CUTTING EDGE

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This e-newsletter - published the CPRA to keep the medical-scientific and patient communities abreast of research advances on Chronic Overlapping Pain Conditions (COPCs) - contains abstracts of studies on the epidemiology, pathophysiology and clinical management of COPCs published between May and July 2019. Prior issues are available on our website, http://www.cpralliance.org. To read the CPRA's White Paper, click here. Please direct any questions or comments to the CPRA's Director, Christin Veasley - cveasley@cpralliance.org. If you are not already on our mailing list would like to sign up to receive future issues of COPCs Research Advances, click here.

In this Issue...

FEATURED ARTICLES

Issues of comorbidity in clinical guidelines and systematic reviews from a rehabilitation perspective.
Meyer T, Wulff K.
Eur J Phys Rehabil Med. 2019 Jun;55(3):364-371. doi: 10.23736/S1973-9087.19.05786-1.

BACKGROUND: Systematic reviews have a major role for evidence-based care and found the basis of clinical guidelines. In rehabilitation, typical patients have co- or even multimorbidities, present in different patterns. The primary aim of this paper is to raise different conceptual and methodological issues regarding the role of comorbidity and multimorbidity in systematic reviews. Specifically, we aim to examine how issues of comorbidity and multimorbidity are addressed in clinical guidelines and systematic reviews with a special emphasis on rehabilitation care. METHODS: We use systematic reviews of interventions in unspecific low back pain (LBP) as a case in point, because of its importance to rehabilitation care and its known comorbidities. We searched the Cochrane Library for systematic reviews on LBP and identified the different ways of handling issues of co-/multimorbidity within these reviews. We also searched for

methodological studies related to co- and multimorbidities within guidelines. RESULTS: We identified 49 systematic reviews on LBP published between 2004 and 2017 and excluded 11 reviews for various reasons. In the remaining 38 reviews we found only scant evidence that comorbidities were considered. Comorbidities are entered in a systematic review, mostly on a superficial level, in terms of introducing LBP as a multifactorial disorder or disorders that are associated with LBP, as a target of an intervention, in the planning of the review in terms of planned subgroup analysis, as exclusion criteria within original studies or systematic reviews, as outcomes, and in the conclusion section as necessary target groups of the intervention (i.e. subgroups). CONCLUSIONS: There is a clear-cut need to address comorbidities both in systematic reviews and clinical guidelines. Systematic reviews should consider co-/multimorbidities in their exclusion/inclusion criteria, should extract data on comorbidities from the original studies, and address the topic of pre-specified subgroup analyses. However, the theoretical and empirical basis for the inclusion of comorbidities issues in systematic reviews has to be further developed both in epidemiological and clinical studies.

ICD-10 codes for the study of chronic overlapping pain conditions in administrative databases.
Schrepf A, Phan V, Clemens JQ, Maixner W, Hanauer D, Williams DA.
J Pain. 2019 May 30. pii: S1526-5900(18)31029-0. doi: 10.1016/j.jpain.2019.05.007.

Chronic Overlapping Pain Conditions (COPCs) are a set of painful chronic conditions characterized by high levels of co-occurrence. It has been hypothesized that COPCs co-occur in many cases because of common neurobiological vulnerabilities. In practice, most research on COPCs has focused upon a single index condition with little effort to assess comorbid painful conditions. This likely means that important phenotypic differences within a sample are obscured. The International Classification of Diseases (ICD) coding system contains many diagnostic classifications that may be applied to individual COPCs, but there is currently no agreed upon set of codes for identifying and studying each of the COPCs. Here we seek to address this issue through three related projects: a) we first compile a set of ICD-10 codes from expert panels for ten common COPCs, b) we then use natural language searches of medical records to validate the presence of COPCs in association with the proposed expert codes, c) finally, we apply the resulting codes to a large administrative medical database to derive estimates of overlap between the ten conditions as a demonstration project. The codes presented can facilitate administrative database research on COPCs. Perspective: This article presents a set of ICD-10 codes that researchers can use to explore the presence and overlap of Chronic Overlapping Pain Conditions (COPCs) in administrative databases. This may serve as a tool for estimating samples for research, exploring comorbidities and treatments for individual COPCs, and identifying mechanisms associated with their overlap.

An overview and proposed research framework for studying co-occurring mental- and physical-health dysfunction.
Hagerty SL, Ellingson JM, Helmuth TB, Bidwell LC, Hutchison KE, Bryan AD.
Perspect Psychol Sci. 2019 Jul;14(4):633-645. doi: 10.1177/1745691619827010.

Mental- and physical-health conditions co-occur at a rate much higher than chance. Of patients who have a mental-health condition, more than half also have a physical disease, and these cases are associated with increased human suffering and societal cost. Comorbidity research to date has focused on co-occurring mental- and physical-health disorders separately, and relatively little research has examined the co-occurrence of mental- and physical-health dysfunction. In addition, even less is known about why mental- and physical-health dysfunction co-occurs or how to treat these cases. Thus, the aims of this article are to highlight the need for research at the intersection of physical- and mental-health dysfunction and to provide guidance on how to research cases of comorbidity. Toward these ends, we begin by presenting a selective overview of the possible role of biological processes in the co-occurrence of physical- and mental-health dysfunction using specific illustrative examples. Specifically, we outline how biological processes within the immune system and gastrointestinal

system could underlie depression, irritable bowel syndrome, and their co-occurrence. We then advance and discuss a proposed research framework, including methodological and analytic guidance, that researchers could use when studying the phenomenon of co-occurring physical- and mental-health dysfunction.

NATIONAL MULTI-SITE STUDIES

Quantitative assessment of nonpelvic pressure pain sensitivity in urologic chronic pelvic pain syndrome: a MAPP Research Network study.
Harte SE, Schrepf A, Gallop R, Kruger GH, Lai HHH, Sutcliffe S, Halvorson M, Ichesco E, Naliboff BD, Afari N, Harris RE, Farrar JT, Tu F, Landis JR, Clauw DJ; MAPP Research Network.
Pain. 2019 Jun;160(6):1270-1280. doi: 10.1097/j.pain.0000000000001505.

Experimental pain sensitivity was assessed in individuals with urologic chronic pelvic pain syndrome (UCPPS) as part of the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network. A series of computer-controlled pressure stimuli were delivered to the thumbnail bed, an asymptomatic site distant from the area of UCPPS pain that is considered to be indicative of overall body pain threshold. Stimuli were rated according to a standardized magnitude estimation protocol. Pain sensitivity in participants with UCPPS was compared with healthy controls and a mixed pain group composed of individuals with other chronic overlapping pain conditions, including fibromyalgia, chronic fatigue, and irritable bowel syndromes. Data from 6 participating MAPP testing sites were pooled for analysis. Participants with UCPPS (n = 153) exhibited an intermediate pain sensitivity phenotype: they were less sensitive relative to the mixed pain group (n = 35) but significantly more sensitive than healthy controls (n = 100). Increased pain sensitivity in patients with UCPPS was associated with both higher levels of clinical pain severity and more painful body areas outside the pelvic region. Exploratory analyses in participants with UCPPS revealed that pain sensitivity increased during periods of urologic symptom flare and that less pressure pain sensitivity at baseline was associated with a greater likelihood of subsequent genitourinary pain improvement 1 year later. The finding that individuals with UCPPS demonstrate nonpelvic pain hypersensitivity that is related to clinical symptoms suggests that central nervous system mechanisms of pain amplification contribute to UCPPS.

PATHOPHYSIOLOGY STUDIES

Polymorphisms in COMT, ADRB2 and HTR1A genes are associated with temporomandibular disorders in individuals with other arthralgias.
Bonato LL, Quinelato V, de Felipe Cordeiro PC, Vieira AR, Granjeiro JM, Tesch R, Casado PL.
Cranio. 2019 Jul 2:1-11. doi: 10.1080/08869634.2019.1632406.

Objective: To evaluate the association between polymorphisms in genes and comorbid presence of arthralgias and TMD. Methods: This is a case-control study. The groups formed were individuals with chronic arthralgia and 1) myofascial pain (n = 42); 2) articular (n = 16); 3) multiple diagnoses (n = 69); 4) with TMD and without some other arthralgia (n = 16); 5) without TMD but with pain in other joints (n = 82); and 6) a control group (n = 72). SNPs in *COMT, ADRB2*, and *HTR1A* genes were investigated. Results: The CT genotype for the *COMT* (rs9332377) gene was associated with the absence of myofascial pain (p = .05). In the *ADRB2* (rs1042713) gene, the AA genotype was associated with the absence of myofascial pain (p = .03). Discussion: This study supports the hypothesis that alterations in the *COMT, ADRB2*, and *HTR1A* genes influence the presence of chronic pain and TMD.

Autonomic neurophysiologic implications of disorders comorbid with bladder pain

syndrome vs myofascial pelvic pain.
Chelimsky GG, Yang S, Sanses T, Tatsuoka C, Buffington CAT, Janata J, McCabe P, Dombroski MA, Ialacci S, Hijaz A, Mahajan S, Zolnoun D, Chelimsky TC.
Neurolurol Urodyn. 2019 Jun;38(5):1370-1377. doi: 10.1002/nau.23995.

