (7 of 99; 7.1%). The odds of IBS was 5.26-fold higher among participants with endometriosis than without (95% CI, 2.13-13.0). In girls with severe acyclic pelvic pain, the odds of IBS was 35.7-fold higher in girls without endometriosis (95% CI, 4.67-272.6) and 12-fold higher in girls with endometriosis (95% CI, 4.2-36.3), compared with no/mild pain. For participants with endometriosis, each 1-point increase in acyclic pain severity increased the odds of IBS by 31% (adjusted odds ratio, 1.31; 95% CI, 1.18-1.47). **Conclusions:** In an analysis of data from a longitudinal study of girls and women with and without endometriosis, we found significant associations between endometriosis and IBS, and a linear relationship between acyclic pelvic pain severity and the odds of IBS. Increased provider awareness and screening for IBS and endometriosis will improve patient outcomes and increase our understanding of these complex disorders.

[Co-occurrence of immune-mediated conditions and endometriosis among adolescents and adult women.](#)

Shafir AL, Palmor MC, Fourquet J, DiVasta AD, Farland LV, Vitonis AF, Harris HR, Laufer MR, Cramer DW, Terry KL, Missmer SA.

Am J Reprod Immunol. 2021 Feb 14;e13404. doi: 10.1111/aji.13404.

Problem: Associations between immune dysfunction conditions (eg, systemic lupus erythematosus, rheumatoid arthritis) and endometriosis have been observed in adult women, but not assessed among a younger population. We investigated the association between immune-mediated conditions and endometriosis among young women. **Method of study:** This cross-sectional analysis in the Women's Health Study: From Adolescence to Adulthood included 551 participants with surgically diagnosed endometriosis (median age=19) and 652 controls without endometriosis (median age=24). Participants completed an expanded Endometriosis Phenome and Biobanking Harmonization Project questionnaire. We used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) to investigate the associations between autoimmune/inflammatory, atopic, chronic pain/fatigue, and endocrine disorders with endometriosis, adjusting for confounders. **Results:** Participants with any autoimmune and/or inflammatory condition had an increased odds of co-occurring endometriosis (OR: 1.87; CI: 0.92-3.80), as did participants with allergies (OR: 1.76; CI: 1.32-2.36), asthma (OR: 1.35; CI: 0.97-1.88), chronic fatigue syndrome and/or fibromyalgia (OR:

5.81; CI: 1.89-17.9), or previous mononucleosis (OR: 1.75; CI: 1.14-2.68). Odds of endometriosis were lower among participants with eczema (OR: 0.68; CI: 0.44-1.04). We observed a positive trend between the number of immune-mediated conditions and the odds of endometriosis (p -trend=0.0002). Endocrine disorders were not associated with endometriosis. Conclusions: Among this population of adolescents and adult women, endometriosis was more likely among participants with autoimmune and/or inflammatory diseases, allergies, asthma, previous mononucleosis infection, and chronic fatigue and/or fibromyalgia. We observed that an increasing number of immune-mediated conditions were positively associated with endometriosis risk. It is important for clinicians who care for adolescents and women with these conditions to consider endometriosis as a comorbidity.

[Evaluation of temporomandibular joint disorder in headache patients.](#)

Memmedova F, Emre U, Yalin OO, Dogan OC.

Neurol Sci. 2021 Feb 18. doi: 10.1007/s10072-021-05119-z.

Objective: The present study is aimed at determining the percentage of temporomandibular joint disorder (TMD) in patients admitted to the neurology outpatient clinic with a headache complaint and to evaluate the association of TMD with the presence of bruxism and headache traits. **Materials and methods:** A total of 349 headache patients were included in the study. The headache type, characteristics of the headache (incidence, duration, and severity of attacks), and the scores of the migraine disability scale (MIDAS) and Allodynia Symptom Scale (ASC-12T) were examined considering the presence of sleep bruxism. The International Classification of Headache Disorders (ICHD-3 Beta) criteria were used for diagnosing headaches. The presence of TMD was evaluated by using the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD). All patients diagnosed with TMD and/or bruxism were evaluated by a dentist. **Results:** A total of 349 patients, 259 females and 90 males, were included in the study. The mean age of the patients was 36 years. Primary and secondary headaches were diagnosed in 317 (90.80%) and 32 (9.20%) patients, respectively. In the primary headache group, there were 227 migraines (182 females, 45 males), 74 tension-type headaches (TTH) (48 females, 26 males), and 15 trigeminal autonomic cephalalgias (TACs) (7 females, 8 males) patients. The remaining patients were diagnosed with other types of diagnoses. The rate of patients with chronic headache was 86.50%. TMD was detected in 89 (25.50%) of the patients while sleep bruxism was present in 80 (23.30%) patients. TMD was detected in 68 (30.0%) migraine patients and 13 (17.60%) TTH patients. The rate of TMD was statistically significantly higher in migraine patients compared to the TTH patients ($p=0.037$). **Conclusion:** Our cross-sectional outpatient-based study determined the incidence of TMD in headache patients as 25%. Among the primary headaches, the incidence of TMD was higher in migraine patients compared to the other diagnoses. Considering these data, the presence of TMD is a clinical condition that should be considered in the pathophysiology of headache, primarily migraine, and especially in cases of non-response to treatment.

[Does irritable bowel syndrome increase the risk of interstitial cystitis/bladder pain syndrome? A cohort study of long term follow-up.](#)

Chang KM, Lee MH, Lin HH, Wu SL, Wu HC.

Int Urogynecol J. 2021 Feb 23. doi: 10.1007/s00192-021-04711-3.

Introduction and hypothesis: Interstitial cystitis/bladder pain syndrome (IC/BPS) and irritable bowel syndrome (IBS) often occur concomitantly without an obvious reason. It is important to determine the relationship between these related diseases. We aimed to determine whether IBS increase the risk of IC/BPS. **Methods:** We identified newly diagnosed IBS patients between 2002 and 2013 from a nationwide database as the IBS cohort. Subjects diagnosed with IC/BPS before IBS were excluded. Cox's regression analysis with a hazard ratio (HR) of IC/BPS between IBS and the non-IBS cohort was applied to unmatched and matched (16 confounders of propensity scores) models. The time from diagnosis of IBS to IC/BPS was also calculated. **Results:** In the unmatched group, which included 100,124 IBS (55% female) and 874,048 non-IBS patients, the IC/BPS adjusted HR was 1.292 (95% confidence interval [CI], 1.131-1.476; $p < 0.0001$) in the IBS cohort compared with the non-IBS cohort. In the matched group, there were 85,359 patients in each cohort, and the IC/BPS HR was 1.599 (95% CI, 1.344-1.903; $p < 0.0001$). The average numbers of years until the development of IC/BPS in the IBS cohort and non-IBS cohort were 4.60 ± 2.58 ($n = 253$) and 5.99 ± 3.49 ($n = 295$) years, respectively. **Conclusions:** IBS was shown to increase the risk of IC/BPS in this 12-year cohort study. The time from the diagnosis of IBS to IC/BPS was 5.35 ± 3.18 years. A common pathophysiology of IBS and IC/BPS is possible. Clinicians should be mindful of the

association and promote collaborative care of these two elusive diseases.

[Phenotypes of women with and without endometriosis and relationship with functional pain disability.](#)

Evans S, Mikocka-Walus A, Olive L, Seidman LC, Druitt M, Payne LA.
Pain Med. 2020 Dec 1;pnaa362. doi: 10.1093/pm/pnaa362.

