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Published by the Chronic Pain Research Alliance and developed to keep the medical-scientific community abreast of research advances, this e-newsletter contains abstracts of studies on the epidemiology, pathophysiology and clinical management of Chronic Overlapping Pain Conditions (COPCs) published between June and September 2017. Prior issues are available on our website, <http://www.cpralliance.org>. To read the CPRA's White Paper, click [here](#). Please direct any questions or comments to the CPRA's Director, Christin Veasley - cveasley@cpralliance.org.

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NATIONAL MULTICENTER STUDIES

[Brain signature and functional impact of centralized pain: a multidisciplinary approach to the study of chronic pelvic pain \(MAPP\) network study.](#)

Kutch JJ, Ichesco E, Hampson JP, Labus JS, Farmer MA, Martucci KT, Ness TJ, Deutsch G, Apkarian AV, Mackey SC, Klumpp DJ, Schaeffer AJ, Rodriguez LV, Kreder KJ, Buchwald D, Andriole GL, Lai HH, Mullins C, Kusek JW, Landis JR, Mayer EA, Clemens JQ, Clauw DJ, Harris RE; MAPP Research Network.

Pain. 2017 Jun 30. doi: 10.1097/j.pain.0000000000001001.

Chronic pain is often measured with a severity score that overlooks its spatial distribution across the body. This widespread pain is believed to be a marker of centralization, a central nervous system process that decouples pain perception from nociceptive input. Here, we

investigated whether centralization is manifested at the level of the brain using data from 1079 participants in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research Network (MAPP) study. Participants with a clinical diagnosis of urological chronic pelvic pain syndrome (UCPPS) were compared to pain-free controls and patients with fibromyalgia, the prototypical centralized pain disorder. Participants completed questionnaires capturing pain severity, function, and a body map of pain. A subset (UCPPS N = 110; fibromyalgia N = 23; healthy control N = 49) underwent functional and structural magnetic resonance imaging. Patients with UCPPS reported pain ranging from localized (pelvic) to widespread (throughout the body). Patients with widespread UCPPS displayed increased brain gray matter volume and functional connectivity involving sensorimotor and insular cortices ($P < 0.05$ corrected). These changes translated across disease diagnoses as identical outcomes were present in patients with fibromyalgia but not pain-free controls. Widespread pain was also associated with reduced physical and mental function independent of pain severity. Brain pathology in patients with centralized pain is related to pain distribution throughout the body. These patients may benefit from interventions targeting the central nervous system.

PATHOPHYSIOLOGY STUDIES

[Classification of common human diseases derived from shared genetic and environmental determinants.](#)

Wang K, Gaitsch H, Poon H, Cox NJ, Rzhetsky A.
Nat Genet. 2017 Sep;49(9):1319-1325. doi: 10.1038/ng.3931.

In this study, we used insurance claims for over one-third of the entire US population to create a subset of 128,989 families (481,657 unique individuals). We then used these data to (i) estimate the heritability and familial environmental patterns of 149 diseases and (ii) infer the genetic and environmental correlations for disease pairs from a set of 29 complex diseases. The majority (52 of 65) of our study's heritability estimates matched earlier reports, and 84 of our estimates appear to have been obtained for the first time. We used correlation matrices to compute environmental and genetic disease classifications and corresponding reliability measures. Among unexpected observations, we found that migraine, typically classified as a disease of the central nervous system, appeared to be most genetically similar to irritable bowel syndrome and most environmentally similar to cystitis and urethritis, all of which are inflammatory diseases.

[Visceral pain as a triggering factor for fibromyalgia symptoms in comorbid patients.](#)

Costantini R, Affaitati G, Wesselmann U, Czakanski P, Giamberardino MA.
Pain. 2017 Jul 3. doi: 10.1097/j.pain.0000000000000992.

Fibromyalgia syndrome (FMS) is a central sensitization syndrome; however, peripheral pain sources potentially exacerbate its symptoms of chronic diffuse musculoskeletal pain and hyperalgesia. This prospective study evaluated visceral pain as a possible triggering factor for FMS pain and hyperalgesia in comorbid patients. Women with (1) FMS + irritable bowel syndrome (IBS); (2) FMS + primary dysmenorrhea (Dys); (3) FMS + Dys secondary to endometriosis (Endo); (4) FMS + colon diverticulosis (Div) were compared with FMS-only women, for fibromyalgia pain (number and intensity of episodes and analgesic consumption) over comparable periods and for somatic hyperalgesia (electrical and pressure pain thresholds) in painful (tender points) and control areas (trapezius, deltoid, quadriceps muscles, and overlying subcutis and skin). In comorbid subgroups, FMS symptoms were also reassessed after treatment of the visceral condition or no treatment. All comorbid groups vs FMS-only had significantly higher FMS pain (number/intensity of episodes and analgesic consumption) and hyperalgesia in deep somatic tissues (subcutis and muscle) at all sites ($0.05 < P < 0.0001$). Visceral pain (number of IBS days, painful menstrual cycles, and abdominal pain episodes from diverticulitis) correlated directly with all parameters of FMS

pain and inversely with muscle pain thresholds at all sites ($0.03 < P < 0.0001$). Fibromyalgia syndrome pain and hyperalgesia in all tissues and all sites significantly decreased in patients after visceral comorbidity treatment (dietary for 6 months [IBS], hormonal for 6 months [dysmenorrhea], laser [endometriosis], and surgery [diverticulosis]) ($0.05 < P < 0.0001$) vs no change in untreated patients. Visceral pain enhances FMS symptoms, probably augmenting the level of central sensitization typical of the syndrome. Systematic assessment and treatment of visceral pain comorbidities should be a part of FMS management strategy.

[Extracellular signal-regulated kinase activation in the spinal cord contributes to visceral hypersensitivity induced by craniofacial injury followed by stress.](#)

Zhao YJ, Li JH, Hu B, Wang Y, Chang XF, Traub RJ, Cao DY.
Neurogastroenterol Motil. 2017 Jul 21. doi: 10.1111/nmo.13161.

BACKGROUND: We previously developed an animal model to examine mechanisms that underlie the emergence of visceral hypersensitivity modeling pain characteristics of temporomandibular disorder (TMD) patients with comorbid irritable bowel syndrome (IBS). In ovariectomized (OVx) rats with estradiol (E2) replacement, visceral hypersensitivity developed subsequent to masseter muscle inflammation followed by repeated forced swim (FS) stress. The purpose of this study was to investigate whether activation of extracellular signal-regulated kinase (ERK) in the spinal cord contributes to visceral hypersensitivity in this overlapping pain model. **METHODS:** In OVx with E2 replacement rats masseter muscle inflammation was followed by 3 day FS (comorbid condition). Depression-like behaviors were assessed by sucrose preference and in the elevated plus maze, and visceral sensitivity was measured by the visceromotor response (VMR) to colorectal distention. The protein level of ERK1/2 and phosphorylated ERK1/2 (p-ERK1/2) in the L6-S2 dorsal spinal cord was analyzed by western blot. **KEY RESULTS:** FS stress decreased sucrose consumption in E2 replaced rats in sucrose preference test. The expression of p-ERK1/2 in the L6-S2 dorsal spinal cord increased significantly in E2 with comorbid rats. Intrathecal injection of mitogen-activated protein kinase (MAPK) kinase (MEK) inhibitor PD98059 blocked the visceral hypersensitivity induced by masseter muscle inflammation combined with FS stress. **CONCLUSIONS & INFERENCES:** These data indicate that ERK1/2 activation contributes to the visceral hypersensitivity evoked by craniofacial inflammation pain combined with stress. The results may provide a new therapeutic avenue for alleviating overlapping pain conditions.