AIMS: The neuropathophysiology of a debilitating chronic urologic pain condition, bladder pain syndrome (BPS), remains unknown. Our recent data suggests withdrawal of cardiovagal modulation in subjects with BPS, in contrast to sympathetic nervous system dysfunction in another chronic pelvic pain syndrome, myofascial pelvic pain (MPP). We evaluated whether comorbid disorders differentially associated with BPS vs MPP shed additional light on these autonomic differences. METHODS: We compared the presence and relative time of onset of 27 other medical conditions in women with BPS, MPP, both syndromes, and healthy subjects. Analysis included an adjustment for multiple comparisons. RESULTS: Among 107 female subjects (BPS alone = 32; BPS with MPP = 36; MPP alone = 9; healthy controls = 30), comorbidities differentially associated with BPS included irritable bowel syndrome (IBS), dyspepsia, and chronic nausea, whereas those associated with MPP included migraine headache and dyspepsia, consistent with the distinct autonomic neurophysiologic signatures of the two disorders. PTSD (earliest), anxiety, depression, migraine headache, fibromyalgia, chronic fatigue, and IBS usually preceded BPS or MPP. PTSD and the presence of both pelvic pain disorders in the same subject correlated with significantly increased comorbid burden. CONCLUSIONS: Our study suggests a distinct pattern of comorbid conditions in women with BPS. These findings further support our hypothesis of primary vagal defect in BPS as compared with primary sympathetic defect in MPP, suggesting a new model for chronic these pelvic pain syndromes. Chronologically, PTSD, migraine, dysmenorrhea, and IBS occurred early, supporting a role for PTSD or its trigger in the pathophysiology of chronic pelvic pain.

BDNF and serum S100B levels according the spectrum of structural pathology in chronic pain patients.
Stefani LC, Leite FM, da Graca L Tarrago M, Zanette SA, de Souza A, Castro SM, Caumo W.
Neurosci Lett. 2019 Jul 27;706:105-109. doi: 10.1016/j.neulet.2019.05.021.

Central sensitivity syndrome (CSS) consists of adaptive pathophysiological changes associated with neuroplasticity in some chronic pain disorders. It could be grouped in two main conceptual conditions: one includes those chronic pain patients without overt structural pathology such as fibromyalgia, and the other subgroup includes conditions with recognizable structural abnormalities, both somatic (osteoarthritis) and visceral (endometriosis). In order to understand the role of neuromodulators in CCS we aim to determine whether brain-derived neurotrophic factor (BDNF) and S100B are associated to specific chronic pain disorders. Serum BDNF and S100B were measured in chronic pain women with different diagnosis: 88 with osteoarthritis, 36 with endometriosis, 117 with fibromyalgia, 33 with chronic tension type headache and in 41 healthy controls. ANCOVA analysis followed by heteroscedasticity-consistent covariance matrix was performed to evaluate BDNF and S100B levels, adjusted for depression severity, pain levels and use of analgesics according different pathologies. Serum BDNF concentrations were higher and not different in patients with fibromyalgia and headache, the CSS group without structural pathology. In contrast, the concentrations of S100B were higher in patients with osteoarthritis and endometriosis, in comparison to controls, fibromyalgia and tensional headache patients. This study supports the hypothesis that BDNF and S100B neuromodulators present different serum levels according to the background disease associated to the chronic pain. These have the potential to be studied as markers of active disease or treatment evolution.

Altered microbiome composition in individuals with fibromyalgia.
Minerbi A, Gonzalez E, Brereton NJB, Anjarkouchian A, Dewar K, Fitzcharles MA, Chevalier S, Shir Y.
Pain. 2019 Jun 18. doi: 10.1097/j.pain.0000000000001640.

Fibromyalgia (FM) is a prevalent syndrome, characterised by chronic widespread pain, fatigue and impaired sleep, that is challenging to diagnose and difficult to treat. The microbiomes of 77 women with FM and that of 79 control participants were compared using 16S rRNA gene amplification and whole genome sequencing. When comparing FM patients to unrelated controls using differential abundance analysis, significant differences were revealed in several bacterial taxa. Variance in the composition of the microbiomes was explained by FM-related variables more than by any other innate or environmental variable and correlated with clinical indices of FM. In line with observed alteration in butyrate metabolising species, targeted serum metabolite analysis verified differences in the serum levels of butyrate and propionate in FM patients. Using machine learning algorithms, the microbiome composition alone allowed for the classification of patients and controls (ROC AUC 87.8%). To the best of our knowledge, this is the first demonstration of gut microbiome alteration in non-visceral pain. This observation paves the way for further studies, elucidating the pathophysiology of FM, developing diagnostic aids and possibly allowing for new treatment modalities to be explored.

Possible molecular mediators involved and mechanistic insight into fibromyalgia and associated co-morbidities.
Singh L, Kaur A, Bhatti MS, Bhatti R.
Neurochem Res. 2019 Jul;44(7):1517-1532. doi: 10.1007/s11064-019-02805-5.

Fibromyalgia is a chronic complex syndrome of non-articulate origin characterized by musculoskeletal pain, painful tender points, sleep problems and co-morbidities including depression, migraine. The etiopathogenesis of fibromyalgia is complex, variable and remains inconclusive. The etiological factors that have been defined include stress, genetic predisposition and environmental components. As per the reports of the American College of Rheumatology (ACR) the prevalence of fibromyalgia varies from 2 to 22% among the general population with poor diagnostic features primarily pain. Fibromyalgia encompasses a spectrum of co-morbid conditions with multifarious pathogenesis. The highly prevalent manifestations of fibromyalgia include heterogeneous pain and aches. Biochemical and neurobiological elements of fibromyalgia include neurotransmitters, hypothalamic pituitary adrenal axis (HPA axis), inflammatory cytokines, monoaminergic pathway, opioid peptides, sex hormones, nerve growth factor (NGF) and local free radical insult. An imbalance in the serotonergic system is the major underlying etiological factor that has been explored most widely. Owing to complex interplay of diverse pathophysiological pathways, overlapping co-morbidities such as depression have been clinically observed. Therapeutic management of fibromyalgia involves both non pharmacological and pharmacological measures. The current review presents various dysregulations and their association with symptoms of fibromyalgia along with their underlying neurobiological aspects.

The neuroinflammatory component of negative affect in patients with chronic pain.
Albrecht DS, Kim M, Akeju O, Torrado-Carvajal A, Edwards RR, Zhang Y, Bergan C, Protsenko E, Kucyi A, Wasan AD, Hooker JM, Napadow V, Loggia ML.
Mol Psychiatry. 2019 May 28. doi: 10.1038/s41380-019-0433-1.

Negative affect (NA) is a significant cause of disability for chronic pain patients. While little is known about the mechanism underlying pain-comorbid NA, previous studies have implicated neuroinflammation in the pathophysiology of both depression and chronic pain. Here, we tested the hypothesis that NA in pain patients is linked to elevations in the brain levels of the glial marker kDa translocator protein (TSPO), and changes in functional connectivity. 25 cLBP patients (42.4 +/- 13 years old; 13F, 12M) with chronic low back pain (cLBP) and 27 healthy control subjects (48.9 +/- 13 years old; 14F, 13M) received an integrated (i.e., simultaneous) positron emission tomography (PET)/magnetic resonance imaging (MRI) brain scan with the second-generation TSPO ligand [^{11}C]PBR28. The relationship between [^{11}C]PBR28 signal and NA was assessed first with regression analyses against Beck Depression Inventory (BDI) scores in patients, and then by comparing cLBP patients with little-to-no, or mild-to-moderate depression against healthy controls. Further, the relationship between PET signal, BDI

and frontolimbic functional connectivity was evaluated in patients with mediation models. PET signal was positively associated with BDI scores in patients, and significantly elevated in patients with mild-to-moderate (but not low) depression compared with controls, in anterior middle and pregenual anterior cingulate cortices (aMCC, pgACC). In the pgACC, PET signal was also associated with this region's functional connectivity to the dorsolateral PFC (pgACC-dlPFC), and mediated of the association between pgACC-dlPFC connectivity and BDI. These observations support a role for glial activation in pain-comorbid NA, identifying in neuroinflammation a potential therapeutic target for this condition.

Anxiety and depression in irritable bowel syndrome: Exploring the interaction with other symptoms and pathophysiology using multivariate analyses.
Midenfjord I, Polster A, Sjovall H, Tornblom H, Simren M.
Neurogastroenterol Motil. 2019 May 5:e13619. doi: 10.1111/nmo.13619.

BACKGROUND: Anxiety or depression, in other words, psychological distress, are common comorbidities in patients with irritable bowel syndrome (IBS), but their interaction with pathophysiological factors and other symptoms are unclear. METHODS: Patients with IBS (Rome III criteria), thoroughly characterized regarding pathophysiology (colonic transit time, visceral sensitivity, and autonomic nervous system [ANS] function), symptom profile (IBS severity, somatic symptoms, gastrointestinal [GI]-specific anxiety and fatigue), and quality of life, were explored for differences regarding pathophysiology and symptoms between patients with and without reported psychological distress in univariate and multivariate analyses (Principal Component Analysis [PCA] with Hotelling's T^2 and Orthogonal Partial Least Squares-Discriminant Analysis [OPLS-DA]). KEY RESULTS: When using Hospital Anxiety and Depression Scale score ≥8 as cut-off score, including both borderline and clinically significant cases, 345 (44.9%) out of 769 IBS patients reported anxiety, and 198 (25.7%) depression. In univariate analyses, patients reporting psychological distress demonstrated more severe GI and non-GI symptoms, fatigue, GI-specific anxiety and lower quality of life, and differences for some pathophysiological measures. IBS patients with and without reported psychological distress showed significant differences between the multivariate means in symptom reporting (PCA; both $P < 0.001$), and in pathophysiological measures in patients with and without anxiety ($P = 0.018$). Visceral hypersensitivity, altered ANS function, more severe GI-specific anxiety, fatigue, and higher somatic non-GI symptoms were the factors that most strongly separated patients with and without psychological distress (OPLS-DA). CONCLUSIONS AND INFERENCES: Reported anxiety and depression are common in IBS patients, and our study demonstrates that they are interwoven in the complex pathophysiological and clinical picture of IBS.

