CUTTING EDGE

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This e-newsletter is published by the Chronic Pain Research Alliance and developed to keep the medical-scientific and patient communities abreast of research advances on Chronic Overlapping Pain Conditions (COPCs). It contains abstracts of studies on the epidemiology, pathophysiology and clinical management of COPCs published between November 2017 and February 2018. 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.

In this Issue...

NATIONAL MULTICENTER STUDIES

Relationships between brain metabolite levels, functional connectivity, and negative mood in urologic chronic pelvic pain syndrome patients compared to controls: A MAPP research network study.

Harper DE, Ichesco E, Schrepf A, Halvorson M, Puiu T, Clauw DJ, Harris RE, Harte SE: MAPP Research Network.

Neuroimage Clin. 2017 Nov 15;17:570-578. doi: 10.1016/j.nicl.2017.11.014. eCollection 2018.

Until recently, the predominant pathology of chronic pelvic pain conditions was thought to reside in the peripheral tissues. However, mounting evidence from neuroimaging studies suggests an important role of the central nervous system in the pathogenesis of these conditions. In the present cross-sectional study, proton magnetic resonance spectroscopy (^{1}H-MRS) of the brain was conducted in female patients with urologic chronic pelvic pain syndrome (UCPPS) to determine if they exhibit abnormal concentrations of brain metabolites (e.g. those indicative of heightened excitatory tone) in regions involved in the processing and modulation of pain, including the anterior cingulate cortex (ACC) and the anterior and posterior insular cortices. Compared to a group of age-matched healthy subjects, there were significantly higher levels of choline ($p = 0.006$, uncorrected) in the ACC

of UCPPS patients. ACC choline levels were therefore compared with the region's resting functional connectivity to the rest of the brain. Higher choline was associated with greater ACC-to-limbic system connectivity in UCPPS patients, contrasted with lower connectivity in controls (i.e. an interaction). In patients, ACC choline levels were also positively correlated with negative mood. ACC γ-aminobutyric acid (GABA) levels were lower in UCPPS patients compared with controls ($p = 0.02$, uncorrected), but this did not meet statistical correction for the 4 separate regional comparisons of metabolites. These results are the first to uncover abnormal GABA and choline levels in the brain of UCPPS patients compared to controls. Low GABA levels have been identified in other pain syndromes and might contribute to CNS hyper-excitability in these conditions. The relationships between increased ACC choline levels, ACC-to-limbic connectivity, and negative mood in UCPPS patients suggest that this metabolite could be related to the affective symptomatology of this syndrome.

PATHOPHYSIOLOGY STUDIES

Comparison of gray matter volume between migraine and "strict-criteria" tension-type headache.

Chen WT, Chou KH, Lee PL, Hsiao FJ, Niddam DM, Lai KL, Fuh JL, Lin CP, Wang SJ.
J Headache Pain. 2018 Jan 15;19(1):4. doi: 10.1186/s10194-018-0834-6.

BACKGROUND: Despite evidently distinct symptoms, tension-type headache (TTH) and migraine are highly comorbid and exhibit many similarities in clinical practice. The purpose of this study was to investigate whether both types of headaches are similar in brain morphology. METHODS: Consecutive patients with TTH and age- and sex-matched patients with migraine and healthy controls were enrolled for brain magnetic resonance imaging examination. Patients with TTH were excluded if they reported any headache features or associated symptoms of migraine. Changes in gray matter (GM) volume associated with headache diagnosis (TTH vs. migraine) and frequency (episodic vs. chronic) were examined using voxel-based morphometry. The correlation with headache profile and the discriminative ability between TTH and migraine were also investigated for these GM changes. RESULTS: In comparison with controls (n=43), the patients with TTH (25 episodic and 24 chronic) exhibited a GM volume increase in the anterior cingulate cortex, supramarginal gyrus, temporal pole, lateral occipital cortex, and caudate. The patients with migraine (31 episodic and 25 chronic) conversely exhibited a GM volume decrease in the orbitofrontal cortex. These GM changes did not correlate with any headache profile. A voxel-wise 2x2 factorial analysis further revealed the substantial effects of headache types and frequency in the comparison of GM volume between TTH and migraine. Specifically, the migraine group (vs. TTH) had a GM decrease in the superior and middle frontal gyri, cerebellum, dorsal striatum, and precuneus. The chronic group (vs. episodic group) otherwise demonstrated a GM decrease in the bilateral insula and anterior cingulate cortex. In receiver operating characteristic analysis, the GM volumes of the left superior frontal gyrus and right cerebellum V combined had good discriminative ability for distinguishing TTH and migraine (area under the curve = 0.806). CONCLUSIONS: TTH and migraine are separate headache disorders with different characteristics in relation to GM changes. The major morphological difference between the two types of headaches is the relative GM decrease of the prefrontal and cerebellar regions in migraine, which may reflect a higher allostatic load associated with this disabling headache.

