CUTTING EDGE

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COPCs Research Advances

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This e-newsletter - published by the CPRA to keep the medical-scientific and patient communities abreast of research advances on Chronic Overlapping Pain Conditions (COPCs) - contains abstracts of studies on the epidemiology, pathophysiology and clinical management of COPCs published between October 2018 and January 2019. Prior issues are available on our website. 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.

In this Issue...

PATHOPHYSIOLOGY STUDIES

A predictive algorithm to identify genes that discriminate individuals with fibromyalgia syndrome diagnosis from healthy controls.

Lukkahatai N, Walitt B, Deandres-Galiana EJ, Fernandez-Martinez JL, Saligan LN.
J Pain Res. 2018 Nov 21;11:2981-2990. doi: 10.2147/JPR.S169499. eCollection 2018.

OBJECTIVES: Fibromyalgia syndrome (FMS) is a chronic and often debilitating condition that is characterized by persistent fatigue, pain, bowel abnormalities, and sleep disturbances. Currently, there are no definitive prognostic or diagnostic biomarkers for FMS. This study attempted to utilize a novel predictive algorithm to identify a group of genes whose differential expression discriminated individuals with FMS diagnosis from healthy controls. METHODS: Secondary analysis of gene expression data from 28 women with FMS and 19 age- and race-matched healthy women. Expression of discriminatory genes were identified using fold-change differential and Fisher's ratio (FR). Discriminatory accuracy of the differential expression of these genes was determined using leave-one-out-cross-validation. Functional networks of the discriminating genes were described from the Ingenuity's Knowledge Base. RESULTS: The small-scale signature contained 57 genes whose expressions were highly discriminatory of the FMS diagnosis. The combination of these high discriminatory genes with FR higher than 1.45 provided a leave-one-out-cross-validation accuracy for the FMS diagnosis of 85.11%. The discriminatory genes were associated with 3 canonical pathways: hepatic stellate cell activation, oxidative phosphorylation, and airway pathology related to

COPD. CONCLUSION: The discriminating genes, especially the 2 with the highest accuracy, are associated with mitochondrial function or oxidative phosphorylation and glutamate signaling. Further validation of the clinical utility of this finding is warranted.

Localized provoked vulvodynia: Association with nerve growth factor and transient receptor potential vanilloid type 1 genes polymorphisms.
Kalfon L, Azran A, Farajun Y, Golan-Hamu O, Toben A, Abramov L, Yeshaya A, Yakir O, Zarfati D, Falik Zaccai TC, Bornstein J.
J Low Genit Tract Dis. 2019 Jan;23(1):58-64. doi: 10.1097/LGT.0000000000000445.

OBJECTIVE: The aim of the study was to study the associations between localized provoked vulvodynia (LPV) and several single-nucleotide polymorphisms (SNPs) in the transient receptor potential vanilloid type 1 (TRPV1), nerve growth factor (NGF), and the heparanase (HPSE) genes. MATERIALS AND METHODS: Prevalence of SNPs among 65 women with moderate or severe primary LPV (initial symptoms occur with first provoking physical contact) and 126 healthy, ethnically matched controls was analyzed in an observational case-control study. Each participant answered a questionnaire addressing familial LPV occurrence and comorbid pain conditions. RESULTS: Familial occurrences of LPV, temporomandibular joint (TMJ) symptoms, recurrent vaginitis, and irritable bowel syndrome were significantly higher among LPV women than healthy controls. Genotyping analyses revealed a novel, statistically significant high prevalence of polymorphism c.945G>C (rs222747) of TRPV1 and a SNP in the promoter region of NGF (rs11102930) in LPV women compared with controls. A logistic regression model for rs222747 and rs11102930 frequent alleles indicates significant LPV association within the entire study group and Ashkenazi Jewish women, respectively. Comparison of pain conditions with frequent alleles showed the rs222747 "CC" genotype of TRPV1 associated with women with TMJ, recurrent vaginitis, and LPV. CONCLUSIONS: Our results suggest novel genetic susceptibility to primary LPV associated with specific alleles in genes TRPV1 and NGF and propose the rs222747 "C" allele of TRPV1 as a common genetic predisposition for other pain syndromes.

Association of fatigue with TPH2 genetic polymorphisms in women with irritable bowel syndrome.
Han CJ, Jarrett ME, Cain KC, Jun S, Heitkemper MM.
Biol Res Nurs. 2018 Oct 11:1099800418806055. doi: 10.1177/1099800418806055.

Fatigue is the most common extraintestinal symptom in women with irritable bowel syndrome (IBS). Genetic polymorphisms of monoamines are associated with fatigue in many chronic diseases. In this pilot exploratory study, the primary aim was to determine whether genetic polymorphisms of tryptophan hydroxylase (TPH1/TPH2), serotonin reuptake transporter (SERT), or catechol-O-methyltransferase (COMT) are associated with fatigue in women with IBS. Additionally, analysis explored whether these genetic associations with fatigue would be present when controlling for abdominal pain, psychological distress, feeling stressed, and sleepiness during the day. Secondary analysis of two randomized controlled trial baseline data sets in Caucasian women with IBS (N=185) was conducted. Participants kept a daily diary with one dimension (i.e., severity) for each of the 26 symptoms, including fatigue, for 28 days prior to randomization. DNA samples were tested for single-nucleotide polymorphisms (SNPs) of TPH1 (four SNPs) /TPH2 (one SNP), SERT (one SNP), and COMT (one SNP). Analysis of covariance was used to examine associations of percentage of diary days with moderate to very severe symptoms with genetic polymorphisms. Only one SNP, TPH2 rs4570625, was significantly associated with fatigue (p=0.005). T-allele (low functional) carriers of TPH2 (i.e., G/T or T/T genotypes) reported a greater percentage of days with moderate to very severe fatigue than G/G homozygotes (p=0.001). Reduced synthesis of tryptophan in the central nervous system may contribute to reports of fatigue in women with IBS. Understanding genetic risk factors for fatigue may elucidate preemptive strategies to reduce fatigue in individuals with IBS.

Genes known to escape X chromosome inactivation predict co-morbid chronic

musculoskeletal pain and posttraumatic stress symptom development in women following trauma exposure.

Yu S, Chen C, Pan Y, Kurz MC, Datner E, Hendry PL Velilla MA, Lewandowski C, Pearson C, Domeier R, McLean SA, Linnstaedt SD.

Am J Med Genet B Neuropsychiatr Genet. 2018 Dec 11. doi: 10.1002/ajmg.b.32706.

Co-morbid chronic musculoskeletal pain (CMSP) and posttraumatic stress symptoms (PTSS) are frequent sequelae of motor vehicle collision, are associated with greater disability than either outcome alone, and are more prevalent in women than men. In the current study we assessed for evidence that gene transcripts originating from the X chromosome contribute to sex differences in vulnerability to CMSP and PTSS after motor vehicle collision. Nested samples were drawn from a longitudinal study of African American individuals, and CMSP (0-10 numeric rating scale) and PTSS (impact of events scale, revised) outcomes were assessed 6 months following motor vehicle collision. Blood RNA were sequenced (n=101) and the relationship between X chromosome mRNA expression levels and co-morbid CMSP and PTSS outcomes was evaluated using logistic regression analyses. A disproportionate number of peritraumatic X chromosome mRNA predicting CMSP and PTSS in women were genes previously found to escape X chromosome inactivation (11/40, z= -2.9, p=0.004). Secondary analyses assessing gene ontology relationships between these genes identified an enrichment in genes known to influence neuronal plasticity. Further, the relationship of expression of two critical regulators of X chromosome inactivation, X-inactive specific transcript (XIST) and Yin Yang 1 (YY1), was different in women developing CMSP and PTSS. Together, these data suggest that X chromosome genes that escape inactivation may contribute to sex differences in vulnerability to CMSP and PTSS after motor vehicle collision.

Sex differences in measures of central sensitization and pain sensitivity to experimental sleep disruption: Implications for sex differences in chronic pain.

Smith MT Jr, Remeniuk B, Finan PH, Speed TJ, Tompkins DA, Robinson M, Gonzalez K, Bjurstrom MF, Irwin MR.

Sleep. 2018 Oct 29. doi: 10.1093/sleep/zsy209.

OBJECTIVES: Females demonstrate heightened central sensitization (CS), a risk factor for chronic pain characterized by enhanced responsivity of central nervous system nociceptors to normal or subthreshold input. Sleep disruption increases pain sensitivity, but sex has rarely been evaluated as a moderator and few experiments have measured CS. We evaluated whether two nights of sleep disruption alters CS measures of secondary hyperalgesia and mechanical temporal summation in a sex dependent manner. We also evaluated differences in measures of pain sensitivity. METHODS: Seventy-nine healthy adults (female n=46) participated in a randomized crossover experiment comparing two consecutive nights of eight pseudo-randomly distributed forced awakenings [FA, (-200 min. sleep time.)] against two nights of undisturbed sleep (US). We conducted sensory testing the mornings following Night 2; the heat-capsaicin pain model was used to induce secondary hyperalgesia. RESULTS: FA reduced total sleep time (REM and NREM Stage 3) more profoundly in males. We observed divergent, sex dependent effects of FA on secondary hyperalgesia and temporal summation. FA significantly increased secondary hyperalgesia in males and significantly increased temporal summation in females. Sex differences were not attributable to differential sleep loss in males. FA also significantly reduced heat pain threshold and cold pressor pain tolerance, independently of sex. CONCLUSIONS: Sleep disruption enhances different pain facilitatory measures of CS in males and females suggesting that sleep disturbance may increase risk for chronic pain in males and females via distinct pathways. Findings have implications for understanding sex differences in chronic pain and investigating sleep in chronic pain prevention efforts.

Chronic linaclotide treatment reduces colitis-induced neuroplasticity and reverses persistent bladder dysfunction.

Grundy L, Harrington AM, Castro J, Garcia-Caraballo S, Deiteren A, Maddern J, Rychkov GY, Ge P, Peters S, Feil R, Miller P, Ghetti A, Hannig G, Kurtz CB, Silos-Santiago I, Brierley SM.

JCI Insight. 2018 Oct 4;3(19). pii: 121841. doi: 10.1172/jci.insight.121841.