Partners in crime: NGF and BDNF in visceral dysfunction.
Coelho A, Oliveira R, Antunes-Lopes, Cruz CD.
Curr Neuropharmacol. 2019 Jun 16. doi: 10.2174/1570159X17666190617095844.

Neurotrophins (NTs), particularly Nerve Growth Factor (NGF) and Brain Derived Neurotrophic Factor (BDNF), have attracted increasing attention in the context of visceral function for some years. Here, we examined current literature and produced a thorough review on the subject. After initial studies linking NGF to cystitis, it is now well-established that this neurotrophin (NT) is a key modulator of bladder pathologies, including Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) and Chronic Prostatitis / Chronic Pelvic Pain Syndrome (CP/CPPS). NGF is upregulated in bladder tissue and its blockade results in major improvements on urodynamic parameters and pain. Further studies expanded showed that NGF is also an intervenient in other visceral dysfunctions such as endometriosis and Irritable Bowel Syndrome (IBS). More recently, BDNF was also shown to play an important role in the same visceral dysfunctions, suggesting that both NTs are determinant factors in visceral pathophysiological mechanisms. While manipulation of NGF and BDNF improves visceral function and reduce pain, suggesting that clinical modulation of these NTs may be important, much is still to be investigated before this step is taken. Another active area of research is centered on urinary NGF and BDNF. Several studies show that both NTs can be found in the urine of patients with

visceral dysfunction in much higher concentration than in healthy individuals, suggesting they could be used as potential biomarkers. However, there are still technical difficulties to be overcome, including the lack of a large multicentre placebo controlled studies to prove the relevance of urinary NTs as clinical biomarkers.

Pathophysiology of interstitial cystitis.
Birder LA.
Int J Urol. 2019 Jun;26 Suppl 1:12-15. doi: 10.1111/iju.13985.

Interstitial cystitis/bladder pain syndrome is a chronic pain syndrome whose causes remains elusive with no generally accepted treatment. A hallmark of functional pain syndromes such as interstitial cystitis/bladder pain syndrome is pain in the absence of demonstrable pathology of the viscera or associated nerves. Patients with chronic pain experience a greater impairment in quality of life than healthy controls. In addition, interstitial cystitis/bladder pain syndrome symptoms can frequently overlap with other conditions including irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, anxiety disorders, and a number of other syndromes not directly related to the urinary bladder. Because of the complex pathophysiology, a number of animal models have been studied over the years to better understand mechanisms underlying patient symptoms. These models can include: bladder centric, complex mechanisms and psychological and physical stress models. Such animal models can aid in the investigation of aspects of interstitial cystitis/bladder pain syndrome that cannot be pursued in humans as well as to develop and test potential therapies. In addition, the search for urinary factors that may be a cause of interstitial cystitis/bladder pain syndrome has resulted in the discovery of a number of potential targets that could serve as predictive biomarkers which can aid in early diagnosis and treatment of this chronic disorder.

Shared microglial mechanisms underpinning depression and chronic fatigue syndrome and their comorbidities.
Chaves-Filho AJM, Macedo DS, de Lucena DF, Maes M.
Behav Brain Res. 2019 May 25;372:111975. doi: 10.1016/j.bbr.2019.111975.

In 2011, it was reviewed that a) there is a strong co-occurrence between major depression and chronic fatigue syndrome (CFS), with fatigue and physio-somatic symptoms being key symptoms of depression, and depressive symptoms appearing during the course of CFS; and b) the comorbidity between both disorders may in part be explained by activated immune-inflammatory pathways, including increased translocation of Gram-negative bacteria and increased levels of pro-inflammatory cytokines, such as interleukin (IL)-1. Nevertheless, the possible involvement of activated microglia in this comorbidity has remained unclear. This paper aims to review microglial disturbances in major depression, CFS and their comorbidity. A comprehensive literature search was conducted using the PubMed / MEDLINE database to identify studies, which are relevant to this current review. Depressed patients present neuroinflammatory alterations, probably related to microglial activation, while animal models show that a microglial response to immune challenges including lipopolysaccharides is accompanied by depressive-like behaviors. Recent evidence from preclinical studies indicates that activated microglia have a key role in the onset of fatigue. In chronic inflammatory conditions, such as infections and senescence, microglia orchestrate an inflammatory microenvironment thereby causing fatigue. In conclusion, based on our review we may posit that shared immune-inflammatory pathways and especially activated microglia underpin comorbid depression and CFS. As such, microglial activation and neuro-inflammation may be promising targets to treat the overlapping manifestations of both depression and CFS.

The exploration of mechanisms of comorbidity between migraine and depression.
Zhang Q, Shao A, Jiang Z, Tsai H, Liu W.
J Cell Mol Med. 2019 Jul;23(7):4505-4513. doi: 10.1111/jcmm.14390.

Migraine comorbid with depression is common and is often encountered in clinical

practice. The comorbidity may lead to more serious conditions with other symptoms and a longer duration of treatment and it may impose heavy economic and social burdens, directly or indirectly, on patients and their families. Numerous studies have been published on the association of migraine with depression. Numerous literature have showed that the comorbidity may have a common complicated pathogenic mechanism involving biopsychosocial characteristics, including abnormal brain development and shared genetic basis, as well as neurotransmitters, sex hormones and stress. In addition, some studies have identified the multiple, bidirectional relationship between migraine and depressive disorder. We searched the literature for the possible common mechanisms between migraine and depression and classified the research results.

Gender differences in the association of brain gray matter and pain-related psychosocial characteristics.
Malfliet A, De Pauw R, Kregel J, Coppieters I, Meeus M, Roussel N, Danneels L, Cagnie B, Nijs J.
Pain Physician. 2019 May;22(3):E191-E203

BACKGROUND: Although the association of gray matter morphology alterations and pain-related psychosocial characteristics with pain intensity and chronification in people with chronic spinal pain is evident, research on their mutual interaction is scarce and does not account for possible gender differences. Gender-based differences are, however, of utmost importance to consider when examining pain neurobiology. OBJECTIVES: To look for gender differences in the association between magnetic resonance imaging- (MRI) derived brain gray matter morphology and self-reported psychosocial characteristics. STUDY DESIGN: An explorative, observational study. SETTING: University Hospitals Ghent and Brussels, Belgium. METHODS: Brain gray matter morphology (using MRI) and self-reported psychosocial characteristics were examined in women and men with nonspecific chronic spinal pain. Statistical analyses were performed in SPSS and R to identify differences between men and women regarding brain gray matter, self-reported psychosocial characteristics, as well as gender differences in the association between those outcome measures. RESULTS: A total of 94 people with chronic spinal pain were studied, including 32 men (15 suffering from neck pain, 17 suffering from low back pain; demographics [mean ± SD] age: 45.00 ± 12.02 years; pain duration: 128.37 ± 110.45 months), and 62 women (36 suffering from neck pain, 26 suffering from low back pain; demographics [mean ± SD] age: 38.78 ± 12.69 years; pain duration: 114.27 ± 92.45 months). Woman showed larger (positive) associations of several central brain areas (paracentral, precentral, postcentral, etc.) with perceived consequences ($p<0.001$), emotional representations ($p<0.001$), chronicity ($p<0.001$), and pain catastrophizing ($p<0.001$). Men showed larger (both positive and negative) associations of the precuneus cortex, the precentral gyrus, and the insula with perceived personal control ($P < 0.001$) and kinesiophobia ($P < 0.001$). LIMITATIONS: Other factors, such as menstrual cycle and medication can have a certain influence, and were only partly taken into consideration in the present investigation to obtain sufficient power. Another limitation is the observational study design, which hampers the possibility to look for causal or temporal interactions. CONCLUSIONS: Gray matter morphology relates differently to psychosocial characteristics in women and men. These explorative findings provide ideas for further research to investigate if targeting perceived negative consequences of the illness, perceived emotional representations, perceived chronicity, and pain catastrophizing in women, and perceived personal control of the illness and kinesiophobia in men, could contribute to the normalization of brain alterations in people with nonspecific chronic spinal pain.

Cardiovascular responses of women with fibromyalgia to a laboratory stressor: Does post-traumatic stress disorder comorbidity matter?
Gonzalez JL, Alonso-Fernandez M, Matias-Pompa B, Carretero I, Nieto-Bona MP, Lopez-Lopez A.
Pain Med. 2019 May 1;20(5):988-999. doi: 10.1093/pm/pny210.

OBJECTIVES: This study compared cardiovascular responses to a laboratory trauma-unrelated stressor of two groups of women diagnosed with fibromyalgia (FM), one of

them with comorbid post-traumatic stress disorder (PTSD), with a group of healthy controls in order to detect the possible existence of differences linked to comorbidity. DESIGN: Case-controls. METHODS: Eighteen women diagnosed with FM and comorbid PTSD, 18 women diagnosed with FM and no PTSD, and 38 healthy women were exposed to an arithmetic task with harassment while blood pressure and heart rate were measured during task exposure and recovery. RESULTS: Although heart rate response evidenced a general blunted reactivity for both groups of FM patients, only those with comorbid PTSD presented lower levels of reactivity in terms of their systolic blood pressure response. In addition, systolic blood pressure response was sensitive to the presence of depression in both groups of FM patients and controls. Finally, although both groups of FM patients showed significantly slower rates of recovery, their final recovery state was not worse after twelve minutes of recording. CONCLUSIONS: Results of this study point to comorbid PTSD as a significant contributor to the blunted cardiovascular reactivity observed in FM patients, which may be dependent to a great extent on depressive symptomatology. As some degree of cardiovascular response to stress is functional in that it mobilizes energy and triggers the necessary compensatory mechanisms to manage stressors, this study supports the well-recognized clinical strategies of detection and treatment of PTSD and concomitant depression in the management of FM.