Objective: Primary dysmenorrhea and secondary dysmenorrhea due to endometriosis share overlapping symptoms and likely demonstrate aspects of central sensitization. The present study aimed to identify distinct phenotypes of women who have dysmenorrhea with and without endometriosis to shed light on the unique mechanisms contributing to the pathogenesis of each condition. **Methods:** An online survey was used to investigate the relationship between ratings of menstrual pain severity, menstrual symptoms (abdominal cramps, abdominal discomfort, low back pain, headache, body aches, bloating, nausea, diarrhea, increased bowel movements), widespread pain, and functional pain disability in a community sample of 1,354 women (aged 18-50) with menstrual pain in Australia. **Results:** Compared with women without endometriosis, those with endometriosis had statistically significant higher menstrual pain severity ($P<0.01$), symptom severity and fatigue (all symptoms $P<0.001$, although only cramps and bloating were clinically significant), widespread pain sites ($P<0.001$), and functional pain disability ($P<0.001$, although this difference was not clinically significant). When examining symptoms by pain severity, women with severe menstrual pain were more likely to experience symptoms than women with less severe pain, regardless of the presence of endometriosis. Similar predictors of functional pain disability emerged for women with and without endometriosis, such as body aches, nausea, fatigue, and widespread pain, respectively, suggesting the presence of central sensitization in both groups. Logistic regression revealed that after accounting for menstrual pain severity (odds ratio [OR], 1.61) and duration (OR, 1.04), symptoms of bloating (OR, 1.12), nausea (OR, 1.07), and widespread pain sites (OR, 1.06) significantly predicted the presence of endometriosis. **Conclusions:** The findings suggest that phenotypes specific to endometriosis can be identified.

[Fibromyalgia pain and fatigue symptoms in Spanish and U.S. men.](#)

Kueny A, Monteso-Curto P, Lunn S, Mohabbat AB, Clark S, Luedtke C, Vincent A, Ruschak I, Mateu-Gil ML, Panisello-Chavarria ML, Rossello L, Guerrero CC, Goncalves AQ, Martin CA, Toussaint L.
Pain Manag Nurs. 2021 Mar 23;S1524-9042(20)30242-3. doi: 10.1016/j.pmn.2020.12.003.

Background and aims: Fibromyalgia Syndrome (FMS) is a chronic centralized pain disorder characterized by widespread pain and fatigue. Of those affected by FMS, the majority are women, and minimal research exists involving men. The purpose of this paper is to describe the pain and fatigue experiences of men with FMS from two Western countries, Spain and the United States, in order to support more accurate and earlier recognition and diagnosis in men. **Design and methods:** We used individual and focus group interviews with qualitative and quantitative assessments. **Settings and participants/subjects:** Ten men in Spain and seven men in the United States provided information about their symptoms, psychosocial and health-seeking behaviors, and gender experiences with FMS. **Results:** Men articulated types, trends, and triggers of pain and fatigue that enrich an understanding of their symptoms. For example, men report more localized pain than generalized pain. Employment status and activities, among other contextual factors, impacted men's pain and fatigue experiences. **Conclusions:** Men experience distinct facets of pain and fatigue compared with women, with notable similarities and differences across the Spanish and U.S. **Samples:** Cross-cultural comparisons highlight contextual factors that may inspire future inquiries about determinants of men's experiences with FMS. **Clinical implications:** The present study could be useful for anyone treating men suffering from FMS, especially care providers in nursing, medical, and psychology fields. These initial findings may prompt a closer examination of recommendations for assessment and diagnostic criteria used internationally for patients with FMS with better recognition of men's experience.

[Psychological, physical, and sleep comorbidities and functional impairment in irritable bowel syndrome: Results from a national survey of U.S. adults.](#)

Grover M, Kolla BP, Pamarthy R, Mansukhani MP, Breen-Lyles M, He JP, Merikangas KR.
PLoS One. 2021 Jan 14;16(1):e0245323. doi: 10.1371/journal.pone.0245323. eCollection 2021.

Background/aims: Patients with irritable bowel syndrome (IBS) in referral practice commonly report mental disorders and functional impairment. Our aim was to determine the prevalence of mental, physical and sleep-related comorbidities in a nationally representative sample of IBS patients and their impact on functional impairment. **Methods:** IBS was defined by modified Rome Criteria based on responses to the chronic conditions section of the National Comorbidity Survey-Replication. Associations between IBS and mental, physical and sleep disorders and 30-day functional impairment were examined using logistic regression models. **Results:** Of 5,650 eligible responders, 186 met criteria for IBS {weighted prevalence 2.5% (SE = 0.3)}. Age >60 years was associated with decreased odds (OR = 0.3; 95% CI:1-.6); low family income (OR = 2.4; 95% CI:1.2-4.9) and unemployed status (OR = 2.3; 95% CI:1.2-4.2) were associated with increased odds of IBS. IBS was significantly associated with anxiety, behavior, mood disorders (ORs 1.8-2.4), but not eating or substance use disorders. Among physical conditions, IBS was associated with increased odds of headache, chronic pain, diabetes mellitus and both insomnia and hypersomnolence related symptoms (ORs 1.9-4.0). While the association between IBS and patients' role impairment persisted after adjusting for mental disorders (OR = 2.4, 95% CI 1.5-3.7), associations with impairment in self-care, cognition, and social interaction in unadjusted models (ORs 2.5-4.2) were no longer significant after adjustment for mental disorders. **Conclusion:** IBS is associated with socioeconomic disadvantage, comorbidity with mood, anxiety and sleep disorders, and role impairment. Other aspects of functional impairment appear to be moderated by presence of comorbid mental disorders.

[Temporal relationship between osteoarthritis and comorbidities: a combined case control and cohort study in the UK primary care setting.](#)

Swain S, Coupland C, Mallen C, Kuo CF, Sarmanova A, Bierma-Zeinstra SMA, Englund M, Prieto-Alhambra D, Doherty M, Zhang W. *Rheumatology (Oxford)*. 2021 Jan 28;keab067. doi: 10.1093/rheumatology/keab067.

Objective: To determine the burden of comorbidities in osteoarthritis (OA) and their temporal relationships in the UK. **Methods:** The Clinical Practice Research Datalink (CPRD) GOLD was used to identify people with incident OA and age, gender and practice matched non-OA controls from UK primary care. Controls were assigned the same index date as matched cases (date of OA diagnosis). Associations between OA and 49 individual comorbidities and multimorbidity (≥ 2 comorbidities excluding OA) both before and after OA diagnosis were estimated, adjusting for covariates, using odds ratios (aOR) and hazard ratios (aHR) respectively. **Results:** During 1997-2017, we identified 221 807 incident OA cases and 221 807 matched controls. Of 49 comorbidities examined, 38 were associated with OA both prior to, and following, the diagnosis of OA, and 2 (dementia and SLE) were associated with OA only following the diagnosis of OA. People with OA had higher risk of developing heart failure (aHR 1.63; 95% CI 1.56-1.71), dementia (aHR 1.62; 95% CI 1.56-1.68), liver diseases (aHR 1.51; 95% CI 1.37-1.67), irritable bowel syndrome (aHR 1.51; 95% CI 1.45-1.58), gastrointestinal bleeding (aHR 1.49; 95% CI 1.39-1.59), 10 musculoskeletal conditions and 25 other conditions following OA diagnosis. The aOR for multimorbidity prior to the index date was 1.71 (95% CI 1.69-1.74), whereas the aHR for multimorbidity after the index date was 1.29 (95% CI 1.28-1.30). **Conclusions:** People with OA are more likely to have other chronic conditions both before and after the OA diagnosis. Further study on shared aetiology and causality of these associations is needed.