Morphology of subcortical brain nuclei is associated with autonomic function in healthy humans.

Ruffle JK, Coen SJ, Giampietro V, Williams SCR, Apkarian AV, Farmer AD, Aziz Q.
Hum Brain Mapp. 2018 Jan;39(1):381-392. doi: 10.1002/hbm.23850

The autonomic nervous system (ANS) is a brain body interface which serves to maintain homeostasis by influencing a plethora of physiological processes, including metabolism, cardiorespiratory regulation and nociception. Accumulating evidence suggests that ANS function is disturbed in numerous prevalent clinical disorders, including irritable bowel syndrome and fibromyalgia. While the brain is a central hub for regulating autonomic function, the association between resting autonomic activity and subcortical morphology has not been comprehensively studied and thus was our aim. In 27 healthy subjects [14 male and 13 female; mean age 30 years (range 22-53 years)], we quantified resting ANS function using validated indices of cardiac sympathetic index (CSI) and parasympathetic cardiac vagal tone (CVT). High resolution structural magnetic resonance imaging scans were acquired, and differences in subcortical nuclei shape, that is, 'deformation', contingent on resting ANS activity were investigated. CSI positively correlated with outward deformation of the brainstem, right nucleus accumbens, right amygdala and bilateral pallidum (all thresholded to corrected $p < 0.05$). In contrast, parasympathetic CVT negatively correlated with inward deformation of the right amygdala and pallidum (all thresholded to corrected $p < 0.05$). Left and right putamen volume positively correlated with CVT ($r=0.62$, $p=0.0047$ and $r=0.59$, $p=0.008$, respectively), as did the brainstem ($r=0.46$, $p=0.049$). These data provide novel evidence that resting autonomic state is associated with differences in the shape and volume of subcortical nuclei. Thus, subcortical morphological brain differences in various disorders may partly be attributable to perturbation in autonomic function. Further work is warranted to investigate these findings in clinical populations.

A test of the adaptive network explanation of functional disorders using a machine learning analysis of symptoms.
Melidis C, Denham SL, Hyland ME.
Biosystems. 2017 Dec 23. pii: S0303-2647(17)30243-5. doi: 10.1016/j.biosystems.2017.12.010.

The classification and etiology of functional disorders is controversial. Evidence supports both psychological and biological (disease) models that show, respectively, that functional disorders should be classified as one (bodily distress syndrome) and many (e.g., irritable bowel syndrome (IBS), fibromyalgia syndrome (FMS), and chronic fatigue syndrome (CFS)). Two network models (symptom network and adaptive network) can explain the specificity and covariation of symptomatology, but only the adaptive network model can explain the covariation of the somatic symptoms of functional disorders. The adaptive network model is based on the premise that a network of biological mechanisms has emergent properties and can exhibit adaptation. The purpose of this study was to test the predictions that symptom similarity increases with pathology and that network connection strengths vary with pathology, as this would be consistent with the notion that functional disorder pathology arises from network adaptation. We conducted a symptom internet survey followed by machine learning analysis. Participants were 1751 people reporting IBS, FMS or CFS diagnosis who completed a 61-item symptom questionnaire. Eleven symptom clusters were identified. Differences in symptom clusters between IBS, FMS and CFS groups decreased as overall symptom frequency increased. The strength of outgoing connections between clusters varied as a function of symptom frequency and single versus multiple diagnoses. The findings suggest that the pathology of functional disorders involves an increase in the activity and causal connections between several symptom causing mechanisms. The data provide support for the proposal that the body is capable of complex adaptation and that functional disorders result when rules that normally improve adaptation create maladaptive change.