Sex differences and the role of ovarian hormones in site-specific nociception of SHR rats.
Maitan Santos B, Nascimento GC, Capel CP, Borges GS, Rosolen T, Sabino JPJ, Leite-Panissi CRA, Branco LGS.
Am J Physiol Regul Integr Comp Physiol. 2019 May 15. doi: 10.1152/ajpregu.00390.2018.

The accurate diagnosis and treatment of pain is dependent upon the knowledge of variables that might alter this response. Some of these variables are the locality of the noxious stimulus, the sex of the individual, and the presence of chronic diseases. Among these chronic diseases, hypertension is considered a serious and silent disease that has been associated with hypoalgesia. The main goal of this study was to evaluate the potential nociceptive differences in spontaneously hypertensive rats (SHR) regarding the locality of the stimulus, *i.e.,* the temporomandibular joint or paw, the sex, and the role of ovarian hormones in a model of mechanical nociception (Von Frey test) or formalin-induced inflammatory nociception. Our results indicate that SHR has lower orofacial mechanical nociception beyond the lower mechanical nociception in the paw compared to WKY rats. In a model of formalin-induced inflammatory nociception, SHR also has a decreased nociception compared to normotensive rats. We also sought to evaluate the influence of sex and ovarian hormones on orofacial mechanical nociception in SHR. We observed that female SHR has higher mechanical nociception than male SHR only in the paw, but it has higher formalin-induced orofacial nociception than male SHR. Moreover, the absence of ovarian hormones caused an increase in mean arterial pressure and a decrease in paw nociception in female SHR.

Sex differences in central nervous system plasticity and pain in experimental autoimmune encephalomyelitis.
Catuneanu A, Paylor JW, Winship I, Colbourne F, Kerr BJ.
Pain. 2019 May;160(5):1037-1049. doi: 10.1097/j.pain.0000000000001483.

Multiple sclerosis (MS) is a neurodegenerative autoimmune disease with many known structural and functional changes in the central nervous system. A well-recognized, but poorly understood, complication of MS is chronic pain. Little is known regarding the influence of sex on the development and maintenance of MS-related pain. This is important to consider, as MS is a predominantly female disease. Using the experimental autoimmune encephalomyelitis (EAE) mouse model of MS, we demonstrate sex differences in measures of spinal cord inflammation and plasticity that accompany tactile hypersensitivity. Although we observed substantial inflammatory activity in both sexes, only male EAE mice exhibit robust staining of axonal injury markers and increased dendritic arborisation in morphology of deep dorsal horn neurons. We propose that tactile hypersensitivity in female EAE mice may be more immune-driven,whereas pain in male

mice with EAE may rely more heavily on neurodegenerative and plasticity-related mechanisms. Morphological and inflammatory differences in the spinal cord associated with pain early in EAE progression supports the idea of differentially regulated pain pathways between the sexes. Results from this study may indicate future sex-specific targets that are worth investigating for their functional role in pain circuitry.

EPIDEMIOLOGY STUDIES

Presurgical comorbidities as risk factors for chronic postsurgical pain following total knee replacement.
Skrejborg P, Petersen KK, Kold S, Kappel A, Pedersen C, Ostgaard SE, Simonsen O, Arendt-Nielsen L.
Clin J Pain. 2019 Jul;35(7):577-582. doi: 10.1097/AJP.0000000000000714.

OBJECTIVES: Chronic postsurgical knee pain (CPSP) is a burden for ~20% of the patients following total knee replacement (TKR). Presurgical pain intensities have consistently been found associated with CPSP, and it is suggested that comorbidities are likewise important for the development of CPSP. This study aimed to identify presurgical risk factors for the development of CPSP 5 years after TKR on the basis of medical records containing information with regard to comorbidities. MATERIALS AND METHODS: Patients undergoing primary TKR surgery were contacted 5 years after TKR. Presurgical Knee Society Score and comorbidities were evaluated. Postsurgical knee pain at 5 years of follow-up was assessed on a Numeric Rating Scale (NRS, 0 to 10). Logistic regression models were utilized to identify patients with moderate-to-severe (NRS≥3) and mild-to-no (NRS<3) CPSP at 5-year follow-up. Odds ratio (OR) for significant factors was calculated. RESULTS: A total of 604 patients were contacted, 493 patients responded, 352 patients provided a completed questionnaire. A total of 107 patients reported NRS≥3 at follow-up. Significant presurgical factors associated with CPSP were fibromyalgia (OR=20.66; P=0.024), chronic pain in body parts other than the knee (OR=6.70; P=0.033), previous diagnosis of cancer (OR=3.06; P=0.001), knee instability (OR=2.16; P=0.021), younger age (OR=2.15; P=0.007), and presurgical knee pain (OR=1.61; P=0.044). Regression analysis identified 36 of 107 (33.6%) patients with CPSP on the basis of presurgical factors, and 231 patients (94.3%) without CPSP were classified correctly. DISCUSSION: The current study found that a variety of presurgical clinical factors can correctly classify 33.6% of patients at risk for developing CPSP 5 years following TKR.

Widespread pain and central sensitization in adolescents with signs of painful temporomandibular disorders.
Campi LB, Visscher CM, Ongaro PCJ, do Vale Braido GV, Fernandes G, Goncalves DAG.
J Oral Facial Pain Headache. 2019 Jun 24. doi: 10.11607/ofph.2288.

AIMS: To investigate the associations between signs of painful temporomandibular disorders (TMD) and number of tender points (TPs) and fibromyalgia in adolescents, as well as the relationship between TPs and pressure-pain threshold (PPT) in individuals presenting with local, regional, or widespread pain as a way to investigate the presence of central sensitization (CS). METHODS: The sample consisted of 690 Brazilian adolescents with and without signs of painful TMD, aged 12 to 14 years old. Painful TMD was classified according to the Research Diagnostic Criteria for TMD (RDC/TMD) Axis I. The criteria established by Yunus were applied to assess juvenile fibromyalgia and TPs. Mann-Whitney and chi-square tests were applied to test the associations between signs of painful TMD and demographic variables. Regression models were used to estimate the association between signs of painful TMD and number of TPs and to determine which additional predictive variables were associated with TPs. Regression analyses were performed to test the associations between PPT values and number of TPs. Fisher test was used to estimate the association between signs of painful TMD and FM. RESULTS: Significant associations between signs of painful TMD and the number of TPs ($P < .001$), as well as between TPs and the PPT values for local, regional, and

widespread pain (P < .001), were found. No association between signs of painful TMD and fibromyalgia was found (P = .158). CONCLUSION: Individuals with signs of painful TMD presented with more TPs compared to pain-free adolescents. Moreover, the higher the number of TPs, the lower the PPT. This finding suggests that adolescents with signs of painful TMD are at increased risk of presenting with CS.

Association between temporomandibular disorders pain and migraine: Results of the Health 2000 survey.
Ashraf J, Zaproudina N, Suominen AL, Sipila K, Narhi M, Saxlin T.
J Oral Facial Pain Headache. 2019 Jun 24. doi: 10.11607/ofph.2213.

AIMS: To study the possible associations of various clinically assessed painful signs of temporomandibular disorders (TMD) with the presence of migraine using a large population-based dataset. METHODS: The data were taken from the nationally representative Health 2000 Survey (BRIF8901). The sample consisted of 5,876 adults (age range 30 to 97 years, mean ± standard deviation 52.5 ± 14.8), 5,378 nonmigraineurs and 498 migraineurs. The study participants answered questions concerning migraine presence, migraine frequency, and migraine medication consumption during a home interview. They also underwent a clinical TMD examination. RESULTS: Based on the multivariate regression models, painful muscular TMD, but not joint-related TMD, was associated with the presence of migraine (odds ratio [OR] = 1.58; 95% confidence interval [CI] = 1.23 to 2.04; P < .01). Migraine with TMD was associated with increased migraine frequency (daily or a few attacks within a week) (OR = 1.93; 95% CI = 1.27 to 2.93; P < .01) and higher migraine medication consumption (OR = 2.37; 95% CI = 1.43 to 3.92; P < .01). CONCLUSION: According to the results of this study, muscle-related TMD pain is associated with the presence of migraine. Additionally, migraine along with painful TMD signs is associated with increased migraine frequency and migraine medication consumption.

Prevalence of function-dependent temporomandibular joint and masticatory muscle pain, and predictors of temporomandibular disorders among patients with lyme disease.
Osiewicz M, Manfredini D, Biesiada G, Czepiel J, Garlicki A, Aarab G, Pytko-Poloncyzk J, Lobbezoo F.
J Clin Med. 2019 Jun 28;8(7). pii: E929. doi: 10.3390/jcm8070929.