[Distribution and prevalence of musculoskeletal pain co-occurring with persistent low back pain: a systematic review.](#)

Overas CK, Johansson MS, de Campos TF, Ferreria ML, Natvig B, Mork PJ, Hartvigsen J. *BMC Musculoskelet Disord*. 2021 Jan 18;22(1):91. doi: 10.1186/s12891-020-03893-z.

Background: Co-occurring musculoskeletal pain is common among people with persistent low back pain (LBP) and associated with more negative consequences than LBP alone. The distribution and prevalence of musculoskeletal pain co-occurring with persistent LBP has not been systematically described, which hence was the aim of this review. **Methods:** Literature searches were performed in MEDLINE, Embase, CINAHL and Scopus. We considered observational studies from clinical settings or based on cohorts of the general or working populations involving adults 18 years or older with persistent LBP (≥ 4 wks) and co-occurring musculoskeletal pain for eligibility. Study selection, data extraction and risk of bias assessment were carried out by independent reviewers. Results are presented according to study population, distribution and location(s) of co-occurring pain. **Results:** Nineteen studies out of 5744 unique records met the inclusion criteria. Studies were from high-income

countries in Europe, USA and Japan. A total of 34,492 people with persistent LBP were included in our evidence synthesis. Methods for assessing and categorizing co-occurring pain varied considerably between studies, but based on the available data from observational studies, we identified three main categories of co-occurring pain - these were axial pain (18 to 58%), extremity pain (6 to 50%), and multi-site musculoskeletal pain (10 to 89%). Persistent LBP with co-occurring pain was reported more often by females than males, and co-occurring pain was reported more often in patients with more disability. Conclusions: People with persistent LBP often report co-occurring neck pain, extremity pain or multi-site pain. Assessment of co-occurring pain alongside persistent LBP vary considerable between studies and there is a need for harmonisation of measurement methods to advance our understanding of how pain in different body regions occur alongside persistent LBP.

[Long-term pain management and health care resource use among an employed population in Japan with knee osteoarthritis combined with low back pain.](#)

Ueda K, Takura T, Fujikoshi S, Meyers J, Nagar SP, Enomoto H.
Pain Med. 2020 Dec 30;pnaa424. doi: 10.1093/pm/pnaa424.

Objective: Assess long-term comorbidity burden and pain management patterns among working-age patients with knee osteoarthritis (KOA) only without low back pain (LBP) (KOA-noLBP) and patients with KOA plus LBP (KOA+LBP) in Japan. Methods: Retrospective claims data analyses were conducted on data from the Japan Medical Data Center (JMDC) database. Adult patients (≥ 40 years) with a diagnosis of knee osteoarthritis (KOA) (January 1, 2011-December 31, 2012) and 5 years of follow-up were evaluated. The first claim with a KOA diagnosis defined the index date. Longitudinal pain management patterns were assessed in both cohorts. Results: Overall, 1,828 patients met study criteria (717 with KOA-noLBP; 1,111 with KOA+LBP). The mean age of patients with KOA-noLBP was 52.1 years, and that of patients with KOA+LBP was 53.1 years, with more females in the KOA+LBP cohort (49.4% vs. 55.0%). Regardless of cohort, $>90\%$ of patients received pharmacological intervention during the 5-year follow-up period. The most common regimen first received was either topical or oral nonsteroidal anti-inflammatory drugs. A higher mean number of pharmaceutical treatments were received by patients in the KOA+LBP cohort (3.6) than by patients in the KOA-noLBP cohort (2.7) during the follow-up period. Regardless of cohort, most of the direct medical cost was derived from medication. Conclusion: This study demonstrates that a greater proportion of the JMDC population of working individuals with KOA were comorbid with LBP and received pain-related treatment in the long-term perspective relative to patients with KOA without LBP. Appropriate pain management for both KOA and LBP would be key for effective resource utilization in an aging society facing socioeconomic burdens.

[Increased prevalence of irritable bowel syndrome in migraine patients: a systematic review and meta-analysis.](#)

Wongtrakul W, Charoenngam N, Ungprasert P.
Eur J Gastroenterol Hepatol. 2021 Jan 18. doi: 10.1097/MEG.0000000000002065.

Objective: Even though evidence showing increased prevalence of irritable bowel syndrome (IBS) among migraine patients exists, it has not been well-established and the magnitude of association varies substantially across the studies. This study aimed to comprehensively compare the prevalence of IBS among migraineurs versus nonmigraineurs using the systematic review and the meta-analysis technique. Methods: Two authors independently conducted a literature search in MEDLINE, EMBASE and Google Scholar database up to April 2020. The eligible study must consist of two groups of participants, migraineurs and nonmigraineurs, and report the prevalence of IBS in both groups. Alternatively, an eligible study may report the odds ratio (OR) with a 95% confidence interval (CI) of the association between migraine and IBS. Point estimates and standard errors from each eligible study were combined together using the generic inverse variance method of DerSimonian and Laird. Results: Of the 2531 articles identified from the three databases, 11 studies with a total of 28 336 migraineurs and 1 535 758 nonmigraineurs met the selection criteria and were included into the meta-analysis. The pooled analysis found that migraineurs had a significantly higher prevalence of IBS than nonmigraineurs with the pooled OR of 2.49 (95% CI, 2.22-2.78; I², 42%). The funnel plot was asymmetric and suggested the presence of publication bias. Conclusion: A significantly increased prevalence of IBS among patients with migraine was demonstrated in this study.

[The level and prevalence of depression and anxiety among patients with different subtypes of](#)

Background: Irritable bowel syndrome (IBS) is a very common functional bowel disorder. However, the difference of depression and anxiety comorbidities among different IBS subtypes is still not well evaluated. This study aims to investigate the difference in the level and prevalence of depression and anxiety among healthy controls and patients with different subtypes of IBS. **Methods:** PubMed, EMBASE and the Cochrane library were searched systematically until August 17, 2020. Studies that investigated depression and/or anxiety levels or prevalence among different IBS-subtype patients measured at baseline or the same point were included. Network meta-analysis was conducted to analyze standardized mean difference (SMD) of anxiety and depression levels, and single arm meta-analysis was performed for prevalence of anxiety and depression among different IBS subtypes. **Results:** Eighteen studies involving 7095 participants were included. Network meta-analyses results showed healthy controls had a lower level of depression than IBS with mixed symptoms of constipation and diarrhea (IBS-M) [SMD = - 1.57; 95% confidence interval (CI) - 2.21, - 0.92], IBS with constipation (IBS-C) (SMD = - 1.53; 95% CI - 2.13, - 0.93) and IBS with diarrhea (IBS-D)(SMD = - 1.41; 95% CI - 1.97, - 0.85), while no significant difference was found between IBS unclassified (IBS-U) and healthy controls (SMD = - 0.58; 95% CI - 2.15, 1.00). There was also no significant difference in the level of depression among different IBS subtypes patients. The results of anxiety were similar to depression. Ranking probability showed that IBS-M was associated with the highest level of depression and anxiety symptoms, followed by IBS-C/IBS-D and IBS-U. Single-arm meta-analysis showed IBS-C had the highest prevalence of depression (38%) and anxiety (40%), followed by IBS-D, IBS-M and IBS-U. **Conclusion:** The results indicated that IBS-M was more likely to be associated with a higher level of depression and anxiety, and the prevalence of depression and anxiety in IBS-C was highest. The psychological screening and appropriate psychotherapy are needed for patients with IBS-C, IBS-D and IBS-M instead of IBS-U.

[The migraine signature study: Methods and baseline results.](#)

Pressman AR, Buse DC, Jacobson AS, Vaidya SJ, Scott AB, Chia VM, Szekely CA, Stewart WF, Lipton RB.

Headache. 2020 Dec 23. doi: 10.1111/head.14033.