[Sleep disturbances and severe stress as glial activators: key targets for treating central sensitization in chronic pain patients?](#)

Nijs J, Loggia ML, Polli A, Moens M, Huysmans E, Goudman L, Meeus M, Vanderweeën L, Ickmans K, Clauw D.
Expert Opin Ther Targets. 2017 Aug;21(8):817-826. doi: 10.1080/14728222.2017.1353603.

INTRODUCTION: The mechanism of sensitization of the central nervous system partly explains the chronic pain experience in many patients, but the etiological mechanisms of this central nervous system dysfunction are poorly understood. Recently, an increasing number of studies suggest that aberrant glial activation takes part in the establishment and/or maintenance of central sensitization. Areas covered: This review focused on preclinical work and mostly on the neurobiochemistry studied in animals, with limited human studies available. Glial overactivation results in a low-grade neuroinflammatory state, characterized by high levels of BDNF, IL-1 β , TNF- α , which in turn increases the excitability of the central nervous system neurons through mechanisms like long-term potentiation and increased synaptic efficiency. Aberrant glial activity in chronic pain might have been triggered by severe stress exposure, and/or sleeping disturbances, each of which are established initiating factors for chronic pain development. Expert opinion: Potential treatment avenues include several pharmacological options for diminishing glial activity, as well as conservative interventions like sleep management, stress management and exercise therapy. Pharmacological options include propentofylline, minocycline, β -adrenergic

receptor antagonists, and cannabidiol. Before translating these findings from basic science to clinical settings, more human studies exploring the outlined mechanisms in chronic pain patients are needed.

[The MNK-eIF4E signaling axis contributes to injury-induced nociceptive plasticity and the development of chronic pain.](#)

Moy JK, Khoutorsky A, Asiedu MN, Black BJ, Kuhn JL, Barragán-Iglesias P, Megat S, Burton MD, Burgos-Vega CC, Melemedjian OK, Boitano S, Vagner J, Gkogkas CG, Pancrazio JJ, Mogil JS, Dussor G, Sonenberg N, Price TJ.

J Neurosci. 2017 Aug 2;37(31):7481-7499. doi: 10.1523/JNEUROSCI.0220-17.2017.

Injury-induced sensitization of nociceptors contributes to pain states and the development of chronic pain. Inhibiting activity-dependent mRNA translation through mechanistic target of rapamycin and mitogen-activated protein kinase (MAPK) pathways blocks the development of nociceptor sensitization. These pathways convergently signal to the eukaryotic translation initiation factor (eIF) 4F complex to regulate the sensitization of nociceptors, but the details of this process are ill defined. Here we investigated the hypothesis that phosphorylation of the 5' cap-binding protein eIF4E by its specific kinase MAPK interacting kinases (MNKs) 1/2 is a key factor in nociceptor sensitization and the development of chronic pain. Phosphorylation of ser209 on eIF4E regulates the translation of a subset of mRNAs. We show that pronociceptive and inflammatory factors, such as nerve growth factor (NGF), interleukin-6 (IL-6), and carrageenan, produce decreased mechanical and thermal hypersensitivity, decreased affective pain behaviors, and strongly reduced hyperalgesic priming in mice lacking eIF4E phosphorylation (eIF4E(S209A)). Tests were done in both sexes, and no sex differences were found. Moreover, in patch-clamp electrophysiology and Ca(2+) imaging experiments on dorsal root ganglion neurons, NGF- and IL-6-induced increases in excitability were attenuated in neurons from eIF4E(S209A) mice. These effects were recapitulated in Mnk1/2(-/-) mice and with the MNK1/2 inhibitor cercosporamide. We also find that cold hypersensitivity induced by peripheral nerve injury is reduced in eIF4E(S209A) and Mnk1/2(-/-) mice and following cercosporamide treatment. Our findings demonstrate that the MNK1/2-eIF4E signaling axis is an important contributing factor to mechanisms of nociceptor plasticity and the development of chronic pain. SIGNIFICANCE STATEMENT Chronic pain is a debilitating disease affecting approximately one in three Americans. Chronic pain is thought to be driven by changes in the excitability of peripheral nociceptive neurons, but the precise mechanisms controlling these changes are not elucidated. Emerging evidence demonstrates that mRNA translation regulation pathways are key factors in changes in nociceptor excitability. Our work demonstrates that a single phosphorylation site on the 5' cap-binding protein eIF4E is a critical mechanism for changes in nociceptor excitability that drive the development of chronic pain. We reveal a new mechanistic target for the development of a chronic pain state and propose that targeting the upstream kinase, MAPK interacting kinase 1/2, could be used as a therapeutic approach for chronic pain.

[Does exercise increase or decrease pain? Central mechanisms underlying these two phenomena.](#)

Lima LV, Abner TSS, Sluka KA.

J Physiol. 2017 Jul 1;595(13):4141-4150. doi: 10.1113/JP273355.

Exercise is an integral part of the rehabilitation of patients suffering a variety of chronic musculoskeletal conditions, such as fibromyalgia, chronic low back pain and myofascial pain. Regular physical activity is recommended for treatment of chronic pain and its effectiveness has been established in clinical trials for people with a variety of pain conditions. However, exercise can also increase pain making participation in rehabilitation challenging for the person with pain. Animal models of exercise-induced pain have been developed and point to central mechanisms underlying this phenomena, such as increased activation of NMDA

receptors in pain-modulating areas. Meanwhile, a variety of basic science studies testing different exercise protocols, show exercise-induced analgesia involves activation of central inhibitory pathways. Opioid, serotonin and NMDA mechanisms acting in rostral ventromedial medulla promote analgesia associated with exercise. This review explores and discusses current evidence on central mechanisms underlying exercised-induced pain and analgesia.

[Neuroplasticity of supraspinal structures associated with pathological pain.](#)

Boadas-Vaello P, Homs J, Reina F, Carrera A, Verdú E.

Anat Rec (Hoboken). 2017 Aug;300(8):1481-1501. doi: 10.1002/ar.23587.