Increased pain sensitivity in migraine and tension-type headache coexistent with low back pain: A cross-sectional population study.
Ashina S, Lipton RB, Bendtsen L, Hajiyeva N, Buse DC, Lynberg AC, Jensen R.
Eur J Pain. 2018 Jan 19. doi: 10.1002/ejp.1176.

BACKGROUND: Low back pain is common in the general population and in individuals with primary headaches. We assessed the relative frequency of self-reported back pain in persons

with and without primary headaches and examined pain sensitivity. METHOD: A population of 796 individuals completed a headache interview based on ICHD criteria and provided data of interest in a self-administered questionnaire. Headache cases were classified into chronic (≥15) (CH) or episodic (<15 headache days/month) (EH). A total of 495 had a pericranial total tenderness score (TTS), and 494 had cephalic and extracephalic pressure pain thresholds (PPTs) assessed. RESULTS: Adjusted for age, gender, education and poor self-rated health, 1-year relative frequency of back pain was higher in individuals with CH (82.5%) and EH (80.1%) compared to no headache group (65.7%). In persons with back pain, TTS was higher in CH, (26.3 ± 12.1) than in EH, (18.5 ± 10.0; $p < 0.001$) and higher in both groups than in those with no headache, 10.8 ± 8.5 ($p < 0.001$ and $p < 0.001$, respectively). In persons with back pain, temporalis PPT were lower in CH, 169.3 ± 57.8, than in EH, 225.2 ± 98.1, and in no headache group, 244.3 ± 105.4 ($p = 0.02$ and $p = 0.01$, respectively). In persons with back pain, finger PPT were lower in CH, 237.1 ± 106.7, than in EH, 291.3 ± 141.3, or in no headache group, 304.3 ± 137.4 ($p = 0.02$ and $p < 0.001$, respectively). CONCLUSION: Back pain is highly frequent in individuals with CH, followed by EH and no headache. In persons with CH, back pain is associated with lower cephalic and extracephalic PPTs suggesting central sensitization may be a substrate or consequence of comorbidity. SIGNIFICANCE: We found that back pain has high relative frequency in individuals with CH followed EH and no headache. Back pain is associated with low cephalic and extracephalic PPTs in individuals with CH. Central sensitization may be a substrate or consequence of this comorbidity of back pain and CH.

Urodynamic characteristics might be variable in bladder pain syndrome/interstitial cystitis patients with different non-bladder co-morbid conditions.
Cheng WM, Fan YH, Lin ATL.
J Chin Med Assoc. 2017 Dec 6. pii: S1726-4901(17)30339-8. doi: 10.1016/j.jcma.2017.06.022.

BACKGROUND: The aim of the study was to identify the impact of non-bladder co-morbid conditions on the urodynamic characteristics of patients with bladder pain syndrome/interstitial cystitis. METHODS: Patients with bladder pain syndrome/interstitial cystitis completed the screening questionnaires for chronic fatigue syndrome, irritable bowel syndrome, fibromyalgia, temporo-mandibular disorders, multiple chemical sensitivities, tension/migraine headache, and localized myofascial pain disorder. They underwent either conventional pressure-flow urodynamic studies or video-urodynamic studies. Urodynamic variables were compared between patients with and those without co-morbid conditions. RESULTS: Of 111 patients (16 males and 95 females) with bladder pain syndrome/interstitial cystitis, 87 (78.4%) had at least one co-morbid condition (62% males vs 82% females, $p = 0.005$). Those with concomitant irritable bowel syndrome were younger and had urodynamic characteristics of smaller catheter-free voided volume, lower catheter-free average flow rate, smaller bladder volume on the first desire to void, and more prevalent dysfunctional voiding than those without irritable bowel syndrome. Patients with concomitant localized myofascial pain disorder also had larger bladder volume at the first desire to void and lower pressure at maximum flow than those without co-morbid myofascial pain disorder. There were no significant differences in urodynamic parameters between bladder pain syndrome/interstitial cystitis patients with and those without other co-morbidities. CONCLUSION: Bladder pain syndrome/interstitial cystitis patients, especially females, are more likely to have non-bladder co-morbidities, especially tension/migraine headache and localized myofascial pain. Bladder pain syndrome/interstitial cystitis patients with co-morbid irritable bowel syndrome are younger and more likely to have abnormal urodynamic findings.