Irritable bowel syndrome (IBS) patients suffer from chronic abdominal pain and extraintestinal comorbidities, including overactive bladder (OAB) and interstitial cystitis/painful bladder syndrome (IC-PBS). Mechanistic understanding of the cause and time course of these comorbid symptoms is lacking, as are clinical treatments. Here, we report that colitis triggers hypersensitivity of colonic afferents, neuroplasticity of spinal cord circuits, and chronic abdominal pain, which persists after inflammation. Subsequently, and in the absence of bladder pathology, colonic hypersensitivity induces persistent hypersensitivity of bladder afferent pathways, resulting in bladder-voiding dysfunction, indicative of OAB/IC-PBS. Daily administration of linaclotide, a guanylate cyclase-C (GC-C) agonist that is restricted to and acts within the gastrointestinal tract, reverses colonic afferent hypersensitivity, reverses neuroplasticity-induced alterations in spinal circuitry, and alleviates chronic abdominal pain in mice. Intriguingly, daily linaclotide administration also reverses persistent bladder afferent hypersensitivity to mechanical and chemical stimuli and restores normal bladder voiding. Linaclotide itself does not inhibit bladder afferents, rather normalization of bladder function by daily linaclotide treatment occurs via indirect inhibition of bladder afferents via reduced nociceptive signaling from the colon. These data support the concepts that cross-organ sensitization underlies the development and maintenance of visceral comorbidities, while pharmaceutical treatments that inhibit colonic afferents may also improve urological symptoms through common sensory pathways.

The relationship between daytime salivary melatonin and gastrointestinal symptoms in young adults seeking psychiatric care.

Soderquist F, Sundberg I, Ramklint M, Widerstrom R, Hellstrom PM, Cunningham JL.
Psychosom Med. 2019 Jan;81(1):51-56. doi: 10.1097/PSY.0000000000000644.

OBJECTIVE: The pathophysiology of irritable bowel syndrome (IBS) is not completely understood, although we do know that patients with IBS have a high prevalence of psychiatric comorbidity (mainly depression and anxiety disorders). Melatonin, produced in the gastrointestinal tract, influences gut motility. Psychiatric conditions are associated with circadian disturbances in peripheral melatonin levels. This study aimed to investigate associations between daytime salivary melatonin and gastrointestinal symptoms in young adult psychiatric patients. METHODS: Ninety-six patients (86% women), aged 18-25 years (M (SD) = 21 (2)), seeking psychiatric care with primarily anxiety disorders, affective disorders, or both were included in the study. Total scores from the Gastrointestinal Symptoms Rating Scale - IBS were compared with salivary melatonin measured at three time points (30 minutes after waking up, at 11:00 hours and 30 minutes after lunch) during the waking hours of 1 day. RESULTS: After adjustment for potential confounders, melatonin levels in saliva 30 minutes after lunch remained significantly correlated to the total Gastrointestinal Symptoms Rating Scale - IBS score after correction for multiple testing (B=0.016, SE 0.006, p=0.015, q=0.045). In a post hoc analysis, symptoms of gastrointestinal pain and bloating contributed most to this association. CONCLUSIONS: In young adult psychiatric patients, salivary melatonin levels after lunch are associated with gastrointestinal symptoms, which is consistent with the proposed effect of elevated levels of gastrointestinal melatonin on gut motility. This result suggests a link between IBS symptoms and regulation of melatonin in patients with psychiatric disorders.

Widespread mechanical pain hypersensitivity in patients with chronic migraine and temporomandibular disorders: relationship and correlation between psychological and sensorimotor variables.

Garrigos-Pedron M, La Touche R, Navarro-Desentre P, Gracia-Naya M, Segura-Orti E.
Acta Odontol Scand. 2019 Jan 10:1-8. doi: 10.1080/00016357.2018.1538533.

OBJECTIVE: This study aimed to assess mechanical hyperalgesia in the trigeminal and extra-trigeminal regions in patients with chronic migraine (CM) and temporomandibular disorders (TMD) in comparison to asymptomatic subjects and to determine the association between

sensorimotor variables and psychological and disability variables and evaluate the prediction of a sensorimotor variables though psychological and disability variables in patients with CM and TMD. MATERIAL AND METHODS: A total of 52 subjects with concomitant CM and TMD and 30 asymptomatic subjects were included in the study. The pressure pain threshold (PPT), maximal mouth opening (MMO) and a series of self-reported factors were compared. RESULTS: There were 52 CM and TMD (92.3% women and 7.7% men; age= 46.2 +/- 9.5) and 30 asymptomatic subjects (80% women and 20% men; age = 47.4 +/- 10). Differences were found between patients with CM and TMD and asymptomatic participants ($p<0.01$) when comparing the PPTs in the trigeminal and extra-trigeminal regions. The PPT for the trigeminal region was predicted by depressive symptoms (variance of 18%) as well as disability and craniofacial pain (variance of 20%). The extra-trigeminal region PPT was predicted by depressive symptoms (variance of 10%), and pain-free MMO was predicted by disability and craniofacial pain (variance of 24%). CONCLUSIONS: This study suggests that patients with CM and TMD present with generalized mechanical hyperalgesia. In addition, an association between sensorimotor, psychological and disability variables was observed.

Medical correlates of chronic multisymptom illness in gulf war veterans.
Blanchard M, Molina-Vicenty HD, Stein PK, Li X, Karlinsky J, Alpern R, Reda DJ, Toomey R.
Am J Med. 2018 Dec 18. pii: S0002-9343(18)31177-X. doi: 10.1016/j.amjmed.2018.11.045.

BACKGROUND: Chronic multisymptom illness is more prevalent among deployed than non-deployed Gulf War 1 veterans. Objective physiologic markers of chronic multisymptom illness are lacking. The purpose of this study is to determine whether measurable abnormalities in the autonomic nervous system or hypothalamic-pituitary adrenal axis would distinguish chronic multisymptom illness cases (CMI+) from controls (CMI-) among deployed veterans of the 1990-1991 Gulf War. METHODS: This is a cross-sectional case-control cohort study that examined deployed veterans who participated in the Phase III study: National Health Survey of Gulf War Veterans and Their Families. Autonomic nervous system and hypothalamic-pituitary adrenal axis function-related measures included: 24-hour heart rate variability, urinary catecholamines and cortisol, hypertension, insulin sensitivity, dyslipidemia, body fat, bone mineral density, and ultrasensitive C-reactive protein. RESULTS: Gulf War 1 veterans with chronic multisymptom illness (n=73) and without the condition (n=111) were studied. Sociodemographic characteristics were similar. Veterans with chronic multisymptom illness reported poorer mental and physical functioning, greater use of prescription medications and more non-routine clinic visits. These veterans were also more likely to have fibromyalgia syndrome, irritable bowel syndrome, metabolic syndrome, and among males, a larger waist-to-hip ratio. Lower values for a non-linear heart-rate-variability parameter-the short-term fractal scaling exponent (DFA1), reflecting an increased randomness of beat-to-beat changes in heart rate-were observed in CMI+ compared with CMI- veterans (1.28+/-0.16 vs 1.35+/-0.15; $p=0.005$). Hypothalamic-pituitary-adrenal axis function measures were similar between groups. CONCLUSION: In this cohort of deployed Gulf War 1 veterans, we identified abnormal heart rate variability in veterans with chronic multisymptom illness compared to veterans without the condition, which suggests abnormal functioning of the autonomic nervous system and possible long-term cardiovascular effects.

The link between idiopathic intracranial hypertension, fibromyalgia, and chronic fatigue syndrome: exploration of a shared pathophysiology.
Hulens M, Rasschaert R, Vansant G, Stalmans I, Bruyninckx F, Dankaerts W.
J Pain Res. 2018 Dec 10;11:3129-3140. doi: 10.2147/JPR.S186878. eCollection 2018.

PURPOSE: Idiopathic intracranial hypertension (IICH) is a condition characterized by raised intracranial pressure (ICP), and its diagnosis is established when the opening pressure measured during a lumbar puncture is elevated >20 cm H_2O in nonobese patients or >25 cm H2O in obese patients. Papilledema is caused by forced filling of the optic nerve sheath with cerebrospinal fluid (CSF). Other common but underappreciated symptoms of IICH are neck pain, back pain, and radicular pain in the arms and legs resulting from associated increased spinal pressure and forced filling of the spinal nerves with CSF.

Widespread pain and also several other characteristics of IICH share notable similarities with characteristics of fibromyalgia (FM) and chronic fatigue syndrome (CFS), two overlapping chronic pain conditions. The aim of this review was to compare literature data regarding the characteristics of IICH, FM, and CFS and to link the shared data to an apparent underlying physiopathology, that is, increased ICP. METHODS: Data in the literature regarding these three conditions were compared and linked to the hypothesis of the shared underlying physiopathology of increased cerebrospinal pressure. RESULTS: The shared characteristics of IICH, FM, and CFS that can be caused by increased ICP include headaches, fatigue, cognitive impairment, loss of gray matter, involvement of cranial nerves, and overload of the lymphatic olfactory pathway. Increased pressure in the spinal canal and in peripheral nerve root sheaths causes widespread pain, weakness in the arms and legs, walking difficulties (ataxia), and bladder, bowel, and sphincter symptoms. Additionally, IICH, FM, and CFS are frequently associated with sympathetic overactivity symptoms and obesity. These conditions share a strong female predominance and are frequently associated with Ehlers-Danlos syndrome. CONCLUSION: IICH, FM, and CFS share a large variety of symptoms that might all be explained by the same pathophysiology of increased cerebrospinal pressure.

Stress, inflammation and natural treatments.
Theoharides TC, Kavalioti M.
J Biol Regul Homeost Agents. 2018 Nov-Dec;32(6):1345-1347.

Stress and inflammation have become the curses of our times and are the main pathogenetic factors in multiple diseases that are often comorbid and include allergies and asthma, eczema and psoriasis, fibromyalgia syndrome, mast cell activation syndrome, irritable bowel syndrome, myalgic encephalomyelitis/chronic fatigue syndrome and autism spectrum disorder (ASD). Unfortunately, there are no effective drugs. Cross-talk between mast cells and microglia in the hypothalamus and amygdala could explain stress-induced inflammation. We recently showed that the "alarmin" IL-33 could play a major role through its synergistic action with the neuropeptide substance P to stimulate human mast cell secretion of the pro-inflammatory molecules IL-1β, TNF and VEGF. A new formulation using pure luteolin with Ashwagandha has now been developed and could be of significant benefit to patients suffering from these diseases.

Clustering a large Spanish sample of patients with fibromyalgia using the FIQR: differences in clinical outcomes, economic costs, inflammatory markers, and gray matter volumes.
Roig S, Penacoba C, Calandre EP, Slim M, Salgueiro M, Feixas G, Luciano JV.
Pain. 2018 Dec 21. doi: 10.1097/j.pain.0000000000001468.