Peripheral nerve and spinal cord injuries, along with other painful syndromes such as fibromyalgia, diabetic neuropathy, chemotherapeutic neuropathy, trigeminal neuralgia, complex regional pain syndrome, and/or irritable bowel syndrome, cause several neuroplasticity changes in the nervous system along its entire axis affecting the different neuronal nuclei. This paper reviews these changes, focusing on the supraspinal structures that are involved in the modulation and processing of pain, including the periaqueductal gray matter, red nucleus, locus coeruleus, rostral ventromedial medulla, thalamus, hypothalamus, basal ganglia, cerebellum, habenula, primary, and secondary somatosensory cortex, motor cortex, mammillary bodies, hippocampus, septum, amygdala, cingulate, and prefrontal cortex. Hyperexcitability caused by the modification of postsynaptic receptor expression, central sensitization, and potentiation of presynaptic delivery of neurotransmitters, as well as the reduction of inhibitory inputs, changes in dendritic spine, neural circuit remodeling, alteration of gray matter, and upregulation of proinflammatory mediators (e.g., cytokines) by reactivation of astrocytes and microglial cells are the main functional, structural, and molecular neuroplasticity changes observed in the above supraspinal structures, associated with pathological pain. Studying these changes in greater depth may lead to the implementation and improvement of new therapeutic strategies against pathological pain.

[Measurement properties of the central sensitization inventory: A systematic review.](#)

Scerbo T, Colasurdo J, Dunn S, Unger J, Nijs J, Cook C.

Pain Pract. 2017 Aug 29. doi: 10.1111/papr.12636. [Epub ahead of print]

BACKGROUND AND OBJECTIVE: Central Sensitization (CS) is a phenomenon associated with several medical diagnoses, including post-cancer pain, low back pain, osteoarthritis, whiplash and fibromyalgia. CS involves an amplification of neural signaling within the central nervous system that results in pain hypersensitivity. The purpose of this systematic review was to gather published studies of a widely used outcome measure (the Central Sensitization Inventory [CSI]), determine the quality of evidence these publications reported, and examine the measurement properties of the CSI. **DATABASES AND DATA TREATMENT:** Four databases were searched for publications from 2011 (when the CSI was developed) to July 2017. The Consensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist was applied to evaluate methodological quality and risk of bias. In instances when COSMIN does not offer a scoring system for measurement properties, qualitative analyses were performed. **RESULTS:** Fourteen studies met inclusion criteria. Quality of evidence examined with COSMIN was determined to be good to excellent for all studies for their respective measurement property reports. Interpretability measures were consistent when publications were analyzed qualitatively and construct validity was strong when examined alongside other validated measures relating to CS. **CONCLUSIONS:** An assessment of the published measurement studies of the CSI suggest the tool generates reliable and valid data that quantifies the severity of several symptoms of CS.

[Hyperacusis in chronic pain: neural interactions between the auditory and nociceptive](#)

OBJECTIVE: Sensory disturbances are common in chronic pain patients. Hyperacusis can be an especially debilitating experience. Here, we review published work on how the auditory and nociceptive systems might interact in chronic pain syndromes to produce pain-hyperacusis. **DESIGN:** Literature review. **STUDY SAMPLE:** The PubMed and Scopus databases were searched for relevant articles published between 2000 and 2017 using the primary search terms "hyperacusis"/"hyperacousis" and "pain". Ten papers were found using this strategy. Supplementary sources were identified by browsing textbooks and the reference lists of identified articles. **RESULTS:** The importance of central mechanisms in pain-hyperacusis was highlighted in the 10 selected papers. Hyperacusis is a significant but under-recognised symptom in conditions such as complex regional pain syndrome and fibromyalgia, and an integral feature of migraine. **CONCLUSIONS:** Nociceptive circuits become hypersensitive in acute and chronic pain; this sensitivity spreads from the periphery to spinal neurons and higher centres in the brain, leading to hyperalgesia or spontaneous pain even in the absence of peripheral nociceptive input. This "central sensitisation" may alter activity at sensory convergence points in the thalamus and brainstem centres such as the locus coeruleus, and give rise to hyperacusis in certain pain syndromes.

[Pain anxiety and fear of \(re\)injury in patients with chronic back pain: Sex as a moderator.](#)

Kreddig N, Hasenbring MI.

Scand J Pain. 2017 Jul;16:105-111. doi: 10.1016/j.sjpain.2017.03.009.

BACKGROUND AND AIMS: Anxiety and fear are increasingly seen as related, but distinct concepts, with anxiety describing a reaction to unclear or future threats, and fear to immediate threats. Anxiety and fear both play influential roles in pain. Yet, the two concepts have not been clearly distinguished in pain research. Their reported intensity differs between the sexes, and sex differences in the way pain anxiety and fear of (re)injury relate to pain intensity have been found separately in previous studies. However, they seem to be of a curious nature: In one study, pain anxiety was associated with elevated pain intensity in men, while in another, fear of (re)injury was associated with elevated pain intensity in women. This indicates a moderator effect of sex. The present study is the first to unite previous findings, and to show a more integrative picture, by examining and discussing this moderator effect of sex in a joint study of both pain-related anxiety and fear in both sexes. **METHODS:** In 133 patients (mean age 43.6 years, 62% female) with chronic low back pain (mean duration 7.7 years), sex differences were examined with correlations and a multiple linear regression analysis with interaction terms. Differences between subgroups of low and high anxiety/fear were explored via t-tests, following previous studies. **RESULTS:** Sex was supported as a moderator in the association of pain intensity with pain anxiety (PASS-20), and fear of (re)injury (TSK). Higher pain intensity was linked to higher pain anxiety only in men, and to higher fear of (re)injury only in women. A basic regression model with fear, anxiety, sex and disability as predictors ($R(2)=.14$, $F(4,123)=3.24$, $p=.042$) was significantly improved by the addition of the interaction terms $Fear \times Sex$ and $Anxiety \times Sex$ ($R(2)=.18$, $F(2,121)=4.90$, $p=.001$), which were both shown as significant predictors for pain intensity. Further t-tests revealed a significant difference in pain intensity between high and low anxiety in men ($t(47)=-2.34$, $p=.023$, $d=-.43$), but not in women. Likewise, a significant difference in pain intensity between high and low fear showed in women ($t(80)=-2.28$, $p=.025$, $d=-.42$), but not in men. **CONCLUSIONS:** The results support a moderator effect of sex and suggest differential mechanisms between the sexes in pain anxiety and fear in development and maintenance of back pain. The current study is the first to report and analyse this moderator effect. As potential underlying mechanisms, evolution and socialization are discussed, which may elucidate why fear might be more relevant for pain in women, and anxiety more relevant for pain in men. **IMPLICATIONS:** The results indicate the need for a more cautious conceptual separation of fear and anxiety in research. Future

studies on fear and anxiety in pain should be aware of the distinction, in order to avoid reporting only half of the picture. The next step would be to solidify the results in different samples, and to examine whether a distinction between anxiety and fear in the sexes could have any benefit in pain treatment.