Clinical significance of anti-dense fine speckled 70 antibody in patients with fibromyalgia.
Jeong J, Kim DH, Park G, Park S, Kim HS.
Korean J Intern Med. 2017 Nov 24. doi: 10.3904/kjim.2016.276.

BACKGROUND/AIMS: Fibromyalgia (FM) is a common rheumatologic disease characterized by chronic widespread pain, along with various clinical manifestations including atypical

autoimmune characteristics. Despite its high prevalence, there remain no approved laboratory tests to identify specific manifestations of FM, or to rule out FM from other rheumatic diseases. Anti-dense fine speckled 70 (anti-DFS70) antibodies were initially identified as a form of anti-nuclear antibodies in a patient with interstitial cystitis. Anti-DFS70 antibodies are found in ≤ 10% of healthy individuals, but have suggestive negative association with autoimmune diseases; however, the clinical significance of these autoantibodies in FM patients remains poorly understood. METHODS: We examined 39 patients with FM, along with 17 patients with systemic lupus erythematosus (SLE), and 19 healthy individuals (HI). Patients were compared based on physical measurements, disease duration, tender point counts, FM Impact Questionnaire (FIQ) scores, visual analog scale (VAS) for pain, somatic symptoms, and anti-DFS70 antibodies. RESULTS: Levels of anti-DFS70 antibodies were significantly higher in the FM and HI groups than in those with SLE. Both anti-DFS70 antibodies and VAS scores were positively correlated with FM. Within the FM group, patients with arthralgia had higher anti-DFS70 antibody values compared to those without arthralgia ($p = 0.024$); antibody levels were also higher in patients with sleep disturbances relative to those without sleep issues ($p = 0.024$). In contrast, there were no correlations between anti-DFS70 antibodies and age, body mass index, disease duration, tender point counts, FIQ, short-form health survey results, or other clinical manifestations. CONCLUSIONS: Anti-DFS70 antibodies may represent a useful biomarker for differentiating between FM and other autoimmune diseases. The levels of anti-DFS70 antibodies were also significantly higher among patients with arthralgia and sleep disturbances. Further investigations are necessary to evaluate the relationships between anti-DFS70 antibodies and other cytokines as a predictive marker for pain.

Inhibition of TNF reduces mechanical orofacial hyperalgesia induced by Complete Freund's Adjuvant by a TRPV1-dependent mechanism in mice.
Lis K, Grygorowica T, Cudna A, Symkowski DE, Balkowiec-Iskra E.
Pharmacol Rep. 2017 Dec;69(6):1380-1385. doi: 10.1016/j.pharep.2017.05.013

BACKGROUND: Inflammation in the orofacial region results in pain and is associated with many pathological states, including migraine, neuralgias and temporomandibular disorder. Although extensively studied, the mechanisms responsible for these conditions are not known and effective treatments are lacking. We reported earlier that the proinflammatory cytokine tumor necrosis factor (TNF) plays an important role in regulation of trigeminal ganglion (TG) neuron function in vitro. In the present study we investigated the role of TNF in mechanical hypersensitivity in mice. METHODS: We employed the Complete Freund's Adjuvant (CFA)-induced model of orofacial pain and evaluated the effect of blocking of soluble TNF activity by peripheral administration of the novel dominant negative TNF biologic, XPro1595. RESULTS: We show that CFA administration into the lower lip causes hyperalgesia and an increase in both expression of transient receptor potential vanilloid subfamily member 1 (TRPV1) mRNA and in the average intensity of TRPV1 protein immunoreactivity in TG neurons. We also show that intraperitoneal administration of XPro1595 prevents both CFA-induced mechanical hypersensitivity and, as shown in immunohistochemical staining - upregulation of TRPV1 protein expression in TG neurons. CONCLUSIONS: We conclude that one of the possible regulatory mechanisms of TNF in pain involves upregulation of the nociceptor TRPV1, and that peripheral treatment with a selective anti-soluble TNF biologic can prevent hyperalgesia caused by inflammation in the orofacial region. Therefore, these new findings suggest that XPro1595 may serve as a novel treatment for orofacial pain disorders.