The aim was to determine the occurrence of temporomandibular disorders (TMDs) in patients with Lyme disease (LD), and to estimate the contribution of factors that may identify TMD among LD patients. In seventy-six (*N* = 76) adult patients with LD (mean age 57.6 ± 14.6 years) and 54 healthy non-Lyme volunteers with a mean age of 56.4 ± 13.5 years, possible function (i.e., non-pain) diagnoses were established using the Research Diagnostic Criteria of Temporomandibular Disorders (RDC/TMD). Pain diagnoses were established by means of the function-dependent dynamic and static tests. The two groups did not significantly differ in the frequency of disc displacements diagnoses and function-dependent pain diagnoses. LD showed a significantly higher frequency ($p < 0.001$) of osteoarthrosis than the control group. For the prediction of pain diagnoses in LD patients, the single regression analyses pointed out an association with age, sleep bruxism (SB), and awake bruxism (AB). Two predictors (i.e., SB ($p = 0.002$) and AB ($p = 0.017$)) were statistically significant in the final multiple variable model. The frequency of TMD in patients with LD based on function-dependent tests was not significantly different from that in the control group. This investigation suggests that the contribution of bruxism to the differentiation between patients with Lyme and TMD is high.

Evaluation of orofacial and general pain location in patients with temporomandibular joint disorder-myofascial pain with referral.
Kuc J, Szarejko KD, Sierpinska T.
Front Neurol. 2019 May 29;10:546. doi: 10.3389/fneur.2019.00546. eCollection 2019.

Introduction: Pain is an emotional experience. As a subjective feeling, it is associated with pathophysiological processes occurring in the central nervous system, which in turn

may negatively affect the psychophysical function, cognitive abilities, level of functioning and quality of life. The Aim: The aim of the study was to assess orofacial and general pain location in patients with temporomandibular joint disorder-myofascial pain with referral. Materials and Methods: The study group consisted of 50 randomly selected, generally healthy people with complete natural dentition (37 women and 13 men) at the age of 23.36 ± 2.14 years, referred to the Department of Prosthodontics of the Medical University. All patients underwent clinical examination according to the Diagnostic Criteria for Temporomandibular Disorders (Axes I and II). The subjects were classified as people with myofascial pain with referral. The evaluation of severity of temporomandibular disorders was based on the Temporomandibular Disorder Pain Screener and the Graded Chronic Pain Scale. In order to assess orofacial and general pain location, a body chart drawing of pain was used. Results: The study group indicated 40 different areas of the body affected by pain. 2-3 isolated pain locations were declared by a total of six subjects. One person identified 17 affected areas. Forty four people reported pain in at least four regions of the body. 70% of patients suffered from pain within the right masseter muscle. Pain of the left masseter muscle was noted in 68% of cases. Cervical ailments were reported by 56% of people. Pain of the left temporomandibular joint was observed in 68% of patients, and of the right one in 54%. Conclusion: The patients with myofascial pain with referral suffer from general ailments in different regions of the body. Only the frequency of pain in the right masseter muscle and right temporomandibular joint differed with respect to gender. The suggestion that the prevalence of pain in other areas of the body varies between men and women has not been confirmed. Due to a small sample size, such differences cannot be excluded. Further studies in this area are needed.

Trigeminal autonomic cephalalgias presenting in a multidisciplinary tertiary orofacial pain clinic.
Wei DY, Moreno-Ajona D, Renton T, Goadsby PJ.
J Headache Pain. 2019 Jun 11;20(1):69. doi: 10.1186/s10194-019-1019-7.

Orofacial pain may have a variety of causes and offers a significant clinical challenge for its diagnosis and management. OBJECTIVE: To assess the headache disorders presenting in a tertiary multidisciplinary orofacial pain clinic, after dental causes have been excluded. METHODS: Clinic letters from the initial consultation and subsequent follow up reviews of the 142 patients, who were seen in the tertiary Multidisciplinary Orofacial Pain clinic between January 2015 until January 2018 were reviewed as a clinical audit. RESULTS: The most common diagnoses were possible trigeminal autonomic cephalalgia (n=62, 44%, migraine (n=38, 27%) and painful post-traumatic trigeminal neuropathy (n=17, 12%). The most common trigeminal autonomic cephalalgia diagnosis was hemicrania continua (n=13, 9%), which is higher than the reported prevalence in neurology and headache clinics. CONCLUSION: This study demonstrates the importance of a multidisciplinary approach to diagnosing complex orofacial pain patients and the importance of awareness of primary headache disorders, in particular trigeminal autonomic cephalalgias, thereby reducing unnecessary diagnostic delays or procedures.

Study on the prevalence and factors associated to vulvodynia in Spain.
Gomez I, Coronado PJ, Martin CM, Alonso R, Guisasola-Campa FJ.
Eur J Obstet Gynecol Reprod Biol. 2019 Jun 21;240:121-124. doi: 10.1016/j.ejogrb.2019.06.005.

OBJECTIVE: To study the prevalence and epidemiological characteristics of women with vulvodynia. To assess the risk factors associated to the disease. STUDY DESIGN: A cross-sectional study was made in which questionnaires were anonymously and confidentially distributed to Spanish women over 18 years of age between April 2016 and September 2017. The questionnaires were distributed by e-mail and through social networks, women's associations and specific websites. This type of questionnaire has been validated and used in many studies of this kind. The women answered questions referred to epidemiological aspects, demographic parameters, medical history, the presence of vulvodynia, associated factors, and comorbidities. RESULTS: A total of 684

questionnaires were completed. The prevalence of vulvodynia was 6.6% (45 women). Thirteen percent (95 women) had experienced vulvodynia at some point in life. The factors associated to vulvodynia were prior vaginal deliveries (p=0.001), vulvovaginal candidiasis (p<0.001) and urinary tract infections (p<0.001). Other pain syndromes such as fibromyalgia (p=0.012), painful bladder syndrome/interstitial syndrome (p<0.001), temporomandibular joint pain (p=0.021), coxofemoral pain (p=0.001) or headache (p=0.001) have also been associated to vulvodynia. CONCLUSIONS: The prevalence of vulvodynia in Spain is similar to that found in other countries. Many factors are involved in its development and persistence, particularly the presence of other pain syndromes and recurrent infections that could trigger complex inflammatory reactions.

A diagnosis of rheumatoid arthritis, endometriosis or IBD is associated with later onset of fibromyalgia and chronic widespread pain.
Larrosa Prado F, Bondesson E, Schelin MEC, Joud A.
Eur J Pain. 2019 May 27. doi: 10.1002/ejp.1432.

BACKGROUND: Widespread pain is a common comorbidity in several chronic diseases and is suspected to be caused by pain resulting from the underlying disease that has provoked a state of central sensitization. However, this argument is currently limited by evidence that has insufficiently captured the temporal nature of the relationship between diagnosis of the underlying disease and onset of widespread pain. The aim of this study was to investigate if patients with rheumatoid arthritis (RA), endometriosis or inflammatory bowel disease (IBD), have a higher risk of developing widespread pain (fibromyalgia or chronic widespread pain [CWP]). METHODS: Using the Swedish Skåne Healthcare register on health care consultation, a cohort of 889,938 adult patients were followed from 2007 to 2016 and incident cases of RA, endometriosis or IBD and of fibromyalgia and CWP were identified by registered diagnoses. Using Poisson regression, we calculated incidence rate ratios (IRR) adjusted for sex, age, education and propensity to seek health care. RESULTS: For patients with RA the IRR for later fibromyalgia was 3.64 (95% CI: 2.75-4.81) compared to patients without RA, for CWP it was 2.96 (95% CI: 1.81-4.86). For endometriosis patients the IRR for fibromyalgia was 2.83 (95% CI: 1.96-4.08) and for CWP 5.02 (95% CI: 3.10-8.13). IBD patients had an IRR = 2.32 (95% CI: 1.58-3.42) for fibromyalgia and 1.42 (95% CI: 0.93-2.17) for CWP. CONCLUSIONS: This study shows that RA, endometriosis and IBD are all risk factors for later fibromyalgia and CWP, consistent with a hypothesis of central sensitization as an effect of a painful underlying condition. SIGNIFICANCE: We show that RA, endometriosis and IBD predisposes for later fibromyalgia and CWP, a common hypothesis previously difficult to verify due to lack of longitudinal data. The results inform further research regarding the aetiology of fibromyalgia and CWP and stress the need of clinical focus on the pain itself in chronic diseases with pain as a symptom.

Insomnia increases symptom severity and health care utilization in patients with fibromyalgia: A population-based study.
Huang CJ, Huang CL, Fan YC, Chen TY, Tsai PS.
Clin J Pain. 2019 Jul 1. doi: 10.1097/AJP.0000000000000738.

OBJECTIVE: This study aimed to determine whether comorbid insomnia is associated with increased use of fibromyalgia-related medications and health resources in fibromyalgia patients. METHODS: We analyzed data retrieved from the Longitudinal Health Insurance Database 2010, which contains claims data of 1 million beneficiaries randomly selected from Taiwan's National Health Insurance program. Patients treated for fibromyalgia (n=17, 920) on two separate visits between 2000 and 2001 were selected and subsequently divided into two groups: patients with and without comorbid insomnia (n=5466 and 12, 454, respectively). Insomnia was identified through diagnosis on two separate visits after the index fibromyalgia date. Fibromyalgia-related pharmacotherapies and ambulatory care visits were tracked from the index date to the end of 2013. RESULTS: Insomnia was associated with increased likelihood of future use of antidepressants (adjusted odds ratio (OR)=3.84, P<0.001), gabapentin (adjusted OR=1.67, P<0.001), pregabalin (adjusted OR=1.79, P=0.046), muscle relaxants (adjusted OR=3.05, P<0.001), and opioids and tramadol (adjusted OR=1.59, P<0.001)

among fibromyalgia patients compared with fibromyalgia patients without insomnia. In addition, a diagnosis of insomnia was associated with an increased frequency of visits to ambulatory care services for both fibromyalgia (β=1.79, 95% CI=1.57-2.02, P<0.001) and other conditions (β=108.51, 95% CI=103.14-113.89, P<0.001). DISCUSSION: This study demonstrates the substantial burden of comorbid insomnia in patients with fibromyalgia.