Objective: To characterize patients who utilize services for migraine in a large integrated health care network, and describe patterns of care and utilization. **Background:** Within health care systems, migraine is a common reason for seeking primary and neurology care, but relatively little is documented about who seeks care and the factors that explain variation in utilization. **Methods:** We conducted a retrospective cohort study using electronic health record (EHR) data from Sutter Health primary care (PC) patients who had at least one office visit to a PC clinic between 2013 and 2017. Migraine status was ascertained from diagnosis codes and medication orders. Control status was assigned to those with no evidence of care for any type of headache. We divided the primary care migraine cohort into two groups: those who received all their care for migraine from PC (denoted PC-M) and those who had ≥ 1 encounter with a neurologist for migraine (denoted N-M). Migraine cases were also designated as having preexisting migraine if they had an encounter with a migraine diagnosis within (\pm) 6 months of their first study period PC visit and, otherwise, designated as first migraine consult. Two levels of contrasts included: patients with migraine and controls; and within the group of patients with migraine, PC-M and N-M groups. Comorbid conditions were determined from EHR encounter diagnosis codes. **Results:** We identified 94,149 patients with migraine (including 21,525 N-M and 72,624 PC-M) and 1,248,763 controls. **Comorbidities:** Proportions of psychiatric [29.8% (n = 28,054) vs. 11.8% (n = 147,043)], autoimmune [(4.4% (n = 4162) vs. 2.6% (n = 31,981)], pain [13.2% (n = 12,439) vs. 5.8% (n = 72,049)], respiratory [24.6% (n = 23,186) vs. 12.3% (n = 153,692)], neurologic [2.9% (n = 2688) vs. 0.9% (n = 11,321)], and cerebrovascular [1.0% (n = 945) vs. 0.6% (n = 7500)] conditions were higher in the migraine group compared to controls, all $p < 0.001$. Among patients with migraine, the N-M group was similar to the PC-M group in sex, age, ethnicity, and marital status, but were more likely to have preexisting migraine (49.9% (n = 10,734) vs. 36.2% (n = 26,317), $p < 0.001$). Proportions of comorbid conditions were higher among the N-M group than the PC-M group {psychiatric [38.5% (n = 8291) vs. 27.2% (n = 19,763)], autoimmune [6.3% (n = 1365) vs. 3.9% (n = 2797)], pain [19.6% (n = 4218) vs. 11.3% (n = 8211)], respiratory [30.3% (n = 6516) vs. 23.0% (n = 16,670)], neurologic [6.0% (n = 1288) vs. 1.9% (n = 1400)], cardiovascular [9.7% (n = 2091) vs. 7.0% (n = 5076)], and cerebrovascular [2.3% (n = 500) vs. 0.6% (n =

445)], all $p < 0.001$ }. Medications: During the study period, 82.6% ($n = 77,762$) of patients with migraine received ≥ 1 prescription order for an acute migraine medication [89.4% ($n = 19,250$) of N-M vs. 80.6% ($n = 58,512$) of PC]. Opioids were prescribed to 52.9% ($n = 49,837$) of patients with migraine [63.5% ($n = 13,669$) for N-M and 49.8% ($n = 36,168$) for PC-M patients]. During the study period, 61.4% ($n = 57,810$) of patients received ≥ 1 prescription for a migraine preventive medication [81.4% ($n = 17,521$) of N-M and 55.5% ($n = 40,289$) of PC-M patients]. The most commonly prescribed classes of preventive medications were antidepressants. Conclusions: Among patients with migraine in a large health system, those who were also cared for in neurology were more likely to receive both acute and preventive medication migraine orders than those patients who did not see a neurologist, with triptans and antidepressants the most commonly prescribed classes of acute and preventive pharmacotherapies, respectively. Opioids were prescribed to approximately half of the total sample and more common in the N-M group. Adjusting for demographics, patients with migraine had higher rates of nearly every comorbidity we assessed and were more likely to utilize services compared to those without migraine. Overall, patients with migraine also cared for in neurology practices used more of all health care resource types under consideration and had more medical issues, which may be due in some part to a more severe, frequent and disabling disease state compared to those who sought care exclusively from PC practices.

[Increased risk of rheumatoid arthritis among patients with endometriosis: a nationwide population-based cohort study.](#)

Xue YH, You LT, Ting HF, Chen YW, Sheng ZY, Xie YD, Wang YH, Chiou JY, Wei JCC. *Rheumatology (Oxford)*. 2020 Dec 17;keaa784. doi: 10.1093/rheumatology/keaa784.

Objectives: Autoimmunity may play a role in endometriosis. The association between endometriosis and RA remains unknown. This study was conducted to identify any evidence for this relationship. **Methods:** This 13-year, nationwide, population-based, retrospective cohort study analysed the risk of RA in a cohort of individuals with endometriosis. We investigated the incidence of RA among patients with endometriosis using data from the Longitudinal Health Insurance Database 2000, which is maintained by the Taiwan National Health Research Institutes. We used propensity scores to match comorbidities in the two cohorts. Kaplan-Meier analysis and Cox proportional hazard model were employed to analyse the association between endometriosis and RA among patients with different potential risks. **Results:** Patients with endometriosis [adjusted hazard ratio (HR) 1.75, 95% CI 1.27, 2.41], aged ≥ 45 years (adjusted HR 1.50, 95% CI 1.06-2.13) and with autoimmune disease (adjusted HR 6.99, 95% CI 2.84-17.21) had a significantly higher risk of RA. The analyses also showed that when stratified by age, comorbidities and medication use, the risk of RA in patients with endometriosis was also higher than in those without endometriosis. **Conclusion:** This 14-year, nationwide, population-based retrospective cohort study revealed that patients with endometriosis have a higher risk of RA. In the clinical management of patients with RA, rheumatologists should be especially mindful of the possibility of underlying endometriosis.

[Hormonal contraceptive treatment may reduce the risk of fibromyalgia in women with dysmenorrhea: A cohort study.](#)

Tu CH, Lin CL, Yang ST, Shen WC, Chen YH. *J Pers Med*. 2020 Dec 14;10(4):280. doi: 10.3390/jpm10040280.

Dysmenorrhea is the most common gynecological disorder for women in the reproductive age. Study has indicated that dysmenorrhea might be a general risk factor of chronic pelvic pain and even chronic non-pelvic pain, such as fibromyalgia. We used the Longitudinal Health Insurance Database 2000 from the Taiwan National Health Research Institutes Database to investigate whether women with dysmenorrhea have a higher risk of fibromyalgia and whether treatment of dysmenorrhea reduced the risk of fibromyalgia. The dysmenorrhea cohort was matched with a non-dysmenorrhea cohort at a 1:1 ratio based on gender, age, and the year of entry study by frequency matching. Multivariable Cox proportional hazard regression models were used to assess the risk of fibromyalgia, with controlling for potential confounding variables such as age, comorbidities, and medication use. After controlling confounding variables, results revealed that women with dysmenorrhea have a significantly higher risk of fibromyalgia than women without dysmenorrhea. However, only treatment of dysmenorrhea with hormonal contraceptives reduce the risk of fibromyalgia. These results indicated that dysmenorrhea may be a risk factor of fibromyalgia, whereas personalized medicine for treatment of dysmenorrhea may be the key to reduce the risk of fibromyalgia.

Future studies are needed to identify the causes and prevention strategies in detail.

[Association between endometriosis and risk of systemic lupus erythematosus.](#)

Fan YH, Leong PY, Chiou JY, Wang YH, Ku MH, Wei JCC.

Sci Rep. 2021 Jan 12;11(1):532. doi: 10.1038/s41598-020-79954-z.