Cross-organ sensitization between the colon and bladder: To pee, or not to pee?
Grundy L, Brierley SM.
Am J Physiol Gastrointest Liver Physiol. 2017 Nov 16:ajpgi002722017. doi: 10.1152/ajpgi.00272.2017.

Chronic abdominal and pelvic pain are common, debilitating clinical conditions experienced by millions of patients around the globe. The origin of such pain commonly arises from the

intestine and bladder, which share common primary roles; the collection, storage and expulsion of waste. These visceral organs are located in close proximity to one another, and also share common innervation from spinal afferent pathways. Chronic abdominal pain, constipation or diarrhoea are primary symptoms for patients with Irritable Bowel Syndrome (IBS) or Inflammatory Bowel Disease (IBD). Chronic pelvic pain, urinary urgency and frequency are primary symptoms experienced by patients with lower urinary tract disorders such as interstitial cystitis/painful bladder syndrome (IC/PBS). It is becoming clear that these symptoms and clinical entities do not occur in isolation, with considerable overlap in symptom profiles across patient cohorts. Here we review recent clinical and experimental evidence documenting the existence of 'cross-organ sensitisation' between the colon and bladder. In such circumstances, colonic inflammation may result in profound changes to the sensory pathways innervating the bladder, resulting in severe bladder dysfunction.

Hyperacusis in chronic pain: neural interactions between the auditory and nociceptive systems.
Suhnan AP, Finch PM, Drummond PD.
Int J Audiol. 2017 Nov;56(11):801-809. doi: 10.1080/14992027.2017.1346303.

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. TUDY 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.

Sex difference in peripheral not central immune responses to pain-inducing injury.
Lopes DM, Malek N, Edye M, Jager SB, McMurray S, McMahon SB, Denk F.
Sci Rep. 2017 Nov 28;7(1):16460. doi: 10.1038/s41598-017-16664-z.

Women suffer chronic pain more frequently than men. It is not clear whether this is due to differences in higher level cognitive processes or basic nociceptive responses. In this study we used a mouse model of neuropathic pain to dissociate these factors. We performed RNA-seq on purified peripheral afferent neurons, but found no striking differences in gene expression between male and female mice, neither before nor after nerve injury. Similarly, spinal cord immune responses between the sexes appeared to be indistinguishable when studied by flow cytometry or qRT-PCR. Differences emerged only upon studying peripheral immune cell infiltration into the dorsal root ganglion, suggesting that adaptive immune responses in neuropathic pain could be sexually dimorphic.

A critical role for dopamine D5 receptors in pain chronicity in male mice.
Megat S, Shiers S, Moy, JK, Barragan-Iglesias P, Pradhan G, Seal RP, Dussor G, Price TJ.
J Neurosci. 2018 Jan 10;38(2):379-397. doi: 10.1523/JNEUROSCI.2110-17.2017.

Dopaminergic modulation of spinal cord plasticity has long been recognized, but circuits affected by this system and the precise receptor subtypes involved in this modulation have not been defined. Dopaminergic modulation from the A11 nucleus of the hypothalamus