EPIDEMIOLOGY STUDIES

[Childhood bladder and bowel dysfunction predicts irritable bowel syndrome phenotype in adult interstitial cystitis/bladder pain syndrome patients.](#)

Doiron RC, Kogan BA, Tolls V, Irvine-Bird K, Nickel JC.
Can Urol Assoc J. 2017 Aug;11(8):255-259. doi: 10.5489/cuaj.4251.

INTRODUCTION: Many clinicians have suggested that a history of bladder and bowel dysfunction (BBD) in childhood predisposes to the development of interstitial cystitis/bladder pain syndrome (IC/BPS) or irritable bowel syndrome (IBS) in adulthood. We hypothesized that BBD symptoms in childhood would predict the IBS-associated phenotype in adult IC/BPS patients. **METHODS:** Consecutive female patients (n=190) with a diagnosis of IC/BPS were administered a modified form of a clinical BBD questionnaire (BBDQ) to capture childhood BBD-like symptoms, as well as Interstitial Cystitis Symptoms Index (ICSI), Interstitial Cystitis Problem Index (ICPI), Pelvic Pain and Urgency/Frequency (PUF) questionnaires and UPOINT categorization. Patients were stratified to IBS-positive or IBS-negative according to clinical assessment of IBS-like symptoms. **RESULTS:** The 127 patients (67%) identified with IBS-like symptoms recalled significantly higher BBDQ scores than the 63 patients (33%) who were IBS-negative (2.8 vs. 2.3; p=0.05). The IBS-positive patients also reported a higher number of UPOINT domains than their non-IBS counterparts (3.8 vs. 2.9; p=0.0001), while their PUF total scores were significantly higher (13.6 vs. 12.3; p=0.04). IBS-positive patients more often recalled that in childhood they did not have a daily bowel movement (BM) (p=0.04) and had "to push for a BM" (p=0.009). In childhood, they "urinated only once or twice per day" (p=0.03) and recalled "painful urination" more than those without IBS (p=0.03). There were no significant differences between the groups in answers to the other five questions of the BBDQ. **CONCLUSIONS:** Our symptom recollection survey was able to predict the IBS phenotype of IC/BPS based on a childhood BBDQ. Further prospective studies are needed to further evaluate these novel findings.

[Comorbid pain and migraine chronicity: The Chronic Migraine Epidemiology and Outcomes Study.](#)

Scher AI, Buse DC, Fanning KM, Kelly AM, Franznick DA, Adams AM, Lipton RB.
Neurology. 2017 Aug 1;89(5):461-468. doi: 10.1212/WNL.0000000000004177.

OBJECTIVE: To identify patterns of noncephalic pain comorbidity in people with episodic migraine (EM; <15 headache-days per month) and chronic migraine (CM; ≥15 headache-days per month) and to examine whether the presence of noncephalic pain is an indicator for the 3-month onset or persistence of CM. **METHODS:** Data from the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study, a prospective, web-based study with cross-sectional modules embedded in a longitudinal design, were analyzed at baseline and the 3-month follow-up. Relationships between the number of noncephalic pain sites and 3-month onset of CM or persistent CM were assessed. **RESULTS:** Of 8,908 eligible respondents, 8,139 (91.4%) had EM and 769 (8.6%) had CM at baseline. At 3 months, the incidence of CM among those with baseline EM was 3.4%. When adjusted for demographics and headache-day frequency, the odds of CM onset among those with baseline EM increased by 30% (95% confidence interval [CI] 1.21-1.40, p < 0.001) for each additional noncephalic pain site at baseline. Among those with CM at baseline, 50.1% had persistent CM at the 3-month follow-up. After adjustment for demographics, individuals with CM were 15% (95% CI 1.07-1.25, p < 0.001) more likely to have persistent CM for each additional noncephalic pain site at baseline. **CONCLUSIONS:** These results suggest that noncephalic pain may be a marker for

headache chronicity that could be used to identify people with EM at risk of the onset of CM and people with CM at risk of persistent CM.

[Factors associated with severity of irritable bowel syndrome symptoms in patient with endometriosis.](#)

Lee CE, Yong PJ, Williams C, Allaire C.

J Obstet Gynaecol Can. 2017 Sep 1. pii: S1701-2163(17)30089-0. doi: 0.1016/j.jogc.2017.06.025.

OBJECTIVE: This study sought to examine factors associated with severity of irritable bowel syndrome (IBS) by using the Birmingham IBS symptom scale in patients presenting with endometriosis to a tertiary referral centre. **METHODS:**

A prospective research cohort of patients presenting to a tertiary referral centre for endometriosis was evaluated for the presence and severity of IBS between December 2013 and April 2015. Patients with endometriosis had a diagnosis of IBS by using the Rome III criteria and were evaluated for severity of IBS symptoms by using the Birmingham IBS symptom scale. Multifactorial variables, including stage of endometriosis at the time of previous surgery, clinical examination findings, mood disorder questionnaire scores, and lifestyle factors, were evaluated using the t test and Spearman rank correlation test. **RESULTS:** A total of 194 of 373 (52%) women with confirmed endometriosis had a diagnosis of IBS. Factors associated with severity of IBS symptoms in patients with endometriosis included lower-stage endometriosis ($p=0.004$), presence of mood disorders ($p<0.001$), tenderness on physical examination ($p\leq 0.001$), a history of sexual assault ($p\leq 0.02$), and presence of sleep disturbance ($p\leq 0.01$). Evaluation of the subscales of the Birmingham IBS symptom scale revealed a strong association between the previously identified factors and the pain subscale. **CONCLUSION:** Using the Birmingham IBS symptom scale, our study revealed more severe IBS symptoms in patients with lower-stage endometriosis and identified other variables highly associated with severity of IBS. Continued research is required to characterize further the clinical importance of IBS symptoms in patients with endometriosis-associated pelvic pain.

[The effect of anxiety and depression on the risk of irritable bowel syndrome in migraine patients.](#)

Wu MF, Yang YW, Chen YY.

J Clin Neurosci. 2017 Jul 7. pii: S0967-5868(17)30394-6. doi: 10.1016/j.jocn.2017.06.009.

Bidirectional co-morbidity between migraine and depression has been observed. Mood disorders are associated with an increased risk of both migraine and irritable bowel syndrome (IBS). The aim of this study was to evaluate the risk of developing IBS in patients with migraine and to compare the risks between those with and without anxiety or depression. This research used the data contained in the National Health Insurance Research Database (NHIRD). A total of 2859 subjects with migraine and 5718 age-, sex-, hypertension-, diabetes-, mood disorder-matched controls were identified. Both cohorts excluded subjects with pre-existing catastrophic illness and IBS diagnosed before the index visit or within 30 days after the index visit. All individuals of both cohorts were tracked until either having the diagnosis of IBS, loss of follow-up, or IBS free up to 7 years. During the 7-year follow-up period, 8.4% of patients with migraine and 5.4% of control cohort developed IBS. Migraine is associated with an increased risk of developing IBS (HR=1.58, 95% CI: 1.33-1.87). When separating the cohort into those with mood disorder and without it, migraine is a significant risk factor of IBS in patients without mood disorders, but not in patients with co-existed mood disorders. The findings of this study suggest that migraine is a risk factor of future IBS development for those without comorbid anxiety or depression. However, migraine does not contribute significantly additional risk to IBS development in patients with comorbid anxiety or depression.