The main objective of this study is to identify fibromyalgia syndrome (FMS) clusters using the Revised Fibromyalgia Impact Questionnaire (FIQR); and to examine whether the clusters differ in sociodemographic characteristics, clinical measures, direct and indirect costs, levels of inflammatory markers and brain morphometry. A hierarchical cluster analysis was performed to classify a large, pooled Spanish sample of patients with FMS (N=947) using the FIQR as clustering variable. A latent profile analysis was subsequently conducted to confirm the optimal number of FMS clusters. To examine external validity, a battery of clinical measures, economic costs, inflammatory markers and gray matter volumes of relevant cortical and subcortical areas were analyzed. We also compared the discriminant validity of the clusters with the original FIQR severity categories. To promote the implementation in real-world clinical practice, we built a free online cluster calculator. Our findings indicated that a four-cluster solution more clearly captured the heterogeneity of FIQR data and provided the best fit. This cluster solution allowed detection of differences for most clinical outcomes and economic costs. Regarding the inflammatory and brain-based biomarkers, differences were found in C-reactive protein, and tendencies were found in the right medial prefrontal cortex, the right parahippocampal gyrus, and the right middle cingulate cortex; brain regions associated with executive functions and pain processing. The original FIQR categories presented similar results, although their precision in discriminating among the non-extreme categories (i.e., moderate and severe) was not sound. These

findings are discussed in relation to previous research on FMS clustering.

A systematic review of growth hormone in pain medicine: From rodents to humans.
Xu J, Casserly E, Yin Y, Cheng J.
Pain Med. 2019 Jan 5. doi: 10.1093/pm/pny280.

OBJECTIVE: Growth hormone (GH) and GH-related signaling molecules play an important role in nociception and development of chronic pain. This review aims to examine the potential molecular mechanisms through which GH-related signaling modulates sensory hypersensitivity in rodents, the clinical pharmacology of GH, and the clinical evidence of GH treatment for several common pain syndromes. METHODS: A search was conducted using the PUBMED / MEDLINE database, Scopus, and the Cochrane library for all reports published in English on GH in pain management from inception through May 2018. A critical review was performed on the mechanisms of GH-related signaling and the pharmacology of GH. The levels of clinical evidence and implications for recommendations of all of the included studies were graded. RESULTS: The search yielded 379 articles, of which 201 articles were deemed irrelevant by reading the titles. There were 53 reports deemed relevant after reading abstracts. All of these 53 articles were retrieved for the analysis and discussion. CONCLUSIONS: Dysfunction of the GH/insulin-like growth factor 1 (IGF-1)/ghrelin axis was linked to hyperalgesia and several common clinical pain syndromes. Low levels of GH and IGF-1 were linked to pain hypersensitivity, whereas ghrelin appeared to provide analgesic effects. Pretreatment of GH reversed mechanical and thermal hypersensitivity in an animal model of inflammatory pain. Clinical trials support GH treatment in a subgroup of patients with fibromyalgia syndrome (level of evidence: 1B+) or chronic lower back pain syndrome (level of evidence: 2C+).

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. 2018 Nov 22. 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.

Characteristics of endometriosis: A case-cohort study showing elevated IgG titers against the TSH receptor (TRAb) and mental comorbidity.
Ek M, Roth B, Nilsson PM, Ohlsson B.
Eur J Obstet Gynecol Reprod Biol. 2018 Dec;231:8-14. doi: 10.1016/j.ejogrb.2018.09.034.

OBJECTIVES: Endometriosis has been associated with a wide range of factors. The disease share immunological features with autoimmune diseases, and the prevalence of both hypo- and hyperthyroidism has been reported to be increased. However, the associations have to be confirmed and the mechanisms explored. The aim of this observational study was to investigate socioeconomic factors, lifestyle habits, and somatic and mental comorbidities in endometriosis compared to the general population. STUDY DESIGN: In all, 172 women with endometriosis completed a study questionnaire and were interviewed regarding socioeconomic factors, lifestyle habits, psychological well-being, and medical history. Bowel symptoms were measured by the Visual Analogue Scale for Irritable Bowel Syndrome (VAS-IBS). Serum was analyzed for IgG levels of TSH receptor antibodies (TRAb) and anti-thyroid peroxidase (TPO) antibodies. Women from the general population served as controls. Differences were calculated by logistic regression, adjusted for confounders. RESULTS: Alcohol intake, leisure time physical activity, body mass index and asthma were inversely, whereas IBS was positively associated with endometriosis. Hypothyroidism and anti-TPO antibodies did not associate, but elevated TRAb antibody titers were associated with endometriosis (odds ratio (OR): 539.26; 95% confidence interval (CI): 114.29-2544.32 for highest versus lowest tertile; p for trend < 0.001). Impaired psychological well-being (p for trend = 0.003) and current intake of antidepressant medication (OR: 3.54; 95% CI: 1.22-10.28; p=0.020) associated with endometriosis, and impaired psychological well-being correlated with all gastrointestinal symptoms measured (all p < 0.001). CONCLUSIONS: Lifestyle habits and asthma are inversely associated, and IBS and impaired psychological well-being are positively associated with endometriosis. TRAb titers are associated with endometriosis, supporting a link between endometriosis, autoimmunity and thyroid pathophysiology, although overt thyroid diseases do not associate.

EPIDEMIOLOGY STUDIES

Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017.

GBD 2017 Disease and Injury Incidence and Prevalence Collaboratros

Lancet. 2018 Nov 10;392(10159):1789-1858. doi: 10.1016/S0140-6736(18)32279-7.

BACKGROUND: The Global Burden of Diseases, Injuries, and Risk Factors Study 2017 (GBD 2017) includes a comprehensive assessment of incidence, prevalence, and years lived with disability (YLDs) for 354 causes in 195 countries and territories from 1990 to 2017. Previous GBD studies have shown how the decline of mortality rates from 1990 to 2016 has led to an increase in life expectancy, an ageing global population, and an expansion of the non-fatal burden of disease and injury. These studies have also shown how a substantial portion of the world's population experiences non-fatal health loss with considerable heterogeneity among different causes, locations, ages, and sexes. Ongoing objectives of the GBD study include increasing the level of estimation detail, improving analytical strategies, and increasing the amount of high-quality data. METHODS: We estimated incidence and prevalence for 354 diseases and injuries and 3484 sequelae. We used an updated and extensive body of literature studies, survey data, surveillance data, inpatient admission records, outpatient visit records, and health insurance claims, and additionally used results from cause of death models to inform estimates using a total of 68,781 data sources. Newly available clinical data from India, Iran, Japan, Jordan, Nepal, China, Brazil, Norway, and Italy were incorporated, as well as updated claims data from the USA and new claims data from Taiwan (province of China) and Singapore. We used DisMod-MR 2.1, a Bayesian meta-regression tool, as the main method of estimation, ensuring consistency between rates of incidence, prevalence, remission, and cause of death for each condition. YLDs were estimated as the product of a prevalence estimate and a disability weight for health states of each mutually exclusive sequela, adjusted for comorbidity. We updated the Socio-

demographic Index (SDI), a summary development indicator of income per capita, years of schooling, and total fertility rate. Additionally, we calculated differences between male and female YLDs to identify divergent trends across sexes. GBD 2017 complies with the Guidelines for Accurate and Transparent Health Estimates Reporting. FINDINGS: Globally, for females, the causes with the greatest age-standardised prevalence were oral disorders, headache disorders, and haemoglobinopathies and haemolytic anaemias in both 1990 and 2017. For males, the causes with the greatest age-standardised prevalence were oral disorders, headache disorders, and tuberculosis including latent tuberculosis infection in both 1990 and 2017. In terms of YLDs, low back pain, headache disorders, and dietary iron deficiency were the leading Level 3 causes of YLD counts in 1990, whereas low back pain, headache disorders, and depressive disorders were the leading causes in 2017 for both sexes combined. All-cause age-standardised YLD rates decreased by 3·9% (95% uncertainty interval [UI] 3·1-4·6) from 1990 to 2017; however, the all-age YLD rate increased by 7·2% (6·0-8·4) while the total sum of global YLDs increased from 562 million (421-723) to 853 million (642-1100). The increases for males and females were similar, with increases in all-age YLD rates of 7·9% (6·6-9·2) for males and 6·5% (5·4-7·7) for females. We found significant differences between males and females in terms of age-standardised prevalence estimates for multiple causes. The causes with the greatest relative differences between sexes in 2017 included substance use disorders (3018 cases [95% UI 2782-3252] per 100,000 males vs 1400 [1279-1524] per 100,000 in females), transport injuries (3322 [3082-3583] vs 2336 [2154-2535]), and self-harm and interpersonal violence (3265 [2943-3630] vs 5643 [5057-6302]). INTERPRETATION: Global all-cause age-standardised YLD rates have improved only slightly over a period spanning nearly three decades. However, the magnitude of the non-fatal disease burden has expanded globally, with increasing numbers of people who have a wide spectrum of conditions. A subset of conditions has remained globally pervasive since 1990, whereas other conditions have displayed more dynamic trends, with different ages, sexes, and geographies across the globe experiencing varying burdens and trends of health loss. This study emphasises how global improvements in premature mortality for select conditions have led to older populations with complex and potentially expensive diseases, yet also highlights global achievements in certain domains of disease and injury.

Changes in health in the countries of the UK and 150 English Local Authority areas 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016.
Steel N, Ford JA, Newton JN, Davis ACJ, Vos T, Naghavi M, Glenn S, Hughes A, Dalton AM, Stockton D, Humphreys C, Dallat M, Schmidt J, Flowers J, Fox S, Abubakar I, Aldridge RW, Baker A, Brayne C, Brugha T, Capewell S, Car J, Cooper C, Ezzati M, Fitzpatrick J, Greaves F, Hay R, Hay S, Fee F, Larson HJ, Lyons RA, Majeed A, McKee M, Rawaf S, Rutter H, Saxena S, Sheikh A, Smeeth L, Viner RM, Vollset SE, Williams HC, Wolfe C, Woolf A, Murray CJL.
Lancet. 2018 Nov 3;392(10158):1647-1661. doi: 10.1016/S0140-6736(18)32207-4.