To examine the association between endometriosis and the risk of systemic lupus erythematosus (SLE), this nationwide, population-based, retrospective cohort study was conducted based on National Health Insurance Research Database in Taiwan. Endometriosis (N = 16,758) and non-endometriosis (N = 16,758) groups were identified by matching baseline characteristics and comorbidities. Student's t-tests and the Kaplan-Meier estimator were utilized to estimate the hazard ratio (HR) and cumulative probability of SLE in the two groups. The endometriosis group showed a significantly higher incidence density rate (0.3 vs. 0.1 per 1000 person-years) and hazard ratio in SLE group (adjusted HR [aHR], 2.37; 95% confidence interval [CI] 1.35-4.14) compared to the non-endometriosis group. Subgroup analysis revealed that patients with endometriosis between 30 and 45 years of age, or were non-steroidal anti-inflammatory drug users, or were hormonal medications-free participants, had higher risks of SLE. For patients with endometriosis, surgical intervention did not significantly impact on the risk of SLE. Our results demonstrated an increased risk of SLE in patients with endometriosis. Clinicians should be aware of this association when managing patients with endometriosis or SLE.

[Baseline characteristics from the women veterans cohort study: Gender differences and similarities in health and healthcare utilization.](#)

Gaffey AE, Burg MM, Rosman L, Portnoy GA, Brandt CA, Cavanagh CE, Skanderson M, Dziura J, Mattocks KM, Bastian LA, Haskell SG.

J Womens Health (Larchmt). 2021 Jan 13. doi: 10.1089/jwh.2020.8732.

Introduction: With the unprecedented expansion of women's roles in the U.S. military during recent (post-9/11) conflicts in Iraq and Afghanistan, the number of women seeking healthcare through the Veterans Health Administration (VHA) has increased substantially. Women Veterans often present as medically complex due to multiple medical, mental health, and psychosocial comorbidities, and consequently may be underserved. Thus, we conducted the nationwide Women Veterans Cohort Study (WVCS) to examine post-9/11 Veterans' unique healthcare needs and to identify potential disparities in health outcomes and care. **Methods:** We present baseline data from a comprehensive questionnaire battery that was administered from 2016 to 2019 to a national sample of post-9/11 men and women Veterans who enrolled in Veterans Affairs care (WVCS2). Data were analyzed for descriptives and to compare characteristics by gender, including demographics; health risk factors and symptoms of cardiovascular disease, chronic pain, and mental health; healthcare utilization, access, and insurance. **Results:** WVCS2 included 1,141 Veterans (51% women). Women were younger, more diverse, and with higher educational attainment than men. Women also endorsed lower traditional cardiovascular risk factors and comorbidities (e.g., weight, hypertension) and greater nontraditional cardiovascular risk factors (e.g., trauma, psychological symptoms). More women reported single-site pain (e.g., neck, stomach, pelvic) and multisite pain, but did not differ from men in posttraumatic stress disorder (PTSD) symptoms or treatment for PTSD. Women seek care at VHA medical centers more frequently, often combined with outside health services, but do not significantly differ from men in their insurance coverage. **Conclusion:** Overall, this investigation indicates substantial variation in risk factors, health outcomes, and healthcare utilization among post-9/11 men and women Veterans. Further research is needed to determine best practices for managing women Veterans in the VHA healthcare system.

[Subjective cognitive impairment in patients with transformed migraine and the associated psychological and sleep disturbances.](#)

Esmael A, Abdelsalam M, Shoukri A, Elsherif M.

Sleep Breath. 2021 Feb 4. doi: 10.1007/s11325-021-02308-0.

Purpose: Migraines are associated with multiple comorbidities like depression, anxiety, poor sleep quality, and subjective cognitive impairment (SCI). This study aimed to evaluate the association of SCI with depression, anxiety, and modalities of sleep in those who have transformed migraines (TM). **Subjects and methods:** The study was conducted on 120 participants with TM and 41 control group participants. The subjective cognitive decline questionnaire classified the participants as SCI and non-SCI. The Headache Impact Test-6, Migraine Disability Assessment, Montreal Cognitive Assessment, Mini-Mental State

Examination, Patient Health Questionnaire-9, Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale, Full Polysomnography, and Beck's Anxiety and the Depression Inventories were used and analyzed between patients with SCI and non-SCI. Results: Patients with TM who had SCI represented 34% with severe headache effects, disability, pain severity, increased depression, and increased anxiety. They showed shorter sleep duration during weekdays, lower sleep quality, less sleep time, lower efficiency, and less REM sleep along with greater sleep latency, periodic limb movements, a higher arousal index, snore index, and percent of NREM3. There was a positive correlation between certain polysomnography parameters like percent NREM3, sleep period, sleep index, sleep latency, sleep arousal index, and periodic limb movements, and an inverse correlation with the percent of REM sleep, total sleep time, and sleep efficiency. Conclusion: Subjective cognitive complaints are common in patients with transformed migraine affecting about 34% of cases. TM patients with SCI had more sleep and psychological disturbances.

[The comorbid relationship between migraine and asthma: A systematic review and meta-analysis of population-based studies.](#)

Wang L, Deng ZR, Zu MD, Zhang J, Wang Y.

Front Med (Lausanne). 2021 Jan 13;7:609528. doi: 10.3389/fmed.2020.609528. eCollection 2020.

Objective: Recent studies have indicated a pathophysiologic link between migraine and asthma. This meta-analysis aimed to comprehensively estimate the risk ratio for migraine in asthma as well as that of asthma in migraine based on available evidence. Method: We systematically searched the electronic databases including PubMed, Web of Science, and SCOPUS for population-based studies that measured either the odds or the risk of asthma in subjects with migraine as well as that of migraine in subjects with asthma. The titles and abstracts were screened by two independent reviewers to identify eligible studies, and this was followed by full-text review of the included studies. Newcastle-Ottawa Scale (NOS) was used to assess the risk of bias of included literature. A meta-analysis was conducted with Review Manager 5.3 Software to calculate the odds ratio (OR) for case-control and cross-sectional studies and either relative ratio (RR) or hazard ratio (HR) for cohort studies, and the source of heterogeneity was assessed. Subgroup and sensitivity analyses were conducted, and the I^2 test were used to assess the source of heterogeneity. The funnel plot, Galbraith plot, and Egger's test were used to evaluate publication bias. Results: Fifteen published studies covering a total of 1,188,780 individuals were identified. Pooled analysis indicated that migraine was associated with increased odds (OR = 1.54; 95% CI: 1.34~1.77) and risk for asthma (HR = 1.42; 95% CI: 1.26~1.60), and asthma associated with increased odds (OR = 1.45; 95% CI: 1.22~1.72) and risk for migraine (HR = 1.47; 95% CI: 1.41~1.52). Conclusion: Migraine is a potential risk indicator for asthma, and *vice versa*, asthma is a potential risk indicator for migraine. However, future prospective cohort studies are warranted to provide more evidence concerning the detailed association between migraine and asthma.

[The migraine-anxiety comorbidity among migraineurs: A systematic review.](#)

Karimi L, Wijeratne T, Crewther SG, Evans AE, Ebaid D, Khalil H.

Front Neurol. 2021 Jan 18;11:613372. doi: 10.3389/fneur.2020.613372. eCollection 2020.