[Irritable bowel symptoms and the development of common mental disorders and functional somatic syndromes identified in secondary care - a long-term, population-based study.](#)

Poulsen CH, Epløv LF, Hjorthøj C, Eliassen M, Skovbjerg S, Dantoft TM, Schröder A, Jørgensen T. Clin Epidemiol. 2017 Jul 31;9:393-402. doi: 10.2147/CLEP.S141344. eCollection 2017.

OBJECTIVE: Irritable bowel syndrome (IBS) is associated with mental vulnerability, and half of patients report comorbid somatic and mental symptoms. We aimed to investigate the relationship between an IBS symptom continuum and the subsequent development of common mental disorders (CMDs) and functional somatic syndromes (FSSs). **METHODS AND STUDY DESIGN:** A longitudinal population-based study comprising two 5-year follow-up studies, Dan-MONICA 1 (1982-1987) and Inter99 (1999-2004), recruited from the western part of Copenhagen County. The total study population (n = 7,278) was divided into symptom groups according to the degree of IBS definition fulfillment at baseline and/or follow-up and was followed until December 2013 in Danish central registries. Cox regression was used for the analyses, adjusting for age, sex, length of education and cohort membership. In a subsequent analysis, we adjusted for mental vulnerability as a risk factor for both CMDs and FSSs, including IBS. **RESULTS:** Over a 5-year period, 51% patients had no IBS symptoms, 17% patients had IBS symptoms without abdominal pain, 22% patients had IBS symptoms including abdominal pain and 10% patients fulfilled the IBS definition. IBS and IBS symptoms including abdominal pain were significantly associated with the development of CMDs and other FSSs identified in secondary care. When adjusting for mental vulnerability, IBS and IBS symptoms including abdominal pain were no longer associated with CMDs, but the significant relationship to other FSSs remained. **CONCLUSION:** In a clinical setting, the perspective should be broadened to individuals not fulfilling the symptom cluster of IBS but who report frequent abdominal pain. Additionally, it is important to combine symptom-based criteria of IBS with psychosocial markers such as mental vulnerability, because it could guide clinicians in decisions regarding prognosis and treatment.

[The influence of fibromyalgia on achieving remission in patients with long-standing rheumatoid arthritis.](#)

Salaffi F, Gerardi MC, Atzeni F, Batticciotto A, Talotta R, Draghessi A, Di Carlo M, Sarzi-Puttini P.

Rheumatol Int. 2017 Sep 5. doi: 10.1007/s00296-017-3792-4.

To investigate the influence of fibromyalgia (FM) on achieving remission defined on the basis of the Simplified Disease Activity Index (SDAI) remission criteria in patients with long-standing rheumatoid arthritis (RA). This observational longitudinal cohort consisted of long-standing RA patients being treated with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) or biological DMARDs (bDMARDs). After 6 months of follow-up, the patients fulfilling or not fulfilling the remission criteria were identified and compared with each other in terms of the presence of FM, neuropathic pain, and other comorbidities. At the end of the 6-month observation period, 24 of the 117 patients (20.4%) met the SDAI remission criteria. Logistic regression analysis showed that the modified Rheumatic Disease Comorbidity Index (mRDCI) (p = 0.0001), the FM presence (p = 0.0001), and the 36-item short-form health survey Mental Component Summary (SF-36 MCS) Score (p = 0.0088) were the strongest predictors of not being in SDAI remission. None of the patients with concomitant FM (17.1%) achieved SDAI remission. In comparison with the non-FM patients, the patients with RA and FM patients had worse scores on the SF-36 MCS (p = 0.011), on the sleep Visual Analogue Scale (VAS) (p = 0.018), on the self-counts of tender joints (p = 0.039), and on the PainDetect Questionnaire (PDQ) (p = 0.001). To avoid over treatment, an assessment of FM should be considered in RA patients who do not fulfil the remission criteria.

[The association between headaches and temporomandibular disorders is confounded by](#)

[bruxism and somatic symptoms.](#)

van der Meer HA, Speksnijder CM, Engelbert RHH, Lobbezoo F, Nijhuis-van der Sanden MWG, Visscher CM.

Clin J Pain. 2017 Sep;33(9):835-843. doi: 10.1097/AJP.0000000000000470.

OBJECTIVES: The objective of this observational study was to establish the possible presence of confounders on the association between temporomandibular disorders (TMD) and headaches in a patient population from a TMD and Orofacial Pain Clinic. **MATERIALS AND METHODS:** Several subtypes of headaches have been diagnosed: self-reported headache, (probable) migraine, (probable) tension-type headache, and secondary headache attributed to TMD. The presence of TMD was subdivided into 2 subtypes: painful TMD and function-related TMD. The associations between the subtypes of TMD and headaches were evaluated by single regression models. To study the influence of possible confounding factors on this association, the regression models were extended with age, sex, bruxism, stress, depression, and somatic symptoms. **RESULTS:** Of the included patients (n=203), 67.5% experienced headaches. In the subsample of patients with a painful TMD (n=58), the prevalence of self-reported headaches increased to 82.8%. The associations found between self-reported headache and (1) painful TMD and (2) function-related TMD were confounded by the presence of somatic symptoms. For probable migraine, both somatic symptoms and bruxism confounded the initial association found with painful TMD. **DISCUSSION:** The findings of this study imply that there is a central working mechanism overlapping TMD and headache. Health care providers should not regard these disorders separately, but rather look at the bigger picture to appreciate the complex nature of the diagnostic and therapeutic process.

[Patterns and predictors of persistent opioid use following hip or knee arthroplasty.](#)

Kim SC, Choudhry N, Franklin JM, Bykov K, Eikermann M, Lii J, Fischer MA, Bateman BT.

Osteoarthritis Cartilage. 2017 Sep;25(9):1399-1406. doi: 10.1016/j.joca.2017.04.002.