BACKGROUND: Previous studies have reported national and regional Global Burden of Disease (GBD) estimates for the UK. Because of substantial variation in health within the UK, action to improve it requires comparable estimates of disease burden and risks at country and local levels. The slowdown in the rate of improvement in life expectancy requires further investigation. We use GBD 2016 data on mortality, causes of death, and disability to analyse the burden of disease in the countries of the UK and within local authorities in England by deprivation quintile. METHODS: We extracted data from the GBD 2016 to estimate years of life lost (YLLs), years lived with disability (YLDs), disability-adjusted life-years (DALYs), and attributable risks from 1990 to 2016 for England, Scotland, Wales, Northern Ireland, the UK, and 150 English Upper-Tier Local Authorities. We estimated the burden of disease by cause of death, condition, year, and sex. We analysed the association between burden of disease and socioeconomic deprivation using the Index of Multiple Deprivation. We present results for all 264 GBD causes of death combined and the leading 20 specific causes, and all 84 GBD risks or risk clusters combined and 17 specific risks or risk clusters. FINDINGS: The leading causes of age-adjusted YLLs in all UK countries in 2016 were ischaemic heart disease, lung cancers, cerebrovascular disease, and chronic obstructive pulmonary disease. Age-standardised rates of YLLs for all causes varied by two times between local

areas in England according to levels of socioeconomic deprivation (from 14,274 per 100,000 population [95% uncertainty interval 12,791-15,875] in Blackpool to 6,888 [6,145-7,739] in Wokingham). Some Upper-Tier Local Authorities, particularly those in London, did better than expected for their level of deprivation. Allowing for differences in age structure, more deprived Upper-Tier Local Authorities had higher attributable YLLs for most major risk factors in the GBD. The population attributable fractions for all-cause YLLs for individual major risk factors varied across Upper-Tier Local Authorities. Life expectancy and YLLs have improved more slowly since 2010 in all UK countries compared with 1990-2010. In nine of 150 Upper-Tier Local Authorities, YLLs increased after 2010. For attributable YLLs, the rate of improvement slowed most substantially for cardiovascular disease and breast, colorectal, and lung cancers, and showed little change for Alzheimer's disease and other dementias. Morbidity makes an increasing contribution to overall burden in the UK compared with mortality. The age-standardised UK DALY rate for low back and neck pain (1,795 [1,258-2,356]) was higher than for ischaemic heart disease (1,200 [1,155-1,246]) or lung cancer (660 [642-679]). The leading causes of ill health (measured through YLDs) in the UK in 2016 were low back and neck pain, skin and subcutaneous diseases, migraine, depressive disorders, and sense organ disease. Age-standardised YLD rates varied much less than equivalent YLL rates across the UK, which reflects the relative scarcity of local data on causes of ill health. INTERPRETATION: These estimates at local, regional, and national level will allow policy makers to match resources and priorities to levels of burden and risk factors. Improvement in YLLs and life expectancy slowed notably after 2010, particularly in cardiovascular disease and cancer, and targeted actions are needed if the rate of improvement is to recover. A targeted policy response is also required to address the increasing proportion of burden due to morbidity, such as musculoskeletal problems and depression. Improving the quality and completeness of available data on these causes is an essential component of this response.

Prevalence of comorbid chronic pain and mental health conditions in Canadian Armed Forces active personnel: analysis of a cross-sectional survey.
Vun E, Turner S, Sareen J, Mota N, Afifi TO, El-Gabalawy R.
CMAJ Open. 2018 Nov 2;6(4):E528-E536. doi: 10.9778/cmajo.20180093.

BACKGROUND: Chronic pain conditions and mental disorders have high prevalence rates in military populations. However, few investigations have examined the comorbidity between chronic pain conditions and specific mental disorders among Canadian active military personnel. METHODS: We conducted a secondary analysis of data from the 2013 Canadian Forces Mental Health Survey (CFMHS) concerning the population of regular members. Diagnostic interviews assessed the presence of mental disorders, and participants self-reported chronic pain conditions (i.e., arthritis, back problems, musculoskeletal conditions, migraines) and indicators of pain severity. We used multiple logistic regressions to assess associations between chronic pain conditions and mental disorders. We used cross-tabulations to assess the prevalence of pain severity indicators in comorbid relationships compared with the chronic pain condition alone. We used moderation analyses to examine the interactions between pain condition by pain severity, and pain condition by activity limitation, respectively, on mental disorders. RESULTS: The CFMHS included data from 6696 regular members and had a response rate of 79.8%. About one-quarter (*n* = 1761) of military personnel reported having chronic pain. In the fully adjusted model, all assessed pain conditions were significantly associated with posttraumatic stress disorder (PTSD) (odds ratio [OR] range 1.86-2.55), and several pain conditions were associated with major depressive episode, generalized anxiety disorder and panic disorder. Back problems were significantly associated with all mental disorders apart from alcohol use disorders (OR range 1.40-2.17). Cross-tabulations showed higher prevalence estimates of endorsement for pain severity indicators among pain conditions and comorbid mental disorders, compared with pain conditions alone. Formal moderation analyses showed a significant relationship between migraine and activity limitation on PTSD. INTERPRETATION: Chronic pain conditions are prevalent and co-occur with mental disorders among Canadian regular force members. Greater understanding of these chronic pain conditions and mental disorders and their

impact on people's abilities to adapt to both military and civilian life is needed.

Living with disabling chronic pain: results from a face-to-face cross-sectional population-based study.
Cabrera-Leon A, Cantero-Braojos MA, Garcia-Fernandez L, Guerra de Hoyos JA.
BMJ Open. 2018 Nov 12;8(11):e020913. doi: 10.1136/bmjopen-2017-020913.

OBJECTIVES: To estimate the prevalence of disabling chronic pain (DCP) in Spanish adults, to analyse its characteristics, to determine its multimorbidity and to identify its associated factors. SETTINGS: 2011 Andalusian Health Survey, a cross-sectional population survey based on face-to-face home interviews. PARTICIPANTS: 6507 people aged 16 years or older and living in Andalusia, Spain. OUTCOMES: The response variable was disabling chronic pain. Multivariate multinomial logistic regression models were used to analyse the association of factors with disabling chronic pain. The sample design was considered throughout the statistical analysis. RESULTS: The prevalence of disabling chronic pain in the Spanish adult population was 11.36% (95% CI 11.23 to 11.49), while that of non-disabling chronic pain was 5.67% (95% CI 5.57 to 5.77). Disabling chronic pain was associated with high multimorbidity (especially in women (51%) and in the elderly (70%) with three or more additional chronic diseases), as well as with disadvantaged social status (such as female gender (OR=2.12), advanced age ($OR_{10\text{-year increase}}$=1.28), unemployment (OR=1.33), manual work (OR=1.26), low income (OR=1.14) and reduced emotional social support (OR=1.04)). Other influential factors were tobacco consumption (OR=1.42), sleeping less than or equal to 7 hours (OR=1.2), environmental or work conditions (OR=1.16) and quality of life (OR-mental=1.21, OR-physical=2.37). CONCLUSIONS: The population with disabling chronic pain was associated with multimorbidity, vulnerable social status and an impaired quality of life. In contrast, the population with non-disabling chronic pain showed almost no differences when compared with the population without chronic pain. The association between DCP and mental disorders highlights the need for psychosocial services in the management of chronic pain.

Comorbidity of chronic back pain and depression in Germany: Results from the GEDA study, 2009 and 2010.
Martini L, Hoffmann F.
Z Evid Fortbild Qual Gesundhwes. 2018 Nov;137-138:62-68. doi: 10.1016/j.zefq.2018.10.003.

BACKGROUND: Depression and chronic back pain are two common disabling diseases. Studies suggest an association of both conditions. We aimed to determine sex- and age-specific prevalence of depression, chronic back pain and the combination of both. Furthermore, influencing factors and resulting consequences were analyzed. METHODS: Data was derived by pooling two representative cross-sectional telephone surveys "German Health Update (GEDA)" 2009 and 2010 including 43,312 adults. Self-reported physician-diagnosed chronic somatic diseases including diagnosed depression and chronic backpain in the past 12 months were assessed. Age- and sex-specific prevalence was calculated. Logistic regression was used to examine their association and identify influencing factors. Sick days, missed workdays and doctor visits were compared for single disease vs. comorbidity. RESULTS: 12-month prevalence for diagnosed depression was 6.7 %, for chronic back pain 21.1 %, and the comorbidity of both was 3.0 %. An association of depression and chronic back pain was found for both sexes and all age groups. The characteristics "female sex", "being 50-64 years of age", "low socioeconomic status" and "low social support" increased the likelihood of comorbid depression and chronic back pain. Comorbid depression and chronic back pain increased the number of sick days, missed workdays and doctor visits significantly. CONCLUSION: The results show a strong association of depression and chronic back pain. The direction of association cannot be determined due to the cross-sectional design of the study. Identifying patients at risk for comorbid depression and chronic back pain early on might improve treatment and reduce the economic impact.

Is endometriosis associated with irritable bowel syndrome? A cross-sectional study.
Schomacker ML, Hansen KE, Ramlau-Hansen CH, Forman A.
Eur J Obstet Gynecol Reprod Biol. 2018 Dec;231:65-69. doi: 10.1016/j.ejogrb.2018.10.023.

OBJECTIVES: Previous studies have found a high prevalence of irritable bowel syndrome (IBS). However, data on this relation in women without bowel endometriosis is limited. The aim of this study was to compare the prevalence of IBS in women with endometriosis to the prevalence in women without endometriosis and to investigate if the prevalence of IBS was associated with bowel involved endometriosis. STUDY DESIGN: Information for this cross-sectional study was collected through an online questionnaire. A total of 373 women completed the questionnaire. After exclusions, 254 with endometriosis and 102 without endometriosis were included (N=356). Endometriosis was identified by self-reported diagnosis. IBS was identified by; 1. self-reported diagnosis prior to the study and 2. fulfillment of ROME III diagnostic criteria in this study. Odds ratios were calculated to estimate the strength of the association between IBS and endometriosis. A separate analysis, restricted to women without bowel involved endometrioses, was conducted. Adjustment for potential confounders (age, gastroenterological comorbidities and length of education) was performed. RESULTS AND CONCLUSIONS: The prevalence of IBS was higher in women with endometriosis compared to the women without endometriosis (OR=5.32 (CI: 2.88;9.81)). In the analysis restricted to women without bowel involved endometriosis, the prevalence was also higher in women with endometriosis compared to women without endometriosis (OR=6.54 (CI 95% 3.22;13.29)). Thus, this study found a higher prevalence of IBS in women with endometriosis compared to women without endometriosis. This finding seems to be unrelated to bowel involvement. This opens new perspectives in relation to treatment of endometriosis.

Painful bladder symptoms related to somatic syndromes in a convenience sample of community women with overactive bladder symptoms.
Kowalik CG, Cohn JA, Delpe S, Kaufman MR, Wein A, Dmochowski RR, Reynolds WS.
J Urol. 2018 Dec;200(6):1332-1337. doi: 10.1016/j.juro.2018.06.070.