Background: Migraine is recognized as a neurological condition that is often associated with comorbid psychiatric symptoms such as anxiety, depression, bipolar disorder and/or panic disorder. Though some studies have demonstrated the link between migraine and anxiety disorders, there are no systematic reviews that have been published in this area to summarize the evidence. The aim of the present study is to systematically review the literature associated with comorbidity of migraine and anxiety disorders among migraineurs compared to non-migraineurs. Methods: The present systematic review included population-based, cohort and cross-sectional studies if they were reporting the frequency of migraine with either anxiety or depression as diagnosed by a medical practitioner according to the International Classification of Headache Disorders (ICHD-2/3). Results: Eight eligible studies from 2060 relevant citations were included in the review. All participants were migraine patients from both primary care and outpatient settings, as well as tertiary headache and anxiety centers, and were compared to non-migraineurs. The results of the systematic review showed that there is a strong and consistent relationship between migraine and anxiety. The co-morbidity of co-occurrence for migraine and anxiety has an average OR of 2.33 (2.20-2.47) among the prevalence and cross sectional studies and an average RR of 1.63 (1.37-1.93) for two cohort studies; The major limitations of included studies were small sample sizes and a lack of adjusting of confounding factors. Conclusion: The results highlight the need for

inclusion of an anxiety screening tool during initial assessments of migraine patients by medical practitioners and/or physicians and may explain why some anxiolytic medications work better than others for migraine mitigation.

[Prevalence and correlates of chronic fatigue syndrome and post-traumatic stress disorder after the outbreak of the COVID-19.](#)

Simani L, Ramezani M, Darazam IA, Sagharichi M, Aalipour MA, Ghorbani F, Pakdaman H. J Neurovirol. 2021 Feb 2;1-6. doi: 10.1007/s13365-021-00949-1.

As the SARS-COV-2 becomes a global pandemic, many researchers have a concern about the long COVID-19 complications. Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a persistent, debilitating, and unexplained fatigue disorder. We investigated psychological morbidities such as CFS and post-traumatic stress disorder (PTSD) among survivors of COVID-19 over 6 months. All COVID-19 survivors from the university-affiliated hospital of Tehran, Iran, were assessed 6 months after infection onset by a previously validated questionnaire based on the Fukuda guidelines for CFS/EM and DSM-5 Checklist for PTSD (The Post-traumatic Stress Disorder Checklist for DSM-5 or PCL-5) to determine the presence of stress disorder and chronic fatigue problems. A total of 120 patients were enrolled. The prevalence rate of fatigue symptoms was 17.5%. Twelve (10%) screened positive for chronic idiopathic fatigue (CIF), 6 (5%) for CFS-like with insufficient fatigue syndrome (CFSWIFS), and 3 (2.5%) for CFS. The mean total scores in PCL-5 were 9.27 ± 10.76 (range:0-44), and the prevalence rate of PTSD was 5.8%. There was no significant association after adjusting between CFS and PTSD, gender, comorbidities, and chloroquine phosphate administration. The obtained data revealed the prevalence of CFS among patients with COVID-19, which is almost similar to CFS prevalence in the general population. Moreover, PTSD in patients with COVID-19 is not associated with the increased risk of CFS. Our study suggested that medical institutions should pay attention to the psychological consequences of the COVID-19 outbreak.

[Attention-deficit hyperactivity disorder symptoms and quality of life in female patients with fibromyalgia.](#)

Turkoglu G.

Turk J Med Sci. 2021 Jan 29. doi: 10.3906/sag-2010-29.

Background/aim: The present study aimed to determine the association between Attention-Deficit Hyperactivity Disorder (ADHD) symptoms severity, fibromyalgia (FM) severity, and QoL. Materials and methods: While the FM group consisted of 113 (74%) patients, the control group consisted of 40 (26%) individuals. FM symptom severity, ADHD symptom severity, and QoL were evaluated using the Fibromyalgia Impact Questionnaire (FIQ), Adult ADHD Self-Report Scale (ASRS), and World Health Organization Quality of Life Scale-Brief Version (WHOQOL-BREF), respectively. Results: It was found that the FM group had significantly higher scores on the ASRS than the control group ($p < 0.05$). There was a significant difference in FIQ scores and three WHOQOL-BREF domain scores between the FM alone and comorbid FM/high probability of ADHD groups ($p < 0.05$). We found a negative correlation between ASRS total scores and all other scale scores (except for the social relationships domain score of the WHOQOL-BREF) and a positive correlation between ASRS total scores and FIQ scores in FM patients. ADHD scores would mediate the relationship between depression severity and QoL. Conclusions: Our findings indicated that the presence of ADHD symptoms was related to greater FM symptom severity and poorer QoL. Also, ADHD scores would mediate the relationship between depression severity and QoL.

[Do patients with central sensitivity syndromes have poor subjective outcomes despite anatomical cure from pelvic organ prolapse surgery?](#)

Vij M, Dua A, Davies A, Freeman R.

Int Urogynecol J. 2021 Jan 18. doi: 10.1007/s00192-020-04655-0.

Introduction: Pelvic organ prolapse (POP) has an adverse impact on quality of life with lifetime risk of surgery varying from 11 to 20%. Conditions such as fibromyalgia (FMS), chronic fatigue syndrome (CFS/ME) and irritable bowel syndrome (IBS), collectively known as central sensitivity syndromes (CSS), may affect the outcome of POP surgery. The aim of this article is to compare the outcomes of vaginal POP surgery between women with and without CSS. Method: This was a prospective cohort study. The validated Central Sensitisation Inventory (CSI) was used to identify women with CSS. Subjective and objective outcomes were compared between the two groups using POP-SS, Expectation and satisfaction/"EGGS", pain

scores and the POP quantification system (POP-Q). A non-parametric test was used for analysis. Result: Seventy-eight women were recruited. Complete data were available in 62 patients; 23 patients had evidence of CSS and 39 did not. Women with CSS had significantly higher pre- and post-operative POP-SS scores than those without ($p < 0.0005$, $p = 0.004$). Seventeen (73.9%) women with CSS compared to 38 (97.4%) women without CSS demonstrated improvement of a minimum 6 points on the POP-SS scale; however, this was not statistically significant. McGill's pain scores were higher in women with CSS both pre- and post-surgery. Ninety-five per cent of women without CSS achieved their goals and were satisfied with the surgery compared to 69.5% of women with CSS ($p < 0.05$). Conclusion: There is a less favourable outcome of POP surgery in women with CSS compared to those without in terms of persistence of symptoms, pain and overall satisfaction.

Clinical Studies

[Predictors of mucosal and muscle pain in vulvodynia: A cross-sectional analysis from the National Vulvodynia Registry.](#)

Lo L, Lamvu G, Alappattu M, Witzeman K, Markovic D, Rapkin A. Pain. 2021 Feb;22(2):161-170. doi: 10.1016/j.jpain.2020.07.001.

Diagnostic criteria for provoked vestibulodynia (PVD) rely on mucosal pain in the vulvar vestibule, with less emphasis on pain from pelvic floor muscles. It is unknown how psychosocial variables associated with PVD are differentially associated with mucosal versus muscle pain. Analysis of data from the National Vulvodynia Registry ($n = 202$) revealed several factors associated with increased mucosal pain: pain duration ($P = .043$), the McGill sensory subscore ($P = .0086$) and the Gracely pain scale ($P < .001$). Increased mucosal pain was also associated with decreased arousal ($P = .036$). On the other hand, factors significantly associated with greater muscle pain included number of comorbid pain conditions ($P = .001$), decreased intercourse frequency post PVD onset ($P = .02$) and higher scores on the McGill sensory ($P = .0001$) and affective ($P = .0002$) subscores, the Gracely pain scale ($P = .0012$), and state anxiety ($P < .001$). Sexual function was also significantly impacted by high pelvic floor muscular pain, with lower scores for arousal ($P = .046$), orgasm ($P = .0014$) and satisfaction ($P = .013$), and higher pain ($P = .01$). Significant differences in the relationship between muscle and mucosal pain for pain duration ($P = .005$), McGill affective score ($P = .001$), orgasm ($P = .049$), change in intercourse frequency ($P = .027$), and state anxiety ($P = .030$) suggest the possibility of mucosal or muscle pain predominant PVD subtypes. PERSPECTIVE: Patients with higher pelvic floor muscle pain scores than mucosal pain scores may represent different subgroups or characteristics of patients with provoked vestibulodynia. This research highlights the importance of assessment of the pelvic floor muscles in addition to the cotton swab test of the vestibule.