Healthcare utilization in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): Analysis of US ambulatory healthcare data, 2000-2009.
Bae J, Lin JS.
Front Pediatr. 2019 May 14;7:185. doi: 10.3389/fped.2019.00185. eCollection 2019.

Background: ME/CFS is a complex and disabling illness with substantial economic burden and functional impairment comparable to heart disease and multiple sclerosis. Many patients with ME/CFS do not receive appropriate healthcare, partially due to lack of diagnostic tests, and knowledge/attitudes/beliefs about ME/CFS. This study was to assess the utility of US ambulatory healthcare data in profiling demographics, co-morbidities, and healthcare in ME/CFS. Methods: Data came from the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS) in the U.S. Weighted analysis was performed. We examined 9.06 billion adult visits from 2000 to 2009 NAMCS/NHAMCS data. ME/CFS-related visits were identified by ICD-9-CM code, 780.71, up to tertiary diagnosis. Results: We estimated 2.9 million (95% CI: 1.8-3.9 million) ME/CFS-related visits during 2000-2009, with no statistical evidence (p-trend = 0.31) for a decline or increase in ME/CFS-related visits. Internists, general and family practitioners combined provided 52.12% of these visits. Patients with ME/CFS-related visits were mostly in their 40 and 50 s (47.76%), female (66.07%), white (86.95%), metropolitan/urban residents (92.05%), and insured (87.26%). About 71% of ME/CFS patients had co-morbidities, including depression (35.79%), hypertension (31.14%), diabetes (20.30%), and arthritis (14.11%). As one quality indicator, physicians spent more time on ME/CFS-related visits than non-ME/CFS visits (23.62 vs. 19.38 min, $p = 0.065$). As additional quality indicators, the top three preventive counseling services provided to patients with ME/CFS-related visits were diet/nutrition (8.33%), exercise (8.21%), and smoking cessation (7.24%). Compared to non-ME/CFS visits, fewer ME/CFS-related visits included counseling for stress management (0.75 vs. 3.14%, $p = 0.010$), weight reduction (0.88 vs. 4.02%, $p = 0.002$), injury prevention (0.04 vs. 1.64%, $p < 0.001$), and family planning/contraception (0.17 vs. 1.45%, $p = 0.037$). Conclusions: Visits coded with ME/CFS did not increase from 2000 to 2009. Almost three quarters of ME/CFS-related visits were made by ME/CFS patients with other co-morbid conditions, further adding to complexity in ME/CFS healthcare. While physicians spent more time with ME/CFS patients, a lower proportion of ME/CFS patients received preventive counseling for weight reduction, stress management, and injury prevention than other patients despite the complexity of ME/CFS. NAMCS/NHAMCS data are useful in evaluating co-morbidities, healthcare utilization, and quality indicators for healthcare in ME/CFS.

Bloating in irritable bowel syndrome is associated with symptoms severity, psychological factors, and comorbidities.
Hod K, Ringel Y, van Tilburg MAL, Ringel-Kulka T.
Dig Dis Sci. 2019 May;64(5):1288-1295. doi: 10.1007/s10620-018-5352-5.

BACKGROUND: Bloating is one of the most bothersome symptoms of irritable bowel syndrome (IBS), but its association with other symptoms is not well described. AIMS: We investigated the association between symptoms of abdominal bloating, other IBS symptoms, psychological distress, and comorbid pain conditions. METHODS: We conducted a cross-sectional study on a large cohort of IBS patients with and without symptoms of abdominal bloating and healthy controls. Subjects were assessed for IBS and its subtypes, pain severity, symptoms severity, psychological disturbances, comorbidities, and dietary restrictions of three fluid groups. RESULTS: A total of 484 subjects were investigated. Compared with IBS-B, IBS+B subjects had higher rates of constipation (30% vs. 15%, p=0.191) and lower rates of diarrhea, (70% vs. 85%,

p=0.191) although these were not statistically significant. Bloating severity correlated with IBS symptoms severity (r-0.397, p=0.000), pain severity (r=0.364, p=0.000), and both anxiety and somatization scores (r=0.167, p=0.015 and r=0.219, p=0.001, respectively). Prevalence of fibromyalgia and depression and somatization scores was significantly higher in IBS with bloating than in IBS without bloating. IBS patients with bloating reported more dietary restriction of three fluid groups to control their symptoms compared with healthy controls and IBS patients without bloating. CONCLUSIONS: Abdominal bloating in IBS is associated with increased symptoms and pain severity, somatization, depression, fibromyalgia, and altered dietary fluids composition. Recognizing and addressing these factors in the diagnosis and management of patients with IBS may improve clinical outcome.

Endometriosis as a comorbid condition in chronic fatigue syndrome (CFS): Secondary analysis of data from a CFS case-control study.
Boneva RS, Lin JS, Wieser F, Nater UM, Ditzen B, Taylor RN, Unger ER.
Front Pediatr. 2019 May 21;7:195. doi: 10.3389/fped.2019.00195. eCollection 2019.

Background: Endometriosis (EM) is a recognized co-morbid condition in women with chronic fatigue syndrome (CFS). This analysis evaluates the impact of EM on the health of women with CFS by comparing selected health characteristics and laboratory parameters in women with CFS with and without EM (CFS+EM and CFS-only). Methods: This secondary analysis included all 36 women with CFS from a cross-sectional study of CFS in Wichita, KS, conducted between 2002 and 2003. The health characteristics and laboratory parameters of interest included functioning, fatigue, CFS-related symptoms, gynecologic history, routine laboratory parameters, inflammatory markers, cortisol levels, allostatic load, and sleep parameters (overnight polysomnography). We used parametric or non-parametric tests to compare group differences in the selected health characteristics and laboratory parameters. For examining the association between EM and variables of interest, logistic regression models were performed and odds ratios (OR) with 95% confidence intervals (CI) were reported for the magnitude of associations. Statistical significance was set at 0.05 (two-sided). Results: The mean age of this study sample was 50.9 years. Of women with CFS, 36.1% reported having EM. Age and body mass index (BMI) did not differ between CFS+EM and CFS-only groups. When examining the impact of EM, compared to women with CFS-only, women with both CFS and EM were more likely to report chronic pelvic pain [OR = 9.00 (95% CI, 1.47-55.25)] and hysterectomy [OR = 10.3 (1.82-58.39)], had more CFS symptoms (6.8 ± 0.3 vs. 5.5 ± 0.3, p= 0.02), younger mean age at menopause onset (36.4 ± 3.0 vs. 47.0 ± 2.7 years, p = 0.03), higher mean number of obstructive apnea episodes per hour (20.3 vs. 4.4, p = 0.05) and reported more negative life events (15.8 vs. 4.4, p = 0.05). Other parameters did not differ significantly between the two groups. Conclusions: We found more than a third of women with CFS reported endometriosis as a comorbid condition. The endometriosis comorbidity was associated with chronic pelvic pain, earlier menopause, hysterectomy, and more CFS-related symptoms.
However, endometriosis in women with CFS did not appear to further impact functioning, fatigue, inflammatory markers, or other laboratory parameters. Further investigations including younger women are warranted.

Prevalence of fibromyalgia among women with deep infiltrating endometriosis.
Coloma JL, Martinez-Zamora MA, Collado A, Gracia M, Rius M, Quintas L, Carmona F.
Int J Gynaecol Obstet. 2019 Aug;146(2):157-163. doi: 10.1002/ijgo.12822.

OBJECTIVE: To estimate the prevalence of fibromyalgia among women with endometriosis and analyze the effect of fibromyalgia on health-related quality of life (HRQoL). METHODS: An observational case-control study conducted at a tertiary hospital in Barcelona between April 2015 and March 2017 among women with deep infiltrating endometriosis (DIE; n=80), women with superficial endometriosis or ovarian endometrioma (non-DIE; n=76), and control women without endometriosis (n=73). Fibromyalgia was assessed via the London Fibromyalgia Epidemiological Study Screening Questionnaire (LFESSQ). HRQoL was evaluated with the 36-Item Short Form (SF-36) questionnaire. The impact of fibromyalgia and other clinical characteristics

was assessed by multivariate regression analysis. RESULTS: More women fulfilled the criteria for fibromyalgia in the DIE group than in the non-DIE and control groups by LFESSQ-4 (31 [39%], 12 [16%], and 6 [8%], respectively; P=0.009) and LFESSQ-6 (22 [28%], 8 [11%], and 4 [5%], respectively; P=0.008). The DIE group reported significantly poorer HRQoL for all SF-36 dimensions. Women with DIE who fulfilled the criteria for fibromyalgia had lower physical component scores (-31.6; 95% confidence interval, -50.8 to -12.3; P=0.003). CONCLUSION: The estimated prevalence of fibromyalgia was higher among women with DIE. Women with DIE and positive fibromyalgia screening had lower HRQoL.

The association between endometriosis and autoimmune diseases: a systematic review and meta-analysis.
Shigesi N, Kvaskoff M, Kirtley S, Feng Q, Fang H, Knight JC, Missmer SA, Rhmioglu N, Zondervan KT, Becker CM.
Hum Reprod Update. 2019 Jul 1;25(4):486-503. doi: 10.1093/humupd/dmz014.