PURPOSE: We investigated the relationship of painful bladder filling and urinary urgency to somatic and chronic pain symptoms in women with overactive bladder without an interstitial cystitis/bladder pain syndrome diagnosis. MATERIALS AND METHODS: Women who met overactive bladder criteria based on symptoms were recruited, including 183 (83.9%) from the community and 35 (16.1%) from the urology clinic to complete validated questionnaires assessing urinary symptoms, somatic symptoms and pain syndromes. Participants were categorized into 1 of 3 groups, including 1) neither symptom, 2) either symptom or 3) both symptoms, based on their reports of painful urinary urgency and/or painful bladder filling. Multivariable regression analyses were performed to determine factors predictive of having painful urgency and/or painful filling. RESULTS: Of 218 women with overactive bladder 101 (46%) had neither painful bladder filling nor urinary urgency, 94 (43%) had either symptom and 23 (11%) had both symptoms. When controlling for age, women with either or both urological pain symptoms were more likely to have irritable bowel syndrome, chronic pelvic pain and temporomandibular disorder than women in the neither group. Additionally, these women had higher pain intensity and somatic symptoms scores than women with neither symptom. CONCLUSIONS: The majority of women with overactive bladder who had not been diagnosed with interstitial cystitis/bladder pain syndrome reported painful urgency and/or painful filling. Experiencing painful urgency and/or filling was associated with an increased somatic symptom burden and greater pain intensity. These findings support the hypothesis that overactive bladder and interstitial cystitis/bladder pain syndrome diagnoses may represent a continuum of bladder hypersensitivity.

Physical-mental comorbidity of pediatric migraine in the Philadelphia Neurodevelopment Cohort.
Lateef T, He JP, Nelson K, Calkins ME, Gur R, Gur R, Merikangas KR.

J Pediatr. 2018 Oct 29. pii: S0022-3476(18)31304-0. doi: 10.1016/j.jpeds.2018.09.033.

OBJECTIVE: To examine the associations between headaches and migraine with physical and mental disorders in a large pediatric registry. STUDY DESIGN: In total, 9329 youth aged 8-21 years from the Philadelphia Neurodevelopmental Cohort were included. Physical conditions, including headache, were ascertained from electronic medical records and in-person interviews. Modified International Classification of Headache Disorders (ICHD-II) criteria were used to classify migraine symptoms. Forty-two other physical conditions were classified into 14 classes of medical disorders. Mental disorders were assessed using an abbreviated version of the Kiddie-Schedule for Affective Disorders and Schizophrenia. RESULTS: Lifetime prevalence of any headache was 45.5%, and of migraine was 22.6%. Any headache was associated with a broad range of physical disorders, attention-deficit/hyperactivity disorder (OR 1.2 [CI 1.1-1.4]), and behavior disorders (1.3[1.1-1.5]). Youth with migraine had greater odds of specific physical conditions and mental disorders, including respiratory, neurologic/central nervous system, developmental, anxiety, behavior, and mood disorders than those with nonmigraine headache (OR ranged from 1.3 to 1.9). CONCLUSIONS: Comorbidity between headaches with a range of physical conditions that have been associated with adult migraine demonstrates that multimorbidity occurs early in development. Comorbidity may be an important index of heterogeneity of migraine that can guide clinical management, genetic investigation, and future research on shared pathophysiology with other disorders.

What is the association between the presence of comorbidities and the appropriateness of care for low back pain? A population-based medical record review study.
Ramanathan S, Hibbert P, Wiles L, Maher CG, Runciman W.
BMC Musculoskelet Disord. 2018 Nov 6;19(1):391. doi: 10.1186/s12891-018-2316-z.

BACKGROUND: Although "non-specific" in 90% of cases, low back pain (LBP) is often treated as an independent entity, even though comorbidities are commonly associated with it. There is evidence that some LBP may be related to chronic conditions or be a symptom of poor health. The purpose of this study was to clarify the extent of comorbidities amongst a cohort of Australian adults with LBP and examine if having concurrent conditions has any association with appropriateness of care for LBP. METHODS: A population-based sample of patients with one or more of 22 common conditions was recruited by telephone; consents were obtained to review their medical records. Trained surveyors extracted information from their medical records to examine the care patients received for their LBP with respect to ten indicators of appropriate care, ratified by LBP experts. Using LBP as the index condition, lists of self-reported comorbidities and those that were documented in medical records were compared. Medical records were reviewed and analysed with respect to appropriateness of care to identify any significant differences in care received between patients with LBP only and those with LBP plus comorbidities. RESULTS: One hundred and sixty four LBP patients were included in the analysis. Over 60% of adults with LBP in Australia had one of 17 comorbidities documented, with females being more likely than males to have comorbid conditions (63% vs 37%, p=0.012). The more comorbidities, the poorer their reported health status (63% vs 30%, p=0.006). Patients with comorbidities were significantly less likely to receive appropriate LBP care on nine of the ten LBP indicators (p<0.05). CONCLUSIONS: This study established that the presence of comorbidities is associated with poorer care for LBP. Understanding why this is so is an important direction for future research. Further studies using a larger cohort are needed to explore the association between comorbidities and appropriateness of care for LBP, to better inform guidelines and practice in this area.

Is chronic low back pain a risk factor for diabetes? The Nord-Trøndelag Health Study.
Heuch I, Heuch I, Hagen K, Sorgjerd EP, Asvold BO, Zwart JA.
BMJ Open Diabetes Res Care. 2018 Oct 23;6(1):e000569. doi: 10.1136/bmjdrc-2018-000569. eCollection 2018.

OBJECTIVE: The purpose of this study was to examine the risk of diabetes associated with the

presence or absence of chronic low back pain, considering both cross-sectional and cohort data. RESEARCH DESIGN AND METHODS: Analyses were based on the Norwegian HUNT2 and HUNT3 surveys of Nord-Trøndelag County. The prevalence of diabetes was compared in groups with and without chronic low back pain among 45 157 participants aged 30-69 years. Associations between low back pain at baseline and risk of diabetes were examined in an 11-year follow-up of 30 380 individuals with no baseline diagnosis of diabetes.
The comorbidity between diabetes and low back pain was assessed at the end of follow-up. All analyses were carried out considering generalized linear models incorporating adjustment for other relevant risk factors. RESULTS: Cross-sectional analyses did not reveal any association between low back pain and diabetes. With adjustment for age, body mass index, physical activity and smoking, the cohort study of women showed a significant association between low back pain at baseline and risk of diabetes (RR 1.30; 95% CI 1.09 to 1.54, p=0.003). The association differed between age groups (p=0.015), with a stronger association in relatively young women. In men, no association was found in the whole age range (RR 1.02; 95% CI 0.86 to 1.21, p=0.82). No association was observed between diabetes and chronic low back pain at the end of follow-up. CONCLUSION: Among younger women, those with chronic low back pain may have an increased risk of diabetes.

Characteristics associated with high-impact pain in people with temporomandibular disorder: A cross-sectional study.
Miller VE, Poole C, Golightly Y, Barrett D, Chen DG, Ohrbach R, Greenspan JD, Fillingim RB, Slade GD.
J Pain. 2018 Oct 4. pii: S1526-5900(18)30665-5. doi: 10.1016/j.jpain.2018.09.007.

High-impact (disabling) pain diminishes the quality of life and increases health care costs. The purpose of this study was to identify the variables that distinguish between high- and low-impact pain among individuals with painful temporomandibular disorder (TMD). Community-dwelling adults (n=846) with chronic TMD completed standardized questionnaires that assessed the following: 1) sociodemographic characteristics, 2) psychological distress, 3) clinical pain, and 4) experimental pain. We used high-impact pain, classified using the Graded Chronic Pain Scale, as the dependent variable in logistic regression modeling to evaluate the contribution of variables from each domain. Cross-validated area under the receiver operating characteristic curve (AUC) quantified model discrimination. One-third of the participants had high-impact pain. Sociodemographic variables discriminated weakly between low- and high-impact pain (AUC =0.61, 95% confidence interval [CI]=0.57, 0.65), with the exception of race. An 18-variable model encompassing all 4 domains had good discrimination (AUC=0.79, 95% CI=0.75, 0.82), as did a simplified model (sociodemographic variables plus catastrophizing, jaw limitation, and number of painful body sites) (AUC=0.79, 95% CI=0.76, 0.82). Duration of pain, sex, and experimental pain testing results were not associated. The characteristics that discriminated most effectively between people with low- and high-impact TMD pain included clinical pain features and the ability to cope with pain. PERSPECTIVE: This article presents the results of a multivariable model designed to discriminate between people with high- and low-impact pain in a community-based sample of people with painful chronic TMD. The findings emphasize the importance of catastrophizing, jaw limitation, and painful body sites associated with pain-related impact.

Alexithymia and temporomandibular joint and facial pain in the general population.
Kindler S, Schwahn C, Terock J, Mksoud M, Bernhardt O, Biffar R, Volzke H, Metelmann HR, Grabe HJ.
J Oral Rehabil. 2018 Nov 25. doi: 10.1111/joor.12748.

BACKGROUND: Associations of alexithymia
with temporomandibular pain disorders (TMD), facial pain, head pain and migraine have been described, but the role of the different dimensions of alexithymia in pain development remained incompletely understood. OBJECTIVES: We sought to investigate the associations of alexithymia and its subfactors with signs of TMD and with facial pain, head pain and

migraine in the general population. METHODS: A total of 1494 subjects from the general population completed the Toronto Alexithymia Scale-20 (TAS-20) and underwent a clinical functional examination with palpation of the temporomandibular joint and masticatory muscles. Facial pain, migraine and head pain were defined by questionnaire. A set of logistic regression analyses was applied with adjustment for age, sex, education, number of traumatic events, depressive symptoms and anxiety. RESULTS: Alexithymia was associated with TMD joint pain (Odds Ratio 2.63; 95% confidence interval 1.60-4.32 for 61 TAS-20 points vs the median of the TAS-20 score) and with facial pain severity (Odds Ratio 3.22; 95% confidence interval 1.79-5.79). Differential effects of the subfactors were discovered with difficulties in identifying feelings as main predictor for joint, facial, and head pain, and externally oriented thinking (EOT) as U-shaped and strongest predictor for migraine. CONCLUSION: Alexithymia was moderately to strongly associated with signs and symptoms of TMD. These results should encourage dental practitioners using the TAS-20 in clinical practice, to screen TMD, facial or head pain patients for alexithymia and could also help treating alexithymic TMD, facial or head pain patients.

The comorbidities of dysmenorrhea: a clinical survey comparing symptom profile in women with and without endometriosis.
Evans SF, Brooks TA, Esterman AJ, Hull ML, Rolan PE.
J Pain Res. 2018 Dec 13;11:3181-3194. doi: 10.2147/JPR.S179409. eCollection 2018.