OBJECTIVE: The relationship between arthroplasty and long-term opioid use in patients with knee or hip osteoarthritis is not well studied. We examined the prevalence, patterns and predictors of persistent opioid use after hip or knee arthroplasty. **METHOD:** Using claims data (2004-2013) from a US commercial health plan, we identified adults who underwent hip or knee arthroplasty and filled ≥ 1 opioid prescription within 30 days after the surgery. We defined persistent opioid users as patients who filled ≥ 1 opioid prescription every month during the 1-year postoperative period based on group-based trajectory models. Multivariable logistic regression was used to determine preoperative predictors of persistent opioid use after surgery. **RESULTS:** We identified 57,545 patients who underwent hip or knee arthroplasty. The mean \pm SD age was 61.5 ± 7.8 years and 87.1% had any opioid use preoperatively. Overall, 7.6% persistently used opioids after the surgery. Among patients who used opioids in 80% of the time for ≥ 4 months preoperatively (n = 3023), 72.1% became persistent users. In multivariable analysis, knee arthroplasty vs hip, a longer hospitalization stay, discharge to a rehabilitation facility, preoperative opioid use (e.g., a longer duration and greater dosage and frequency), a higher comorbidity score, back pain, rheumatoid arthritis, fibromyalgia, migraine and smoking, and benzodiazepine use at baseline were strong predictors for persistent opioid use (C-statistic = 0.917). **CONCLUSION:** Over 7% of patients persistently used opioids in the year after hip or knee arthroplasty. Given the adverse health effects of persistent opioid use, strategies need to be developed to prevent persistent opioid use after this common surgery.

[Chronic pain in older adults: prevalence, incidence, and risk factors.](#)

Larsson C, Hansson EE, Sundquist K, Jakobsson U.

Scand J Rheumatol. 2017 Jul;46(4):317-325. doi: 10.1080/03009742.2016.1218543.

OBJECTIVES: Chronic pain is common in older adults, yet little is known of its development

and the factors that predict its persistence and onset at old age. The aims of this longitudinal cohort study were to examine the prevalence and incidence of chronic pain and to explore possible risk factors for its persistence and onset in a representative sample of older Swedish adults. **METHOD:** Data were collected through questionnaires and followed up after 12 and 24 months. Chronic pain was defined as pain symptoms that lasted more than 3 months, regardless of the specific cause or site. Logistic regression analyses were used to identify odds ratios (ORs) with 95% confidence intervals (CIs) for potential predictors. **RESULTS:** Out of 2000 older adults approached (aged 65-103 years), 1141 were included in the study. Chronic pain was reported among 38.5% of the participants, and was more common among females and among adults over 85 years of age. The incidence was estimated to be 5.4% annually. Being female (OR 3.19, 95% CI 1.04-9.59), having a lower body mass index (BMI; OR 0.89, 95% CI 0.79-0.99), more than one pain location (OR 4.02, 95% CI 1.56-10.35), higher severity (OR 1.79, 95% CI 1.13-2.83), and longer duration (OR 1.08, 95% CI 1.01-1.15) were associated with the persistence of chronic pain, but this association did not remain significant for men when divided by gender. Younger age (OR 0.89, 95% CI 0.89-0.99) was associated with new onset of chronic pain. **CONCLUSIONS:** Even though pain was often highly prevalent and persistent, our results show that both recovery and onset of pain occurred. Pain characteristics, rather than age-related symptoms and psychosocial variables, predicted pain persistence among older women but not among older men. These findings highlight the importance of early pain management in the prevention of future pain.

[Pain sensitivity and its relation to spreading on the body, intensity, frequency, and duration of pain: A cross-sectional population-based study \(SwePain\).](#)

Larsson B, Gerdle B, Björk J, Grimby-Ekman A.

Clin J Pain. 2017 Jul;33(7):579-587. doi: 10.1097/AJP.0000000000000441.

OBJECTIVES: Individuals with chronic pain often report increased pain sensitivity compared with pain-free individuals; hence, it is crucial to determine whether and how different pain characteristics influence or interact with pain sensitivity. An alternative to experimental pain sensitivity testing is the self-reported pain sensitivity questionnaire (PSQ), which captures pain sensitivity in various body areas. This study compares PSQ in individuals with and without pain and clarifies how pain sensitivity relates to spreading of pain on the body, and to intensity, frequency, duration of pain and to age and sex. **MATERIALS AND METHODS:** A total of 5905 individuals with pain and 572 individuals without pain from the general population in southeastern Sweden completed and returned a postal questionnaire. **RESULTS:** The mean PSQ score was 3.9 (95% confidence interval [CI], 3.88-3.98) in individuals with pain and 3.5 (95% CI, 3.38-3.64) in pain-free individuals. Hence, PSQ was the highest among individuals with pain, with a difference of 0.4 (95% CI, 0.30-0.56). There was a considerable variation in the PSQ values (mean=3.5; SD=1.54) among pain-free individuals. Pain sensitivity was positively related to spreading, intensity, and frequency of pain, with a correlation coefficient of 0.3. PSQ was higher in widespread pain, 4.5 (95% CI, 4.27-4.69) in women and 4.3 (95% CI, 3.94-4.71) in men, than in local pain, 3.7 (95% CI, 3.61-3.91) in women and 3.8 (95% CI, 3.66-3.95) in men. The score for women with regional pain was between local and widespread pain at 4.0 (95% CI, 3.95-4.11) and that for men with regional pain was 3.8 (95% CI, 3.69-3.87), which is equal to that of local pain. **DISCUSSION:** The positive association between pain sensitivity and spreading of pain on the body provides some evidence that the extent of spreading may be related to the degree of pain sensitivity. Before clinical use of PSQ, psychometric development and further research are needed.

[Distinctive subgroups derived by cluster analysis based on pain and psychological symptoms in Swedish older adults with chronic pain - a population study \(PainS65+\).](#)

Larsson B, Gerdle B, Bernfort L, Levin LÅ, Dragioti E.

BMC Geriatr. 2017 Sep 2;17(1):200. doi: 10.1186/s12877-017-0591-4.

BACKGROUND: Improved knowledge based on clinical features of chronic pain in older adults

would be valuable in terms of patient-orientated approaches and would provide support for health care systems in optimizing health care resources. This study identifies subgroups based on pain and psychological symptoms among Swedish older adults in the general population and compares derived subgroups with respect to socio-demographics, health aspects, and health care costs. METHODS: This cross-sectional study uses data collected from four registers and one survey. The total sample comprised 2415 individuals ≥ 65 years old. A two-step cluster analysis was performed. Data on pain intensity, number of pain sites, anxiety, depression, and pain catastrophizing were used as classification variables. Differences in socio-demographics, quality of life, general health, insomnia, and health care costs among the clusters were investigated. Association of the clusters with the above parameters was further evaluated using multinomial logistic regression. RESULTS: Four major clusters were identified: Subgroup 1 (n = 325; 15%) - moderate pain and high psychological symptoms; Subgroup 2 (n = 516; 22%) - high pain and moderate psychological symptoms; Subgroup 3 (n = 686; 30%) - low pain and moderate psychological symptoms; and Subgroup 4 (n = 767; 33%) - low pain and low psychological symptoms. Significant differences were found between the four clusters with regard to age, sex, educational level, family status, quality of life, general health, insomnia, and health care costs. The multinomial logistic regression analysis revealed that Subgroups 1 and 2, compared to Subgroup 4, were significantly associated with decreased quality of life, decreased general health, and increased insomnia. Subgroup 3, compared to Subgroup 4, was associated with decreased general health and increased insomnia. In addition, compared to Subgroup 4, Subgroups 1 and 2 were significantly associated with higher health care costs. CONCLUSIONS: Two high risk clusters of older adults suffering from chronic pain; one mainly based on psychological symptoms and one mainly on pain intensity and pain spread, associated with decreased quality of life and health and increased health care costs were identified. Our findings indicate that subgroup-specific treatment will improve pain management and reduce health care costs.