BACKGROUND: Endometriosis is a chronic gynaecological disorder that affects 2-10% of women of reproductive age. The aetiology of endometriosis is largely under-explored, yet abnormalities in the immune system have been suggested to explain the origin of ectopic endometrial tissues, and an association between endometriosis and autoimmune diseases has been proposed. Evaluation of current evidence investigating the association between endometriosis and autoimmune diseases from population-based studies will facilitate our understanding of the causes and consequences of endometriosis and provide a reference for better healthcare practices population-wide. OBJECTIVE AND RATIONALE: The aim of this study was to systematically review the literature on population-based studies investigating an association between endometriosis and autoimmune diseases and to conduct a meta-analysis of combinable results to investigate the extent and robustness of evidence. SEARCH METHODS: Four electronic databases were searched (MEDLINE, Embase, Web of Science, and CINAHL) from each database inception date until 7 April 2018. Search terms included a combination of database-specific controlled vocabulary terms and free-text terms relating to 'endometriosis' and 'autoimmune diseases'. Study inclusion criteria focused on peer-reviewed published articles that reported an association between endometriosis and autoimmune diseases, excluding case reports/series, review papers, meta-analyses, organizational guidelines, editorial letters, expert opinions, and conference abstracts. Quality assessment of included studies was performed based on GRADE criteria. Key information of eligible studies was abstracted into a standard form. Meta-analysis was performed for autoimmune diseases with combinable study results from at least three studies investigating an association with endometriosis. For cross-sectional studies and case-control studies, raw data from each study were documented to calculate a Mantel-Haenszel odds ratio with 95% CIs. For cohort studies, an inverse variance probability weighted model was used to pool study results to calculate a rate ratio (a hazard ratio or a standardized incidence rate) with 95% CIs. OUTCOMES: A total of 26 published population-based cross-sectional, case-control, and cohort studies that investigated the association between endometriosis and autoimmune diseases met all eligible criteria and were included in the review. The studies quantified an association between endometriosis and several autoimmune diseases, including systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), rheumatoid arthritis (RA), autoimmune thyroid disorder, coeliac disease (CLD), multiple sclerosis (MS), inflammatory bowel disease (IBD), and Addison's disease. However, the quality of the evidence was generally poor due to the high risk of bias in the majority of the chosen study designs and statistical analyses. Only 5 of the 26 studies could provide high-quality evidence, and among these, 4 supported a statistically significant association between endometriosis and at least 1 autoimmune disease: SLE, SS, RA, CLD, MS, or IBD. WIDER IMPLICATIONS: The observed associations between endometriosis and autoimmune diseases suggest that clinicians need to be aware of the potential coexistence of endometriosis and autoimmune diseases when either is diagnosed. Scientists interested in research studies on endometriosis or autoimmune diseases should consider the likelihood of comorbidity when studying these two types of health conditions. Well-designed large prospective cohort studies with confounding control and

mediation quantification, as well as genetic and biological studies, are needed to generate further insights into whether endometriosis is a risk factor for, or a consequence of, autoimmune diseases, and whether these two types of disorders share pathophysiological mechanisms even if they arise independently. Such insights may offer opportunities for the development of novel non-hormonal medications such as immuno-modulators or repurposing of existing immunomodulatory therapies for endometriosis.

Systemic exertion intolerance disease/chronic fatigue syndrome is common in sleep centre patients with hypersomnolence: A retrospective pilot study.
Maness C, Saini P, Bliwise DL, Olvera V, Rye DB, Trotti LM.
J Sleep Res. 2019 Jun;28(3):e12689. doi: 10.1111/jsr.12689.

Symptoms of the central disorders of hypersomnolence extend beyond excessive daytime sleepiness to include non-restorative sleep, fatigue and cognitive dysfunction. They share much in common with myalgic encephalomyelitis / chronic fatigue syndrome, recently renamed systemic exertion intolerance disease, whose additional features include post-exertional malaise and orthostatic intolerance. We sought to determine the frequency and correlates of systemic exertion intolerance disease in a hypersomnolent population. One-hundred and eighty-seven hypersomnolent patients completed questionnaires regarding sleepiness and fatigue; questionnaires and clinical records were used to assess for systemic exertion intolerance disease. Sleep studies, hypocretin and cataplexy were additionally used to assign diagnoses of hypersomnolence disorders or sleep apnea. Included diagnoses were idiopathic hypersomnia (n = 63), narcolepsy type 2 (n = 25), persistent sleepiness after obstructive sleep apnea treatment (n = 25), short habitual sleep duration (n = 41), and sleepiness with normal sleep study (n = 33). Twenty-one percent met systemic exertion intolerance disease criteria, and the frequency of systemic exertion intolerance disease was not different across sleep diagnoses (p = .37). Patients with systemic exertion intolerance disease were no different from those without this diagnosis by gender, age, Epworth Sleepiness Scale, depressive symptoms, or sleep study parameters. The whole cohort reported substantial fatigue on questionnaires, but the systemic exertion intolerance disease group exhibited more profound fatigue and was less likely to respond to traditional wake-promoting agents (88.6% versus 67.7%, p = .01). Systemic exertion intolerance disease appears to be a common co-morbidity in patients with hypersomnolence, which is not specific to hypersomnolence subtype but may portend a poorer prognosis for treatment response.

Low bladder capacity is an important predictor for comorbidity of interstitial cystitis with Hunner's lesion in patients with refractory chronic prostatitis/chronic pelvic pain syndrome.
Ueda M, Sengiku A, Kono J, Negoro H, Saito R, Yoshimura N, Ogawa O, Ueda T.
Int J Urol. 2019 Jun;26 Suppl 1:53-56. doi: 10.1111/iju.13975.

OBJECTIVE: To evaluate the predictive factors for comorbidity of Hunner-type interstitial cystitis in patients with chronic prostatitis/chronic pelvic pain syndrome using urethrocystoscopy. METHODS: Thirty-two male patients were included in this study. Between April 2012 and April 2016 they were diagnosed with chronic prostatitis/chronic pelvic pain syndrome according to the National Institutes of Health classification. Their symptoms were not improved by 3 months of behavioral and pharmacological therapies. They all underwent narrow band imaging-assisted urethrocystoscopy to assess whether the presence of Hunner's lesions correlated with other variables. RESULTS: Thirteen out of 32 patients (41%) had Hunner's lesions. Of the variables, maximal voided volume per micturition (106 ± 29 mL vs 171 ± 61 mL) and bladder capacity (267 ± 121 mL vs 407 ± 137 mL) were significantly smaller in patients with Hunner's lesions compared to those without. Other variables, apart from age, were not significantly different. Furthermore, patients with voided volume less than 150 mL were more likely to have Hunner's lesions than those with voided volume exceeding 150 mL. CONCLUSIONS: Hunner-type interstitial cystitis is a common comorbidity among patients with refractory chronic prostatitis/chronic pelvic pain syndrome. In cases where voided volume is small,

performing narrow band imaging-assisted urethrocystoscopy would be very helpful for detecting bladder mucosal changes such as Hunner's lesions.

The effects of depression, low back pain and comorbidities on pain after total knee arthroplasty for osteoarthritis are modified by sex.
Perruccio AV, Fitzpatrick J, Power JD, Gandhi R, Rampersaud YR, Mahomed NN, Davey JR, Syed K, Veilette C, Badley EM.
Arthritis Care Res (Hoboken). 2019 Jun 14. doi: 10.1002/acr.24002.

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

Effects of sex and adaptation on migraine frequency and perceived stress: A cross-sectional case-control study.
An YC, Liang CS, Lee JT, Lee MS, Chen SJ, Tsai CL, Lin GY, Lin YK, Yang FC.
Front Neurol. 2019 Jun 5;10:598. doi: 10.3389/fneur.2019.00598. eCollection 2019.

Background: Perceived stress has been related to migraine. The relationship between sex, migraine frequency, and severity of perceived stress remains unclear. We investigated perceived stress among migraineurs. Methods: This cross-sectional case-control study involved 577 clinical outpatients at a tertiary hospital in Taiwan. Demographic and clinical data, including migraine characteristics, were collected. Migraineurs were stratified by episode frequency, aura and sex, and analyses were controlled for confounding variables. Multivariable linear regressions were used to inspect whether migraine frequency (1-4, 5-8, 9-14, or ≥15 headache days per month) was associated with perceived stress as assessed by the Perceived Stress Scale (PSS). Results: Perceived stress was significantly higher in high frequency migraineurs (mean ± standard deviation (SD), 23.3 ± 8.7) than in low frequency migraineurs (mean ± SD, 21.9 ± 9.2; $P < 0.05$). After stratifying the analysis by sex, this result was observed in male subjects, but was insignificant in female subjects. In addition, the relationship between migraine frequency and perceived stress was not prominent in aura-present or -absent subgroups. Conclusions: Higher perceived stress was associated with higher migraine frequency, but not in chronic migraine and female subgroups. Adaptation to migraine and various psychiatric comorbidities may contribute to these associations.

Migraine comorbidity and cognitive performance in patients with focal epilepsy.
Begasse de Dhaem OAJ, French J, Morrison C, Meador KJ, Hesdorffer DC, Cristofaro S, Minen MT; HEP Investigators.
Epilepsy Behav. 2019 Jun 7;97:29-33. doi: 10.1016/j.yebeh.2019.05.008.