PURPOSE: Dysmenorrhea is a common disorder that substantially disrupts the lives of young women. The frequency of 14 associated symptoms both within and outside the pelvis was determined. PATIENTS AND METHODS: Symptom questionnaires were completed by 168 women with dysmenorrhea, allocated to three groups based on their diagnostic status for endometriosis confirmed (Endo+), endometriosis excluded (Endo-), or endometriosis diagnosis unknown (No Lap). Those with endometriosis confirmed were further divided into current users (Endo+ Hx+) and non-users of hormonal treatments (Endo+ Hx-). Users of hormonal treatments were further divided into users (Endo+ Hx+ LIUCD+) and non-users (Endo+ Hx+ LIUCD-) of a levonorgestrel-releasing intra-uterine contraceptive device (LIUCD). The frequency and number of symptoms within groups and the effect of previous distressing sexual events were sought. RESULTS: Women with and without endometriosis lesions had similar symptom profiles, with a mean of 8.5 symptoms per woman. Only 0.6% of women reported dysmenorrhea alone. The presence of stabbing pelvic pains was associated with more severe dysmenorrhea (P=0.006), more days per month of dysmenorrhea (P=0.003), more days per month of pelvic pain (P=0.016), and a diagnosis of migraine(P=0.054). The symptom profiles of the Endo+ Hx+ and Endo+ Hx- groups were similar. A history of distressing sexual events was associated with an increased number of pain symptoms (P=0.003). CONCLUSION: Additional symptoms are common in women with dysmenorrhea, and do not correlate with the presence or absence of endometriosis lesions. Our study supports the role of central sensitization in the pain of dysmenorrhea. The presence of stabbing pelvic pains was associated with increased severity of dysmenorrhea, days per month of dysmenorrhea, days per month of pelvic pain, and a diagnosis of migraine headache. A past history of distressing sexual events is associated with an increased number of pain symptoms.

Cognitive-behavioural and social factors do not predict recurrent secondary healthcare use in patients with fibromyalgia: a longitudinal study.
Vervoort VM, Vriezekolk JE, Olde Hartman TC, van Helmond T, van der Laan WH, Geenen R, van den Ende CH.
Clin Exp Rheumatol. 2018 Nov 29.

OBJECTIVES: Healthcare use in fibromyalgia (FM) is relatively high. Besides disease-related variables, cognitive-behavioural factors have been concurrently associated with healthcare use. It is unknown whether cognitive-behavioural and social factors also predict future healthcare use. The aim of this study was to identify cognitive-behavioural and social factors predicting recurrent secondary healthcare use in FM. METHODS: Using self-reported

questionnaires, healthcare use, cognitive-behavioural, social, sociodemographic and disease-related variables including comorbidities were collected in 199 patients with FM, in a prospective longitudinal cohort spanning 18 months. Patients were recruited after receiving their diagnosis and protocolled treatment advice by a rheumatologist. Univariate and multivariate logistic regression models examined whether and which variables were predictors for recurrent secondary healthcare use. Internal validation was performed to correct for over-fit of the final multivariate model. RESULTS: Recurrent secondary healthcare use was lower than initial secondary healthcare use. Univariate analysis showed that having at least one comorbidity, depressive feelings, severe consequences of FM, low personal control and a high severity of fibromyalgia predicted recurrent secondary healthcare use. In the multivariate model, having at least one comorbidity was the only remaining predictor for recurrent secondary healthcare use. CONCLUSIONS: Our results suggest that the existence of comorbidities as communicated by the patient is the strongest warning signal for recurrent secondary healthcare use in FM. There seems no value in using cognitive-behavioural and social factors for early identification of patients with FM at risk for recurrent secondary healthcare use.

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. 2018 Dec 18. 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.

Physical activity and sleep in chronic fatigue syndrome and fibromyalgia syndrome: Associations with symptom severity in the general population cohort lifelines.
Joustra ML, Zijlema WL, Rosmalen JGM, Janssens KAM.
Pain Res Manag. 2018 Nov 4;2018:5801510. doi: 10.1155/2018/5801510. eCollection 2018.

OBJECTIVE: The aim of the current study was to compare physical activity and sleep duration between patients with chronic fatigue syndrome (CFS), patients with fibromyalgia syndrome (FMS), and controls and to examine the association between physical activity level and sleep duration with symptom severity within these patient groups. METHODS: This study used data of LifeLines, a general population cohort in which 1.0% (*n*=943, 63.7% female, age 44.9 (SD 11.6) years) reported CFS, 3.0% (*n*=2,714; 91.6% female; age 48.4 (SD 10.7) years) reported FMS, and 95.7% (*n*=87,532; 57.9% female; age 44.3 (SD 12.4) years) reported neither CFS nor FMS. Physical activity, sleep duration, and symptom severity were assessed by questionnaires and analysed using ANCOVA and regression analyses, adjusted for age, sex,

body mass index, smoking, and educational level. RESULTS: Patients with CFS and FMS had significantly lower physical activity scores (8834 ± 5967 and 8813 ± 5549 MET ∗ minutes) than controls (9541 ± 5533; $p < 0.001$). Patients with CFS had the longest sleep duration (466 ± 86 minutes) compared to patients with FMS and controls (450 ± 67 and 446 ± 56; $p < 0.001$). A linear association between physical activity, sleep duration, and symptom severity was only found in controls, in whom higher physical total activity scores and longer sleep duration were associated with a lower symptom severity. In contrast, quadratic associations were found in all groups: both relatively low and high physical activity scores and relatively short and long sleep duration were associated with higher symptom severity in CFS, FMS, and controls. CONCLUSION: This study indicates that patients with CFS or FMS sleep longer and are less physically active than controls on average. Both low and high levels of physical activity and short and long sleep duration are associated with higher symptom severity, suggesting the importance of patient-tailored treatment.

Clinical features contributing to cortical thickness changes in chronic migraine - A pilot study.
Woldeamanuel YW, DeSouza DD, Sanjanwala BM, Cowan RP.
Headache. 2018 Nov 23. doi: 10.1111/head.13452.

OBJECTIVES: The objectives of this cross-sectional pilot study were threefold: to identify regions of cortical thickness that differentiate chronic migraine (CM) from controls, to assess group differences in interregional cortical thickness covariance, and to determine group differences in associations between clinical variables and cortical thickness. BACKGROUND: Cortical thickness alterations in relation to clinical features have not been adequately explored in CM. Assessment of this relationship can be useful to describe cortical substrates for disease progression in migraine and to identify clinical variables that warrant management emphasis. METHODS: Thirty CM cases (mean age 40 years; male-to-female 1:4) and 30 sex-matched healthy controls (mean age 40 years) were enrolled. Participants completed self-administered and standardized questionnaires assessing headache-related clinical features and common psychological comorbidities. T1-weighted brain images were acquired on a 3T MRI. A whole-brain cortical thickness analysis was performed. Additionally, correlations between all brain regions were assessed to examine interregional cortical thickness covariance. Interactions were analyzed to identify clinical variables that were significantly associated with cortical thickness. RESULTS: The whole brain cortical thickness analysis revealed no significant differences between CM patients and controls. However, significant associations between clinical features and cortical thickness were observed for the patients only. These associations included the right superior temporal sulcus (R^2 = 0.72, P = .001) and the right insula (R^2 = 0.71, P = .002) with distinct clinical variables ie, longer history of CM, posttraumatic stress disorder (PTSD), sleep quality, pain self-efficacy, and somatic symptoms. Higher interregional cortical covariance was found in CM compared to controls (OR = 3.1, CI 2.10-4.56, P < .0001), such that cortical thickness between regions tended to be more correlated in patients, particularly in the temporal and frontal lobes. CONCLUSION: CM patients have significantly greater cortical covariance compared to controls. Cortical thickness in CM patients was predominantly accounted for by CM duration, PTSD, and poor sleep quality, while improved pain self-efficacy buffered cortical thickness. While it is important to address all CM features and comorbidities, it may be useful to emphasize optimizing the management of certain clinical features that contribute to cortical abnormalities including managing PTSD, early management to shorten duration of CM, and improving pain self-efficacy and sleep quality.

Distribution of depression, somatization and pain-related impairment in patients with chronic temporomandibular disorders.
Canales GT, Guarda-Nardini L, Rizzatti-Barbosa CM, Conti PCR, Manfredini D.
J Appl Oral Sci. 2019 Jan 7;27:e20180210. doi: 10.1590/1678-7757-2018-0210.

OBJECTIVE: The aim of this study was to describe the frequency of psychosocial diagnoses in a large sample of patients attending a tertiary clinic for treatment of temporomandibular

disorders (TMD). MATERIAL AND METHODS: Six hundred and ninety-one patients who sought treatment for pain-related TMD were selected. Chronic pain-related disability (Graded Chronic Pain Scale, GCPS), depression [Symptoms Checklist-90 (SCL-90) scale for depression, DEP] and somatization levels (SCL-90 scale for non-specific physical symptoms, SOM) were evaluated through the Research Diagnostic Criteria for TMD (RDC/TMD) Axis II psychosocial assessment; TMD diagnoses were based on the Axis I criteria. RESULTS: The majority of patients presented a low disability or no disability at all, with only a small portion of individuals showing a severely limiting, high disability pain-related impairment (4.3%). On the other hand, abnormal scores of depression and somatization were high, with almost half of the individuals having moderate-to-severe levels of depression and three-fourths presenting moderate-to-severe levels of somatization. The prevalence of high pain-related disability (GCPS grades III or IV), severe / moderate depression and somatization was 14.3%, 44% and 74.1% respectively. Gender differences in scores of SCL-DEP (p=0.031) and SCL-SOM (p=0.001) scales were significant, with females presenting the highest percentage of abnormal values. CONCLUSION: patients with TMD frequently present an emotional profile with low disability, high intensity pain-related impairment, and high to moderate levels of somatization and depression. Therefore, given the importance of psychosocial issues at the prognostic level, it is recommended that clinical trials on TMD treatment include an evaluation of patients' psychosocial profiles.

Irritable bowel syndrome, mental health, and quality of life: Data from a population-based survey in Germany (SHIP-Trend-0).
Schauer B, Grabe HJ, Ittermann T, Lerch MM, Weiss FU, Monnikes H, Volzke H, Enck P, Schwille-Kiuntke J.
Neurogastroenterol Motil. 2018 Nov 15:e13511. doi: 10.1111/nmo.13511.