[Comorbidities in the diseasome are more apparent than real: What Bayesian filtering reveals about the comorbidities of depression.](#)

Marx P, Antal P, Bolgar B, Bagdy G, Deakin B, Juhasz G.

PLoS Comput Biol. 2017 Jun 23;13(6):e1005487. doi: 10.1371/journal.pcbi.1005487. eCollection 2017 Jun.

Comorbidity patterns have become a major source of information to explore shared mechanisms of pathogenesis between disorders. In hypothesis-free exploration of comorbid conditions, disease-disease networks are usually identified by pairwise methods. However, interpretation of the results is hindered by several confounders. In particular a very large number of pairwise associations can arise indirectly through other comorbidity associations and they increase exponentially with the increasing breadth of the investigated diseases. To investigate and filter this effect, we computed and compared pairwise approaches with a systems-based method, which constructs a sparse Bayesian direct multimorbidity map (BDMM) by systematically eliminating disease-mediated comorbidity relations. Additionally, focusing on depression-related parts of the BDMM, we evaluated correspondence with results from logistic regression, text-mining and molecular-level measures for comorbidities such as genetic overlap and the interactome-based association score. We used a subset of the UK Biobank Resource, a cross-sectional dataset including 247 diseases and 117,392 participants who filled out a detailed questionnaire about mental health. The sparse comorbidity map confirmed that depressed patients frequently suffer from both psychiatric and somatic comorbid disorders. Notably, anxiety and obesity show strong and direct relationships with depression. The BDMM identified further directly co-morbid somatic disorders, e.g. irritable bowel syndrome, fibromyalgia, or migraine. Using the subnetwork of depression and metabolic disorders for functional analysis, the interactome-based system-level score showed the best agreement with the sparse disease network. This indicates that these epidemiologically strong disease-disease relations have improved correspondence with expected molecular-level mechanisms. The substantially fewer number of

comorbidity relations in the BDMM compared to pairwise methods implies that biologically meaningful comorbid relations may be less frequent than earlier pairwise methods suggested. The computed interactive comprehensive multimorbidity views over the diseases are available on the web at Co=MorNet:bioinformatics.mit.bme.hu/UKBNetworks.

[From acute to chronic back pain: Using linear mixed models to explore changes in pain intensity, disability, and depression.](#)

Bendayan R, Ramírez-Maestre C, Ferrer E, López A, Esteve R.
Scand J Pain. 2017 Jul;16:45-51. doi: 10.1016/j.sjpain.2017.02.009.

BACKGROUND/AIMS: This longitudinal study investigated the pattern of change in pain intensity, disability, and depression in 232 chronic pain patients who were followed up for 2 years since pain onset. Most studies that have investigated changes in these variables over time have used participants who had already been in pain for more than 3 months. Few studies have followed up individuals from the acute phase onward and such studies used traditional statistical methods that cannot identify transition points over time or measure inter-individual variability. **METHODS:** We followed up individuals with chronic pain from pain onset up to 18 months and we examined their pain intensity, disability and depression trajectories using a modelling approach that allows to account for between and within-individual variability. We compared three patterns of change based on theoretical criterions: a simple linear growth model; a spline model with a 3-month transition point; and a spline model with a 6-month transition point. Time with pain was selected as time metric to characterise the change in these variables in the transition from acute to chronic pain. Sex and age differences were also examined. **RESULTS:** The results showed that the pain intensity trajectory was best represented by the spline model with a 3-month transition point, whereas disability and depression were best explained by linear growth models. There were sex differences at intercept level in all the models. There were age differences at baseline for pain intensity. No sex or age differences were found for the slope. **CONCLUSIONS:** Pain intensity decreased in the first 3 months but underwent no further change. Disability and depression slightly but constantly decreased over time. Although women and older individuals are more likely to report higher pain intensity or pain-related disability in the first three months with pain, no differences by sex or age appear to be associated with the changes in pain intensity, depression and disability through the process of chronification. **IMPLICATIONS:** Our findings suggest that pain chronification could be considered a continuous process and contribute to the ongoing discussion on the utility of standard classifications of pain as acute or chronic from a clinical point of view. Clinical and intervention decisions based in these standard classifications should consider the differences in the trajectories of pain related variables over time. In addition, this article illustrates a statistical procedure that can be of utility to pain researchers.

CLINICAL STUDIES

[Pain and psychology-a reciprocal relationship.](#)

Vadivelu N, Kai AM, Kodumudi G, Babayan K, Fontes M, Burg MM.
Ochsner J. 2017 Summer;17(2):173-180.

BACKGROUND: Depression typically affects 5% of the general population, but among patients with chronic pain, 30%-45% experience depression. Studies have shown that the relationship between depression and pain is bidirectional: depression is a positive predictor of the development of chronic pain, and chronic pain increases the risk of developing depression. **METHODS:** This literature review focuses on the relationship between psychology and pain, covering studies that have investigated the association between depression, pain sensitivity, opioid abuse, and gender differences in pain perception. We conducted a PubMed search pairing the word pain with depression, opioid use, and gender differences. **RESULTS:** The

relationship between depression and pain is complex, as suggested by numerous studies that propose depression to be a moderator of the relationship between pain severity, physical functioning, and opioid use. Neuroimaging also suggests an anatomic overlap in the pathway of chronic pain and depression. Positive psychological factors, namely hope, pain acceptance, and optimism, affect the adjustment to persistent pain. CONCLUSION: The intricate relationship between pain and psychology is evidenced by the clinical overlap in their presentations and the overlap between the anatomic regions in the brain associated with the emotional and sensory features of pain and the areas affected by depression. Studies are beginning to improve our understanding of these two systems, but more studies are needed to elucidate the relationship.

[New evidence for a pain personality? A critical review of the last 120 years of pain and personality.](#)

Naylor B, Boag S, Gustin SM.

Scand J Pain. 2017 Jul 28;17:58-67. doi: 10.1016/j.sjpain.2017.07.011.