[Widespread myofascial dysfunction and sensitisation in women with endometriosis-associated chronic pelvic pain: A cross-sectional study.](#)

Phan VT, Stratton P, Tandon HK, Sinaii N, Aredo JV, Karp BI, Merideth MA, Shah JP. Eur J Pain. 2021 Apr;25(4):831-840. doi: 10.1002/ejp.1713.

Background: Chronic pelvic pain persists in some women with endometriosis even after lesion removal and optimized hormonal treatment. Objective: Characterize the presence and distribution of pain, myofascial dysfunction and sensitisation beyond the pelvis in women with endometriosis-associated chronic pelvic pain. Methods: Cross-sectional study of 30 women prior to participation in a clinical trial. Evaluation included pain-focused abdominopelvic gynaecologic examination with the identification of pelvic floor muscle spasm. Neuro-musculoskeletal examination assessed paraspinal allodynia and hyperalgesia bilaterally and myofascial trigger points in 13 paired muscles. Pressure-pain thresholds were measured over interspinous ligaments and trigger points. Women completed the body territories element of the Body Pain Index. Results: All women had a pelvic floor muscle spasm that they self-identified as a major focus of pain. Twenty of 30 women described their pelvic pain as focal. However, all demonstrated widespread myofascial dysfunction with low pressure-pain thresholds and trigger points in over two-thirds of 26 assessed regions. Widespread spinal segmental sensitisation was present in 17/30, thoracic in 21/30 and lumbosacral/pelvic in 18/30. Cervical sensitisation manifested as low pressure-pain thresholds with 23/30 also reporting recurrent, severe headaches and 21/30 experiencing orofacial pain. Those reporting diffuse pelvic pain were more likely to have widespread ($p = .024$) and lumbosacral/pelvic ($p =$

.036) sensitisation and report over 10 painful body areas ($p = .009$). Conclusions: Women with endometriosis-associated chronic pelvic pain often have myofascial dysfunction and sensitisation beyond the pelvic region that may be initiated or maintained by on-going pelvic floor spasm. These myofascial and nervous system manifestations warrant consideration when managing pain in this population. Significance: Women with endometriosis often have pelvic pain persisting after surgery despite hormonal therapies and these women have regional pelvic sensitisation and myofascial dysfunction. Pelvic floor muscle spasm is a major pain focus in this population. Sensitisation and myofascial dysfunction are widespread, beyond the pelvic region. On-going pelvic floor spasm may initiate or maintain sensitisation. Myofascial/sensitisation manifestations warrant consideration when managing pain in this population.

[Endometriosis and chronic overlapping pain conditions \[article in German\].](#)

Hauser W.

Schmerz. 2021 Feb 11. doi: 10.1007/s00482-021-00535-8.

Background: The concept of chronic overlapping pain conditions (COPC) is relatively unknown in German pain medicine. **Aims:** Definition, prevalence, shared etiological and pathophysiological mechanisms of COPC. **Summary of recommendations of the interdisciplinary S2k guidelines on diagnostics and treatment of endometriosis relevant for pain physicians.** **Methods:** Selective search of literature in PubMed and selection of recommendations of the S2k guidelines on diagnostics and treatment of endometriosis. **Results:** According to the US National Institutes of Health, COPCs comprise chronic fatigue syndrome, chronic (unspecific) low back pain, chronic tension headache, endometriosis, fibromyalgia syndrome, migraine, painful bladder syndrome, temporomandibular disorder and vulvodynia. Shared etiological factors are family aggregation, childhood adversities and major or traumatic life events. A major shared pathophysiological mechanism is altered processing of stimuli in the central nervous system. Patients with endometriosis should be screened for other chronic pain conditions and psychological distress. The physical examination should check for local (myofascial trigger points) and generalized signs of hyperalgesia and allodynia indicating central sensitization. In cases of endometriosis with COPCs repeated surgery for pain relief should be avoided. Amitriptyline and duloxetine can be considered as pharmacological treatment options. **Discussion:** Pain physicians can play a role in the management of patients with endometriosis and COPCs. A multimodal therapy should include physiotherapy and pain-related psychological treatment and possibly centrally acting pain modulation medication.

[Beyond bones: The relevance of variants of connective tissue \(hypermobility\) to fibromyalgia, ME/CFS and controversies surrounding diagnostic classification: an observational study.](#)

Eccles JA, Thompson B, Themelis K, Amato ML, Stocks R, Pound A, Jones AM, Cipinova Z, Shah-Goodwin L, Timeyin J, Thompson CR, Batty T, Harrison NA, Critchley HD, Davies KA. Clin Med (Lond). 2021 Jan;21(1):53-58. doi: 10.7861/clinmed.2020-0743.

Background: Fibromyalgia and myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) are poorly understood conditions with overlapping symptoms, fuelling debate as to whether they are manifestations of the same spectrum or separate entities. Both are associated with hypermobility, but this remains significantly undiagnosed, despite impact on quality of life. **Objective:** We planned to understand the relevance of hypermobility to symptoms in fibromyalgia and ME/CFS. **Method:** Sixty-three patient participants presented with a confirmed diagnosis of fibromyalgia and/or ME/CFS; 24 participants were healthy controls. Patients were assessed for symptomatic hypermobility. **Results:** Evaluations showed exceptional overlap in patients between fibromyalgia and ME/CFS, plus 81% met Brighton criteria for hypermobility syndrome (odds ratio 7.08) and 18% met 2017 hypermobile Ehlers-Danlos syndrome (hEDS) criteria. Hypermobility scores significantly predicted symptom levels. **Conclusion:** Symptomatic hypermobility is particularly relevant to fibromyalgia and ME/CFS, and our findings highlight high rates of mis-/underdiagnosis. These poorly understood conditions have a considerable impact on quality of life and our observations have implications for diagnosis and treatment targets.

[Fibromyalgia pain and depression: An update on the role of repetitive transcranial magnetic stimulation.](#)

Ansari AH, Pal A, Ramamurthy A, Kabat M, Jain S, Kumar S.

ACS Chem Neurosci. 2021 Jan 20;12(2):256-270. doi:

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Fibromyalgia is a musculoskeletal pain of different parts of the body, which is also associated with fatigue, lack of sleep, cognition deficits, family history, gender bias, and other disorders such as osteoarthritis and rheumatoid arthritis. It is generally initiated after trauma, surgery, infection, or stress. Fibromyalgia often coexists with several other conditions or disorders such as temporomandibular joint disorders, bowel and bladder syndrome, anxiety, depression, headaches, and interstitial cystitis. While there is no permanent cure for fibromyalgia, some interventions are available with multiple side effects. rTMS (repetitive transcranial magnetic stimulation), a noninvasive management strategy is used widely for various pain-related etiologies including fibromyalgia in both the laboratory and clinical settings. In this Review, we discuss the role and mechanism of action of rTMS in fibromyalgia patients and on associated comorbidities including anxiety, pain, depression, neurotransmitter alterations, sleep disorders, and overall quality of life of the patients suffering from this chronic problem. We also provide an update on the rTMS application in the clinical trials of fibromyalgia patients and prospective management therapy for multiple problems that these patients suffer.