BACKGROUND: Irritable bowel syndrome (IBS) is associated with reduced quality of life and high healthcare costs. This study aimed to assess the prevalence and risk factors for IBS in a general adult population. METHODS: The Study of Health in Pomerania (SHIP) is a population-based cohort study in northeastern Germany. SHIP-Trend-0 participants enrolled from 2008 to 2012 were grouped according to Rome III criteria (main criteria: abdominal discomfort or crampy or bloating pain for at least six months plus 2/3 additional criteria). Factors associated with IBS were assessed using survey-weighted backward stepwise logistic regression. KEY RESULTS: The final data set included 4194 records. IBS prevalence was 3.5% (3.0%-4.2%). Unemployment (OR: 2.02, 1.26-3.21), headaches (OR: 2.37, 1.59-3.52), mental quality of life (OR: 0.95 per unit increase, 0.93-0.97), and interactions between gender and physical quality of life (P = 0.004) and gender and alexithymia (P = 0.002) predicted IBS probability. The model resulted in a good discrimination (area under the curve = 75.4%) and model fit (F = 0.72, P = 0.69). History of depression (OR: 2.77, 1.94-3.95), back pain (OR: 2.38, 1.69-3.35), early trauma (OR: 1.03, 1.02-1.04), and duration of inpatient treatment within the last twelve months (OR: 1.02, 1.01-1.04) lost their significance in multivariable analysis. CONCLUSIONS & INFERENCES: IBS prevalence was relatively low compared to other studies. Factors predicting IBS were of biological, psychological, and social nature. The association between IBS and pain in different areas of the body indicates a potential underlying complex somatic symptom disorder.

Factors associated with more frequent diagnostic tests and procedures in patients with irritable bowel syndrome.
Lacy B, Ayyagari R, Guerin A, Lopez A, Shi S, Luo M.
Therap Adv Gastroenterol. 2019 Jan 1;12:1756284818818326. doi: 10.1177/1756284818818326. eCollection 2019.

BACKGROUND: Irritable bowel syndrome (IBS) reduces quality of life and burdens healthcare systems. This study identified factors associated with frequent use of IBS diagnostic tests and procedures. METHODS: Using a United States claims database (2001-2012), tests and procedures in IBS patients occurring in the 2-year study period (12 months before/following the first IBS diagnosis) were analyzed: endoscopy, GI transit testing, anorectal procedures,

and radiologic imaging. Patients were classified based on test/procedure frequency (3+, 1-2, or 0). Multivariate logistic regression identified factors associated with more frequent tests / procedures. RESULTS: Among 201,322 IBS patients, 41.7% had 3+ tests/procedures, 35.1% had 1-2, and 23.3% had 0. Patients with more tests/procedures were older [mean age 50.6 (3+ group), more likely to be female and had more comorbidities, including anxiety, depressive disorders, and somatization. Dyspepsia [odds ratio (95% confidence interval): 1.80 (1.72-1.87)], interstitial cystitis [1.60 (1.45-1.77)], gastroesophageal reflux disease [1.59 (1.55-1.63)], constipation [1.50 (1.45-1.54)], and dyspareunia [1.38 (1.25-1.52)] were significantly associated with more tests/procedures (3+ *versus* 1-2), while anxiety, depressive disorders, and somatization were not. Patients with more frequent specialist visits [emergency department (ED; 1.10 (1.09-1.11)) and gastroenterologists (1.26 (1.26-1.27))] or at least one GI-related ED visit or inpatient admission [1.95 (1.86-2.04) and 3.67 (3.48-3.87), respectively] were more likely to have more tests/procedures (all $p < 0.05$). CONCLUSIONS: Test frequency in patients with IBS is strongly associated with demographic and clinical characteristics, especially comorbid conditions related to IBS. Presence of common overlapping comorbid conditions should increase clinicians' confidence in making the diagnosis of IBS, thus curtailing redundant testing and reducing healthcare costs.

Cross-sectional analysis of the associations between fibromyalgia and diabetes mellitus.
Lichtenstein A, Tiosano S, Comaneshter D, Amital H, Cohen AD, Amital D.
Reumatologia. 2018;56(5):275-278. doi: 10.5114/reum.2018.79496.

BACKGROUND: The fibromyalgia syndrome (FMS) is a chronic condition consisting of widespread musculoskeletal pain and tenderness together with mood and cognitive dysfunction. Diabetes mellitus (DM) is a common condition causing significant and detrimental morbidity and mortality. Data on the association between the two conditions is scarce and mainly based on small populations therefore lack solid evidence. OBJECTIVES: To evaluate the association of FMS with DM. MATERIAL AND METHODS: This cross-sectional study used the Clalit Health Services database, the largest Health Maintenance Organization in Israel, serving 4,400,000 members. FMS patients were compared to age- and sex-matched controls regarding chronic comorbid conditions. χ^2 and student's t-tests were used for univariate analysis. RESULTS: The study included 14,296 FMS patients and 71,324 age- and sex-matched controls. The FMS group had a significantly higher proportion of DM patients compared to non-FMS controls (19.8% and 17.4 respectively; OR 1.17, 95% CI: 1.12-1.23, $p < 0.001$). CONCLUSIONS: DM was found to be more common amongst FMS patients compared to matched controls to suggest that the pathophysiology of DM might lead a patient to develop FMS. Consequently, physicians treating DM patients should be aware of the possible risk and asses for clinical signs of FMS in order to diagnose and treat it in time to better their patients' quality of life and disease management.

Prevalence of autism traits and attention-deficit hyperactivity disorder symptoms in a clinical sample of children and adolescents with chronic pain.
Lipsker CW, Bolte S, Hirvikoski T, Lekander M, Holmstrom L, Wicksell RK.
J Pain Res. 2018 Nov 8;11:2827-2836. doi: 10.2147/JPR.S177534. eCollection 2018.

PURPOSE: Recent research has suggested that autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD) may be comorbid to pediatric chronic pain, but the empirical support is yet scarce. Therefore, the current study aimed to investigate the occurrence of traits and symptoms consistent with clinically significant ASD and ADHD in a group of children and adolescents with chronic debilitating pain and examine potential differences in pain and demographic variables between children with and without clinically significant traits and symptoms of ASD and ADHD. PATIENTS AND METHODS: This cross-sectional study included 146 parent-child dyads (102 girls, 111 mothers, children 8-17 years) consecutively referred to a tertiary pain clinic. Parents completed the Social Responsiveness Scale to assess autistic traits, and Conners-3 to measure symptoms of ADHD in their children. Children completed the Lubeck Pain Questionnaire to evaluate experienced pain. RESULTS: Among children, 20 (13.7%) received scores consistent with

clinically significant ASD and 29 (19.9%) received scores consistent with clinically significant ADHD, with a combined prevalence of clinically significant ASD/ADHD traits and symptoms of 26% of the total sample. Only 4.8% of children were previously diagnosed with either disorder. Among children with clinically significant ASD traits, girls were more prevalent, parents reported lower health, and the pain was more likely triggered by being in school. Among children with clinically significant ADHD symptoms, there were no gender differences and pain was more likely triggered by the family situation and new situations. No differences regarding pain intensity, duration, or frequency were found between children with and without clinically significant ASD traits or ADHD symptoms. CONCLUSION: Children with debilitating chronic pain, particularly girls, may present with an elevated risk of having a comorbid, possibly high-functioning, neurodevelopmental disorder. Results suggest that clinical assessment of pediatric chronic pain should include screening for neurodevelopmental disorders.

CLINICAL STUDIES

Chronic pain as a symptom or a disease: The IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11).
Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Korwisi B, Kosek E, Lavand'homme P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen JWS, Wang SJ.
Pain. 2019 Jan;160(1):19-27. doi: 10.1097/j.pain.0000000000001384.

Chronic pain is a major source of suffering. It interferes with daily functioning and often is accompanied by distress. Yet, in the International Classification of Diseases, chronic pain diagnoses are not represented systematically. The lack of appropriate codes renders accurate epidemiological investigations difficult and impedes health policy decisions regarding chronic pain such as adequate financing of access to multimodal pain management. In cooperation with the WHO, an IASP Working Group has developed a classification system that is applicable in a wide range of contexts, including pain medicine, primary care, and low-resource environments. Chronic pain is defined as pain that persists or recurs for more than 3 months. In chronic pain syndromes, pain can be the sole or a leading complaint and requires special treatment and care. In conditions such as fibromyalgia or nonspecific low-back pain, chronic pain may be conceived as a disease in its own right; in our proposal, we call this subgroup "chronic primary pain." In 6 other subgroups, pain is secondary to an underlying disease: chronic cancer-related pain, chronic neuropathic pain, chronic secondary visceral pain, chronic posttraumatic and postsurgical pain, chronic secondary headache and orofacial pain, and chronic secondary musculoskeletal pain. These conditions are summarized as "chronic secondary pain" where pain may at least initially be conceived as a symptom. Implementation of these codes in the upcoming 11th edition of International Classification of Diseases will lead to improved classification and diagnostic coding, thereby advancing the recognition of chronic pain as a health condition in its own right.

Fibromyalgia and irritable bowel syndrome in female pelvic pain.
Johnson CM, Makai GEH.
Semin Reprod Med. 2018 Mar;36(2):136-142. doi: 10.1055/s-0038-1676090.

Fibromyalgia and irritable bowel syndrome are common disorders which often coexist in women with chronic pelvic pain. Like pelvic pain, these disorders describe symptoms without pathologic findings. Women with chronic pelvic pain have a higher prevalence of fibromyalgia (4-31%) and irritable bowel syndrome (8-41%) than the general population. Aberrant pain processing and psychosocial stressors are implicated in the co-occurrence of these pain syndromes (chronic overlapping pain conditions), but active epidemiologic, psychosocial, and neurobiologic research is ongoing. Given the higher prevalence of fibromyalgia and irritable bowel syndrome in women with chronic pelvic pain, gynecologists should have more education in diagnosis and treatment of these and other chronic

overlapping pain conditions to improve care for women.

The role of sleep quality and fatigue on the benefits of an interdisciplinary treatment for adults with chronic pain.
de la Vega R, Racine M, Castarlenas E, Sole E, Roy R, Jensen MP, Miro J, Cane D.
Pain Pract. 2018 Nov 17. doi: 10.1111/papr.12746.

BACKGROUND: Interdisciplinary chronic pain treatment is effective for reducing pain intensity and pain-related disability, and for improving psychological function. However, the mechanisms that underlie these treatment-related benefits are not yet well understood. Sleep problems and fatigue are modifiable factors often comorbid with chronic pain. The goal of this study was to evaluate the role that changes in sleep quality and fatigue might have on the benefits of an interdisciplinary chronic pain treatment. METHODS: A total of 125 adults with chronic pain participated in a 4-week interdisciplinary pain management program. Measures of depression, sleep disturbance, fatigue, pain intensity, and physical function were administered at pre- and post-treatment. Three regression analyses were conducted to evaluate the contribution of pre- to post-treatment improvements in fatigue and sleep disturbance to the pre- to post-treatment improvements in pain intensity, disability, and depression, while controlling for demographic characteristics (age and sex) and pain intensity. RESULTS: Changes in fatigue and sleep disturbance made independent and significant contributions to the prediction of treatment-related benefits in pain intensity; improvements in depressive symptoms were predicted by improvements in fatigue, and improvements in disability were only predicted by pre-treatment and pre- to post-treatment decreases in pain intensity (one of the control variables). CONCLUSIONS: In addition to sleep, fatigue emerged as a key potential mechanism of multidisciplinary chronic pain treatment-related improvements, suggesting that interventions including elements that effectively target sleep and fatigue may enhance the efficacy of interdisciplinary chronic pain programs. This possibility should be evaluated in future research.