BACKGROUND: Migraine and epilepsy are comorbid conditions. While it is well known that epilepsy can have an impact on cognitive abilities, there is conflicting evidence in the

literature on the relationship between migraine and cognitive function. The aim of this study was to assess whether migraine comorbidity in patients with newly diagnosed focal epilepsy is associated with cognitive dysfunction. METHODS: This is a post hoc analysis of data prospectively collected for the Human Epilepsy Project (HEP). There were 349 participants screened for migraine with the 13 questions used in the American Migraine Prevalence and Prevention (AMPP) study. Participants were also screened for depression using the Neurological Disorder Depression Inventory for Epilepsy (NDDI-E) and the Center for Epidemiologic Studies Depression Scale (CES-D) and for anxiety using the Generalized Anxiety Disorder-7 (GAD-7) scale. Cognitive performance was assessed with the Cogstate Brief Battery and Aldenkamp-Baker Neuropsychological Assessment Schedule (ABNAS). RESULTS: About a fifth (21.2%) of patients with a new diagnosis of focal epilepsy screened positive for migraine. There were more women and less participants employed full time among the participants with comorbid migraine. They reported slightly more depressive and anxious symptoms than the participants without migraine. Migraine comorbidity was associated with ABNAS memory score (median: 2, range: 0-12, Mann Whitney U p-value: 0.015). However, migraine comorbidity was not associated with Cogstate scores nor ABNAS total scores or other ABNAS domain scores. In linear regressions, depression and anxiety scores were associated with the ABNAS memory score. CONCLUSION: In this study, there was no association between migraine comorbidity and objective cognitive scores in patients with newly diagnosed focal epilepsy. The relationship between migraine comorbidity and subjective memory deficits seemed to be mediated by the higher prevalence of depression and anxiety symptoms in patients with epilepsy with comorbid migraine.

Twenty-Five and Up (25Up) Study: A new wave of the Brisbane Longitudinal Twin Study.
Mitchell BL, Campos AI, Renteria ME, Parker R, Sullivan L, McAloney K, Couvy-Duchesne B, Medland SE, Gillespie NA, Scott J, Zietsch BP, Lind PA, Martin NG, Hickie IB.
Twin Res Hum Genet. 2019 Jun;22(3):154-163. doi: 10.1017/thg.2019.27.

The aim of the 25 and Up (25Up) study was to assess a wide range of psychological and behavioral risk factors behind mental illness in a large cohort of Australian twins and their non-twin siblings. Participants had already been studied longitudinally from the age of 12 and most recently in the 19Up study (mean age = 26.1 years, SD = 4.1, range = 20-39). This subsequent wave follows up these twins several years later in life (mean age = 29.7 years, SD = 2.2, range = 22-44). The resulting data set enables additional detailed investigations of genetic pathways underlying psychiatric illnesses in the Brisbane Longitudinal Twin Study (BLTS). Data were collected between 2016 and 2018 from 2540 twins and their non-twin siblings (59% female, including 341 monozygotic complete twin-pairs, 415 dizygotic complete pairs and 1028 non-twin siblings and singletons). Participants were from South-East Queensland, Australia, and the sample was of predominantly European ancestry. The 25Up study collected information on 20 different mental disorders, including depression, anxiety, substance use, psychosis, bipolar and attention-deficit hyper-activity disorder, as well as general demographic information such as occupation, education level, number of children, self-perceived IQ and household environment. In this article, we describe the prevalence, comorbidities and age of onset for all 20 examined disorders. The 25Up study also assessed general and physical health, including physical activity, sleep patterns, eating behaviors, baldness, acne, migraines and allergies, as well as psychosocial items such as suicidality, perceived stress, loneliness, aggression, sleep-wake cycle, sexual identity and preferences, technology and internet use, traumatic life events, gambling and cyberbullying. In addition, 25Up assessed female health traits such as morning sickness, breastfeeding and endometriosis. Furthermore, given that the 25Up study is an extension of previous BLTS studies, 86% of participants have already been genotyped. This rich resource will enable the assessment of epidemiological risk factors, as well as the heritability and genetic correlations of mental conditions.

CLINICAL STUDIES

Orofacial motor functions and temporomandibular disorders in patients with Sjogren's Syndrome.
Zanin MC, Garcia DM, Rocha EM, de Felicio CM.
Arthritis Care Res (Hoboken). 2019 Jun 17. doi: 10.1002/acr.24001.

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

Response to BotulinumtoxinA in a migraine cohort with multiple comorbidities and widespread pain.
Barad M, Sturgeon JA, Fish S, Dexter F, Mackey S, Flood PD.
Reg Anesth Pain Med. 2019 Jun;44(6):660-668. doi: 10.1136/rapm-2018-100196.

BACKGROUND: The phase III research evaluating migraine prophylaxis therapy (PREEMPT) protocol was developed in low-risk migraine patients. We studied longitudinal response to treatment in a sequential retrospective observational cohort to evaluate predictors of effectiveness in patients with multiple overlapping pain syndromes treated in a quaternary pain management clinic. METHODS: We evaluated indicators of individual response in 402 consecutive chronic migraine patients who provided demographic information and used the Collaborative Health Outcomes Information Registry. RESULTS: The patients were middle aged 47 (38-56) median (IQR) years old and 83% women. They reported multiple complex pain problems with 11 (6-18) regions represented on a pain body map. Evaluated with National Institutes of Health Patient-Reported Outcomes Measurement Information System measures, they reported higher scores for sleep impairment and disturbance, anxiety, depression, fatigue, pain behavior, pain interference and worse function and satisfaction with social roles compared with the general US population; p<0.001 for all domains. Within 120 days of treatment, 62% of patients reported reduced headache frequency. The best multivariable model developed for prediction of reduced headache frequency in response to treatment included lower treatment number, lower pain interference score, and less depression (p=0.001, 0.002, and 0.009). Depression may have been an obstacle to successful treatment; there was no association between depression score and number of treatments (p=0.54). CONCLUSIONS: Our findings point to the importance of identifying and addressing pain interference and depression early in chronic migraine management and, more broadly, highlights the importance of multidisciplinary evaluation and treatment in chronic migraine.

Sleep and tension-type headache.
Cho SJ, Song TJ, Chu MK.
Curr Neurol Neurosci Rep. 2019 May 30;19(7):44. doi: 10.1007/s11910-019-0953-8.

PURPOSE OF REVIEW: Tension-type headache (TTH) is a common neurological condition that is related to sleep dysfunction. This review discusses recent evidence for the association between TTH and sleep disturbances. RECENT FINDINGS: There is an increasing evidence for the association of TTH with sleep disturbances including insomnia, poor sleep quality, excessive daytime sleepiness, insufficient sleep, and shift working. Most studies have reported that sleep disturbances are more prevalent among subjects with TTH than among subjects without headaches. Clinical presentations of TTH are more exacerbated in TTH subjects with sleep disturbances than in those without sleep disturbances. Further, the close association of TTH with sleep disturbances is more robust in subjects with chronic TTH than in those with episodic TTH. Growing evidence highlights the association of TTH with psychiatric comorbidity, which is closely associated with sleep disturbances. Recent advances in our understanding of the association between sleep and TTH will help in improved diagnosis and treatment of TTH and sleep disturbances.

Comorbid fibromyalgia in migraine patients: clinical significance and impact on daily life.
Onder H, Hamamci M, Alpua M, Ulusoy EK.
Neurol Res. 2019 Jun 20:1-7. doi: 10.1080/01616412.2019.1630164.

Objective: Herein, we aimed to investigate the impact of FM in migraine patients and the specific features and discriminations of this group of migraineurs with FM according to patients without FM. Methods: 102 consecutive migraine patients among 18-50 years old who accepted to involve in the study were included. All patients were asked to complete the following self-report questionnaires for the assessment of pain-related disability, migraine-related disability, anxiety, depression, sleep disturbance and quality of life. All statistical analyses were performed using the SPSS statistics 20 program. Results: 92% of the patients were diagnosed with episodic migraine, whereas 8% of them was diagnosed with chronic migraine (CM). Comorbid FM which was detected to present in 30.3% of the patients. FM was more frequent in CM patients and in migraine patients with aura. The analyses comparing FM (+) and FM (-) migraineurs revealed that headache frequency, migraine disease duration, headache impact test, MIDAS scores were significantly higher in FM (+) migraineurs. Furthermore, the vitality and role-emotional domains of the SF-36 resulted in worse scores in the group of FM (+) migraineurs. Conclusion: The results of our study may suggest the presence of FM as a clinical sign of a more severe migraine. However, the long-term prospective studies including these group of patients are needed to understand the prognostic impact and importance of the comorbid FM in migraine.

Sex, symptom severity, and quality of life in rheumatology.
Krasselt M, Baerwald C.
Clin Rev Allergy Immunol. 2019 Jun;56(3):346-361. doi: 10.1007/s12016-017-8631-6.

Inflammatory rheumatic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) show a striking female predominance ranging from 3:1 in RA up to 9:1 in SLE. The background for those gender bias is not fully understood yet, but seems to be the result of a complex interaction between sex hormones, (epi-)genetics, and possibly even the composition of gut microbiota. Moreover, time of disease onset, the clinical phenotype including comorbidities as well as the course of the diseases during life differ between genders. The patient's sex therefore plays an emerging role for individual therapy decisions and co-morbidity screening in rheumatologic care. Male lupus patients, for example, tend to show more severe features such as renal involvement, pleurisy, and serositis, when being compared to female patients. Among RA patients, women are more likely to acquire conditions like thyroid dysfunctions, fibromyalgia, and depression than their male counterparts. These examples emphasize the importance of the patient's gender for the clinical routine and the resulting implications for prevention and therapy. The present article is going to review potential causes for the female predominance of rheumatic diseases and will examine the gender's impact on the disease phenotype, symptom severity, co-morbidities, and quality of life. For reasons of scope, the focus will be on RA and SLE as two of the most important rheumatic diseases with a large socioeconomic impact on society due to their

incidence as well as mortality.

About the Chronic Pain Research Alliance

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

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

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