[High efficacy of onabotulinumtoxinA treatment in patients with comorbid migraine and depression: a meta-analysis.](#)

Affatato O, Moulin TC, Pisanu C, Babsieva VS, Russo M, Aydinlar EI, Torelli P, Chubarev VN, Tarasov VV, Schioth HB, Mwinyi J.
J Transl Med. 2021 Mar 31;19(1):133. doi: 10.1186/s12967-021-02801-w.

Background: Migraine and depression are highly prevalent and partly overlapping disorders that cause strong limitations in daily life. Patients tend to respond poorly to the therapies available for these diseases. OnabotulinumtoxinA has been proven to be an effective treatment for both migraine and depression. While many studies have addressed the effect of onabotulinumtoxinA in migraine or depression separately, a growing body of evidence suggests beneficial effects also for patients comorbid with migraine and depression. The current meta-analysis systematically investigates to what extent onabotulinumtoxinA is efficient in migraineurs with depression. Methods: A systematic literature search was performed based on PubMed, Scopus and Web of Science from the earliest date till October 30th, 2020. Mean, standard deviation (SD) and sample size have been used to evaluate improvement in depressive symptoms and migraine using random-effects empirical Bayes model. Results: Our search retrieved 259 studies, eight of which met the inclusion criteria. OnabotulinumtoxinA injections administered to patients with both chronic migraine and major depressive disorder led to mean reduction of -8.94 – 8.94 points (CI $[-10.04, -7.84]$ – $10.04, -7.84$], $p < 0.01$) in the BDI scale, of -5.90 – 5.90 points (CI $[-9.92, -1.88]$ – $9.92, -1.88$], $p < 0.01$) in the BDI-II scale and of -6.19 – 6.19 points (CI $[-9.52, -2.86]$ – $9.52, -2.86$], $p < 0.01$) in the PHQ-9 scale, when evaluating depressive symptoms. In the case of the migraine-related symptoms, we found mean reductions of -4.10 – 4.10 (CI $[-7.31, -0.89]$ – $7.31, -0.89$], $p = 0.01$) points in the HIT6 scale, -32.05 – 32.05 (CI $[-55.96, -8.14]$ – $55.96, -8.14$], $p = 0.01$) points in the MIDAS scale, -1.7 – 1.7 (CI $[-3.27, -0.13]$ – $3.27, -0.13$], $p = 0.03$) points in the VAS scale and of -6.27 – 6.27 (CI $[-8.48, -4.07]$ – $8.48, -4.07$], $p < 0.01$) migraine episodes per month. Comorbid patients showed slightly better improvements in BDI, HIT6 scores and migraine frequency compared to monomorbid patients. The latter group manifested better results in MIDAS and VAS scores. Conclusion: Treatment with onabotulinumtoxinA leads to a significant reduction of disease severity of both chronic migraine and major depressive disorder in patients comorbid with both diseases. Comparative analyses suggest an equivalent strong effect in monomorbid and comorbid patients, with beneficial effects specifically seen for certain migraine features.

[Dopa responsive irritable bowel syndrome: restless bowel syndrome or a gastrointestinal variant of restless legs syndrome?](#)

Prakash S, Prakash A.

BMJ Case Rep. 2021 Mar 24;14(3):e240686. doi: 10.1136/bcr-2020-240686.

In addition to the legs, restless legs syndrome (RLS) affects various other parts of the body, including the arms, abdomen, face, head-neck, oral cavity, genital area and bladder. RLS is also associated with several comorbid conditions, including irritable bowel syndrome (IBS). We are reporting two cases of RLS who also had IBS, fulfilling the Rome IV criteria. The administration of levodopa and dopamine agonists provided a complete improvement in both IBS and RLS. Review of the literature suggest that the clinical semiology and clinical pattern

of IBS (urge to defecate, abdominal pain, abdominal distension, bloating, disturbed sleep and circadian rhythm) simulate the semiology and pattern of RLS. Similarities are also noted in the associated comorbid conditions, effective drugs and proposed hypotheses for both clinical syndromes. We hypothesise that RLS may affect intestine, and IBS-like symptoms in a subset of patients with RLS may be the part of RLS symptoms complex.

[Effect of comorbid migraine on propranolol efficacy for painful TMD in a randomized controlled trial.](#)

Tchivileva IE, Ohrbach R, Fillingim RB, Lim PF, Di Giosia M, Rebeiro-Dasilva M, Campbell JH, Hadgraft H, Willis J, Arbes Jr SJ, Slade GD.

Cephalalgia. 2021 Feb 9;333102421989268. doi: 10.1177/0333102421989268.

Introduction: The migraine-preventive drug propranolol is efficacious in reducing pain from temporomandibular disorder, suggesting potential modifying or mediating effects of comorbid migraine. Methods: In this randomized controlled trial, myofascial temporomandibular disorder patients were treated with propranolol or placebo for 9 weeks. The primary endpoint was change in a facial pain index derived from daily symptom diaries. Linear and logistic regression models tested for a migraine × treatment-group interaction in reducing facial pain index. Counterfactual models explored changes in headache impact and heart rate as mediators of propranolol's efficacy. Results: Propranolol's efficacy in reducing facial pain index was greater among the 104 migraineurs than the 95 non-migraineurs: For example, for the binary ≥ 30% reduction in facial pain index, odds ratios were 3.3 (95% confidence limits: 1.4, 8.1) versus 1.3 (0.5, 3.2), respectively, although the interaction was statistically non-significant ($p = 0.139$). Cumulative response curves confirmed greater efficacy for migraineurs than non-migraineurs (differences in area under the curve 26% and 6%, respectively; $p = 0.081$). While 9% of the treatment effect was mediated by reduced headache impact, 46% was mediated by reduced heart rate. Conclusions: Propranolol was more efficacious in reducing temporomandibular disorder pain among migraineurs than non-migraineurs, with more of the effect mediated by reduced heart rate than by reduced headache impact.

[Clinical manifestations of overactive bladder with migraine as a comorbidity: A prospective cross-sectional study.](#)

Baser A, Eliacik S, Baykam MM, Tan FU.

Int Neurourol J. 2020 Dec;24(4):375-381. doi: 10.5213/inj.2040186.093.

Purpose: The aim of this study was to investigate the clinical manifestations of overactive bladder (OAB) with migraine as a comorbidity and to shed light on possible new treatment strategies. Methods: This study included patients aged 18 years and older who were admitted to urology and neurology outpatient clinics between March 1, 2019 and March 1, 2020 for OAB and migraine. The study questionnaire contained 3 sections: (1) questions on demographic characteristics, (2) a migraine ID test, and (3) the Overactive Bladder Inquiry Form - V8 (OAB-V8) form. Results: A total of 265 patients participated in the study. The average age of the participants was 39.75 ± 11.93 years. The patients were divided into 3 groups according to the coexistence of OAB with migraine: group 1, OAB(+)/migraine(+); group 2, OAB(+)/migraine(-); and group 3, OAB(-)/migraine(+). The mean OAB-V8 score was 22.82 ± 8.15 in group 1 and 25.64 ± 7.49 in group 2. The mean OAB-V8 score of OAB patients with migraine as a comorbidity was statistically significantly lower than that of OAB patients without migraine ($P=0.015$). The median visual analogue scale (VAS) score was 7.11 (range, 2-10) in group 1 and 5.95 (range, 2-10) in group 3. This finding indicates that in patients with migraine, having OAB was associated with significantly higher VAS scores ($P<0.001$). Conclusion: OAB and migraine may be comorbid conditions coexisting in a single patient. This comorbidity may lead to a lower perception of OAB symptoms in OAB patients or, conversely, to a higher perception of migraine pain. Further studies are needed to elucidate how treatments for each of these diseases can affect the other disease.

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

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