Cost-effectiveness of interventions for medically unexplained symptoms: A systematic review.
Wortman MSH, Lokkerbol J, van der Wouden JC, Visser B, van der Horst HE, Olde Hartman TC.
PLoS One. 2018 Oct 15;13(10):e0205278. doi: 10.1371/journal.pone.0205278. eCollection 2018.

BACKGROUND: In primary and secondary care medically unexplained symptoms (MUS) or functional somatic syndromes (FSS) constitute a major burden for patients and society with high healthcare costs and societal costs. Objectives were to provide an overview of the evidence regarding the cost-effectiveness of interventions for MUS or FSS, and to assess the quality of these studies. METHODS: We searched the databases PubMed, PsycINFO, the National Health Service Economic Evaluation Database (NHS-EED) and the CEA registry to conduct a systematic review. Articles with full economic evaluations on interventions focusing on adult patients with undifferentiated MUS or fibromyalgia (FM), irritable bowel syndrome (IBS) and chronic fatigue syndrome (CFS), with no restrictions on comparators, published until 15 June 2018, were included. We excluded preventive interventions. Two reviewers independently extracted study characteristics and cost-effectiveness data and used the Consensus on Health Economic Criteria Checklist to appraise the methodological quality. RESULTS: A total of 39 studies out of 1,613 articles met the inclusion criteria. Twenty-two studies reported costs per quality-adjusted life year (QALY) gained and cost-utility analyses (CUAs). In 13 CUAs the intervention conditions dominated the control conditions or had an incremental cost-effectiveness ratio below the willingness-to-pay threshold of € 50,000 per QALY, meaning that the interventions were (on average) cost-effective in comparison with the control condition. Group interventions focusing on MUS (n = 3) or FM (n = 4) might be more cost-effective than individual interventions. The included studies were heterogeneous with regard to the included patients, interventions, study design, and outcomes. CONCLUSION: This review provides an overview of 39 included studies of interventions for patients with MUS and FSS and the methodological quality of these studies.

Considering the limited comparability due to the heterogeneity of the studies, group interventions might be more cost-effective than individual interventions.

Effect of adding medical cannabis to analgesic treatment in patients with low back pain related to fibromyalgia: an observational cross-over single centre study.
Yassin M, Oron A, Robinson D.
Clin Exp Rheumatol. 2018 Oct 30.

OBJECTIVES: Low back pain (LBP) occurs in many patients with fibromyalgia (FM). The current study aimed to assess the possible pain and function amelioration associated with medical cannabis therapy (MCT) in this setting. METHODS: 31 patients were involved in an observational cross-over study. The patients were screened, treated with 3 months of standardised analgesic therapy (SAT): 5 mg of oxycodone hydrochloride equivalent to 4.5 mg oxycodone and 2.5 mg naloxone hydrochloride twice a day and duloxetine 30 mg once a day. Following 3 months of this therapy, the patients could opt for MCT and were treated for a minimum of 6 months. Patient reported outcomes (PRO's) included: FIQR, VAS, ODI and SF-12 and lumbar range of motion (ROM) was recorded using the modified Schober test. RESULTS: While SAT led to minor improvement as compared with baseline status, the addition of MCT allowed a significantly higher improvement in all PRO's at 3 months after initiation of MCT and the improvement was maintained at 6 months. ROM improved after 3 months of MCT and continued to improve at 6 months. CONCLUSIONS: This observational cross-over study demonstrates an advantage of MCT in FM patients with LBP as compared with SAT. Further randomised clinical trial studies should assess whether these results can be generalised to the FM population at large.

Evaluation of OnabotulinumtoxinA treatment in patients with concomitant chronic migraine and temporomandibular disorders.
Kocaman G, Kahraman N, Koseoglu BG, Bilgic B, Matur Z, Ertas M, Gulsen Y, Baykal BB.
Noro Psikiyatr Ars. 2018 Dec;55(4):330-336. doi: 10.5152/npa.2017.19257.

INTRODUCTION: Migraine and temporomandibular disorders (TMD) are both common diseases and TMD are reported as a risk factor in migraine progression. OnabotulinumtoxinA is used in the treatment of chronic migraine (CM), and also has a potential role in TMD treatment. In this study, it is aimed to compare the efficacy of onabotulinumtoxinA treatment in CM patients with and without TMD. METHODS: In this retrospective study, 30 CM patients (age range: 18-65 years), satisfying the inclusion and follow-up criteria in their medical records were investigated. The PREEMPT injection protocol was taken as reference and onabotulinumtoxinA 155-195 U with fixed-dose has been administered into 31 specific sites within the head/neck muscles in included subjects. Two cycles of treatment were assessed in all patients at the baseline and 12 weeks later. The headache diaries, which were completed routinely one month before, and during 6 months follow-up after the treatment, were assessed. The effect of onabotulinumtoxinA treatment was compared between CM patients with and without TMD/bruxism. RESULTS: Of 30 female patients, 17 had concomitant TMD. In week 24, there were significant improvement in the groups with and without TMD regarding to the mean change of frequencies in the days with migraine compared to the initial findings ($p<0.001$). However, there was no significant difference between the two groups. CONCLUSIONS: OnabotulinumtoxinA is an effective and safe treatment for CM. Its efficacy appears to be similar in CM patients with and without TM, speculating that the comorbidity of TMD did not play a role for the treatment response.

Perceived helpfulness of treatments for myofascial TMD as a function of comorbid widespread pain.
Santiago V, Raphael KG.
Clin Oral Investig. 2019 Jan 8. doi: 10.1007/s00784-018-02797-6.

OBJECTIVE: This study examined whether patients with myofascial temporomandibular disorder (mTMD) comorbid with fibromyalgia (FM) receive

different treatments or respond differently to these treatments than mTMD-only patients. MATERIALS AND METHODS: A total of 125 mTMD+ women were enrolled (26 FM+ and 98 FM-). mTMD and FM were assessed via clinical research examinations. Treatment histories and self-reported treatment-related improvement were obtained via interview. RESULTS: The top 3 most common treatments reported were oral appliances (59%), physical therapy (54%), and jaw exercises at home (34%). Use of alternative medicine was reported more frequently among FM+ women, but self-reported improvement did not differ by comorbid FM. Physical therapy was as likely reported by FM status but self-reported improvement scores trended higher for FM+ women. CONCLUSIONS: Oral appliances were as likely to be reported by FM comorbid as FM- women. Oral appliances did not outperform self-management treatments on self-reported improvement of facial pain. CLINICAL RELEVANCE: Results support the use of self-management as first-line treatment for mTMD and potential utility of inquiring about widespread pain for treatment planning.

Chronic widespread pain in a tertiary pain clinic: Classification overlap and use of a patient generated quality of life instrument.
Tschudi-Madsen H, Rodevand LN, Boymo Kaarbo M, Granan LP.
Scand J Pain. 2018 Nov 22. pii: /j/sjpain.ahead-of-print/sjpain-2018-0097/sjpain-2018-0097.xml. doi: 10.1515/sjpain-2018-0097.

Background and aims This study has two main aims: (1) To explore the overlap between classification criteria in patients with Chronic Widespread Pain (CWP) and (2) To explore the use of the Patient Generated Index (PGI) as a quality of life (QoL) measure in this patient group. Methods Patients with Widespread Pain (ICD-11: pain in four or more out of five bodily regions, i.e. the four quadrants and axially) in a tertiary pain outpatient clinic were assessed according to classification criteria for Fibromyalgia [FM, American College of Rheumatology (ACR) criteria of 1990, 2010, 2011 and 2016], Chronic Fatigue Syndrome [CFS, Fukuda, Canada and International Consensus Criteria (ICC)] and Bodily Distress Syndrome (BDS). Furthermore, patients completed the PGI to assess QoL, and electronic questionnaires including demographic variables and standardised patient-reported outcome measures (PROMs). Results All patients (n=33) fulfilled the criteria for musculoskeletal type single-organ BDS, 81.8% met the 2016 modified criteria for FM, 30.3% met the Canada criteria for CFS and 24.2% met the criteria for multi-organ type BDS. There was substantial agreement between the 2016 and the 2011 and 2010 criteria sets for FM compared to the 1990 criteria (κ=0.766 and 0.673 compared to 0.279). Patients generally scored low on the PGI, indicating poor QoL (mean PGI 28.9, SD 19.8, range 0-100). Conclusions Our findings support the use of the term musculoskeletal type single-organ BDS to describe patients with CWP and the 2016 revision of the FM criteria. The PGI provides useful clinical information which is not captured by standardised PROMs. Implications The terminology of CWP has become less ambiguous as the new ICD-11 is closely related to the generalised pain criterion of the modified 2016 FM definition. Studies based on the 1990 classification criteria for FM should not be directly compared to studies based on later criteria set. The PGI may be a supplement to other measurements to portray patients' individual concerns in patients with complex symptom disorders.

Autonomic dysfunction and HPV immunization: an overview.
Blitshteyn S, Brinth L, Hendrickson JE, Martinez-Lavin M.
Immunol Res. 2018 Nov 27. doi: 10.1007/s12026-018-9036-1.

This article reviews the case series reported from several countries describing patients with suspected severe side effects to the HPV vaccines. The described symptom clusters are remarkably similar and include disabling fatigue, headache, widespread pain, fainting, gastrointestinal dysmotility, limb weakness, memory impairment episodes of altered awareness, and abnormal movements. This constellation of symptoms and signs has been labeled with different diagnoses such as complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS), small fiber neuropathy (SFN), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), or fibromyalgia. It is known that

autoimmunity and autoantibodies are present in a subset of patients with CRPS, POTS, SFN, ME/CFS, and fibromyalgia. This article proposes that vaccine-triggered, immune-mediated autonomic dysfunction could lead to the development of de novo post-HPV vaccination syndrome possibly in genetically susceptible individuals. Being cognizant that a temporal relationship between vaccination and symptom onset does not necessarily equate to causality, mounting evidence of case series calls for well-designed case-control studies to determine the prevalence and possible causation between these symptom clusters and HPV vaccines. Since personalized medicine is gaining momentum, the use of adversomics and pharmacogenetics may eventually help identify individuals who are predisposed to HPV vaccine adverse events.

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 donate 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; and iii) advance industry efforts to research and develop safe and effective therapies for COPCs.