BACKGROUND: Personality traits may influence development and adjustment to ongoing pain. Over the past 120 years, there has been considerable research into the relationship between pain and personality. This paper presents new evidence for common personality traits found amongst chronic pain sufferers. In particular, it evaluates evidence for Cloninger's biopsychosocial model of personality in distinguishing typical personality features of chronic pain sufferers. It evaluates this evidence in the context of the past 120 years of research including psychodynamic formulations, MMPI studies, personality disorder investigations, and the influence of neuroticism on chronic pain. METHODS: A literature search was conducted using PubMed, Medline, PsycINFO, SCOPUS and Cochrane library. Search terms included chronic pain, pain, personality, neuroticism, harm avoidance, self-directedness, attachment, Temperament and Character Inventory (TCI-R), MMPI, MMPI-2, NEO-PI, EPI, Millon Clinical Multiaxial Inventory, Millon Behavioral Health Inventory, Millon Behavioral Medicine Diagnostic, the Personality Assessment Inventory, the Locus of Control Construct and different combinations of these terms. CONCLUSIONS: Recent descriptive studies using Cloninger's Temperament and Character Inventory (TCI-R) suggest that higher harm avoidance and lower self-directedness may be the most distinguishing personality features of chronic pain sufferers. High harm avoidance refers to a tendency to be fearful, pessimistic, sensitive to criticism, and requiring high levels of re-assurance. Low self-directedness often manifests as difficulty with defining and setting meaningful goals, low motivation, and problems with adaptive coping. Evidence for this personality profile is found across a wide variety of chronic pain conditions including fibromyalgia, headache and migraine, temporomandibular disorder, trigeminal neuropathy, musculo-skeletal disorders and heterogeneous pain groups. Limitations are also discussed. For example, high harm avoidance is also found in those suffering anxiety and depression. While many studies control for such factors, some do not and thus future research should address such confounds carefully. The evidence is also evaluated within the context of past research into the existence of 'a pain personality'. Psychodynamic formulations are found to be deficient in objective scientific methods. MMPI studies lack sufficient evidence to support 'a pain personality' and may be confounded by somatic items in the instrument. More recent neuroticism studies suggest a relationship between neuroticism and pain, particularly for adjustment to chronic pain. Personality disorders are more prevalent in chronic pain populations than non-pain samples. CLINICAL IMPLICATIONS: Because harm avoidance reflects a tendency to developed conditioned fear responses, we suggest that higher harm avoidance may create more vulnerability to developing a fear-avoidance response to chronic pain. Furthermore, lower self-directedness may contribute to keeping a sufferer within this vicious cycle of fear, avoidance and suffering. Moreover, we suggest that harm avoidance and self-directedness are broader and more complex constructs than current clinical targets of CBT such as fear-avoidance and self-efficacy. Thus, assessing such personality traits may help to address the complexity of chronic pain presentations. For example, it may help to identify and treat sufferers more resistant to treatment, more prone to comorbidity and

more vulnerable to entering the vicious cycle of chronic pain, suffering and disability.

[Deep dyspareunia in endometriosis: A proposed framework based on pain mechanisms and genito-pelvic pain penetration disorder.](#)

Yong PJ.

Sex Med Rev. 2017 Aug 1. pii: S2050-0521(17)30069-0. doi: 10.1016/j.sxmr.2017.06.005.

INTRODUCTION: Endometriosis is a common chronic disease affecting 1 in 10 women of reproductive age, with half of women with endometriosis experiencing deep dyspareunia. A review of research studies on endometriosis indicates a need for a validated question or questionnaire for deep dyspareunia. Moreover, placebo-controlled randomized trials have yet to demonstrate a clear benefit for traditional treatments of endometriosis for the outcome of deep dyspareunia. The reason some patients might not respond to traditional treatments is the multifactorial nature of deep dyspareunia in endometriosis, which can include comorbid conditions (eg, interstitial cystitis and bladder pain syndrome) and central sensitization underlying genito-pelvic pain penetration disorder. In general, there is a lack of a framework that integrates these multifactorial causes to provide a standardized approach to deep dyspareunia in endometriosis. **AIM:** To propose a clinical framework for deep dyspareunia based on a synthesis of pain mechanisms with genito-pelvic pain penetration disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. **METHODS:** Narrative review after literature search with the terms (endometriosis AND dyspareunia) OR (dyspareunia AND deep) and after analysis of placebo-controlled randomized trials. **MAIN OUTCOME MEASURES:** Deep dyspareunia presence or absence or deep dyspareunia severity on a numeric rating scale or visual analog scale. **RESULTS:** Four types of deep dyspareunia are proposed in women with endometriosis: type I that is directly due to endometriosis; type II that is related to a comorbid condition; type III in which genito-pelvic pain penetration disorder is primary; and type IV that is secondary to a combination of types I to III. **CONCLUSION:** Four types of deep dyspareunia in endometriosis are proposed, which can be used as a framework in research studies and in clinical practice. Research trials could phenotype or stratify patients by each type. The framework also could give rise to more personalized care for patients by targeting appropriate treatments to each deep dyspareunia type.

[Sexual pain in women: quality of sex life and marital relations.](#)

Ghizzani A, Orlandini C, Bernardi MG, Cevenini G, Luisi S.

Minerva Ginecol. 2017 Aug;69(4):381-389. doi: 10.23736/S0026-4784.17.04054-0.

Common gynecological and dermatological conditions resulting in sexual pain are often observed in gynecological practice and are easily diagnosed with visual observation and laboratory tests. The lower genital tract diseases we are referring to are vaginitis, vaginosis, dermatoses, hypoestrogenism and endometriosis. All of them affect the vaginal mucosa with diverse mechanisms, their effects lasting for only few days or many months. Furthermore, they change the women's sense of wellbeing sometimes significantly and for a long period. The conditions we mentioned above are recognized promptly with basic gynecological interventions but when burning or sharp pain occurs with light pressure (as in case of penetration attempts) without physical signs we must suspect the genitopelvic pain penetration disorder. This condition was defined for the first time in the Diagnostic and Statistical Manual of Mental Disorders-5 and its dimensions include difficulty or pain at penetration associated with fear, anxiety, and pelvic floor hypertonus. Pain is most often localized at the vulvar vestibule and described as burning, pressure, and itching. These dimensions are iconic of sexual pain associated with vulvodynia and vaginismus but are common also in fibromyalgia, a syndrome of widespread chronic pain of unknown origin; sexual pain in fibromyalgia is mostly attributed both to the joint pathology and to the lower sensitive threshold that are the pathognomonic signs of this condition. In our study we analyzed the characteristics of pain as reported for each disease to evaluate its influence on

sexuality and marital relations.

[Is there an association between migraine and gastrointestinal disorders?](#)

Doulberis M, Saleh C, Beyenburg S.

J Clin Neurol. 2017 Jul;13(3):215-226. doi: 10.3988/jcn.2017.13.3.215.

Migraine is a primary episodic headache disorder that represents a substantial burden and disability worldwide. Its pathogenesis is multifactorial and remains hitherto poorly elucidated. An interesting but less-well-known association is that between migraine and gastrointestinal disorders. We have reviewed the literature for relevant papers reporting on the clinical association between migraine and gastrointestinal symptoms. Several studies have shown different gastrointestinal diseases to be associated with migraine, but the underlining pathophysiology remains elusive. The data gathered and analyzed have shown great variability across studies, making it impossible to draw definitive conclusions. Further research is required to elucidate this potential relationship. An understanding of the relationship between migraine and gastrointestinal disorders is of great clinical importance for prompt diagnosis and treatment.

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 vulvodinia, 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.

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