contributes to plasticity in a model of chronic pain called hyperalgesic priming. Here we tested the hypothesis that the key receptor subtype mediating this effect is the D5 receptor (D5R). We find that a spinally directed lesion of dopaminergic neurons reverses hyperalgesic priming in both sexes and that a D1/D5 antagonist transiently inhibits neuropathic pain. We used mice lacking D5Rs (*DRD5KO* mice) to show that carrageenan, interleukin 6, as well as BDNF-induced hyperalgesia and priming are reduced specifically in male mice. These male *DRD5KO* mice also show reduced formalin pain responses and decreased heat pain. To characterize the subtypes of dorsal horn neurons engaged by dopamine signaling in the hyperalgesic priming model, we used c-fos labeling. We find that a mixed D1/D5 agonist given spinally to primed mice activates a subset of neurons in lamina III and IV of the dorsal horn that co-express PAX2, a transcription factor for GABAergic interneurons. In line with this, we show that gabazine, a GABA-A receptor antagonist, is anti-hyperalgesic in primed mice exposed to spinal administration of a D1/D5 agonist. Therefore, the D5R, in males, and the D1R, in females, exert a powerful influence over spinal cord circuitry in pathological pain likely via modulation of deep dorsal horn GABAergic neurons.
SIGNIFICANCE STATEMENT: Pain is the most prominent reason why people seek medical attention, and chronic pain incidence worldwide has been estimated to be as high as 33%. This study provides new insight into how descending dopamine controls pathological pain states. Our work demonstrates that dopaminergic spinal projections are necessary for the maintenance of a chronic pain state in both sexes; however, D5 receptors seem to play a critical role in males whereas females rely more heavily on D1 receptors, an effect that could be explained by sexual dimorphisms in receptor expression levels. Collectively, our work provides new insights into how the dopaminergic system interacts with spinal circuits to promote pain plasticity.

Sex differences and estradiol involvement in hyperalgesia and allodynia in an experimental model of fibromyalgia.
Hernandez-Leon A, De la Luz-Cuellar YE, Granados-Soto V, Gonzalez-Trujano ME, Fernandez-Guasti A.
Horm Behav. 2018 Jan;97:39-46. doi: 10.1016/j.yhbeh.2017.10.011.

Fibromyalgia (FM) is a musculoskeletal chronic pain syndrome. Its prevalence in women is higher than in men possibly by hormonal factors given that symptoms are aggravated during sex hormone-related events, such as the premenstrual period, pregnancy, postpartum or menopause. The aim of the present study was to investigate whether hyperalgesia and allodynia, in reserpine-induced experimental FM, depend on sex, estrous cycle, ovariectomy and replacement with 17β-estradiol. To fulfill this objective, we compared males, intact females with known estrous cycle phases and ovariectomized (OVX) rats treated with 17β-estradiol. Data demonstrated that reserpine administration disrupted the normal estrous cycle and produced that all females entered metestrus/diestrus. In addition, this treatment leads to muscle hyperalgesia and tactile allodynia in a similar manner in male and intact female rats. However, the absence of ovarian hormones (in OVX rats) increased muscle nociception. 17β-estradiol (2.5-10μg/rat) produced antihyperalgesic and antiallodynic effects 24h, but not 8h, after its administration, suggesting a genomic mechanism. The present results support the validity of the reserpine-induced FM model for searching alternatives of treatment, particularly during endocrine phases when pain is exacerbated such as menopause, and that 17β-estradiol replacement might be useful.

Sex differences in primary muscle afferent sensitization following ischemia and reperfusion injury.
Ross JL, Queme LF, Lamb JE, Green KJ, Jankowski MP.
Biol Sex Differ. 2018 Jan 3;9(1):2. doi: 10.1186/s13293-017-0163-5.

BACKGROUND: Chronic pain conditions are more prevalent in women, but most preclinical studies into mechanisms of pain generation are performed using male animals. Furthermore, whereas group III and IV nociceptive muscle afferents provoke central sensitization more effectively than their cutaneous counterparts, less is known about this critical population of

muscle nociceptors. Here, we compare the physiology of individual muscle afferents in uninjured males and females. We then characterize the molecular, physiological, and behavioral effects of transient ischemia and reperfusion injury (I/R), a model we have extensively studied in males and in females. METHODS: Response properties and phenotypes to mechanical, thermal, and chemical stimulation were compared using an ex vivo muscle/nerve/dorsal root ganglia (DRG)/spinal cord recording preparation. Analyses of injury-related changes were also performed by assaying evoked and spontaneous pain-related behaviors, as well as mRNA expression of the affected muscle and DRGs. The appropriate analyses of variance and post hoc tests (with false discovery rate corrections when needed) were performed for each measure. RESULTS: Females have more mechanically sensitive muscle afferents and show greater mechanical and thermal responsiveness than what is found in males. With I/R, both sexes show fewer cells responsive to an innocuous metabolite solution (ATP, lactic acid, and protons), and lower mechanical thresholds in individual afferents; however, females also possess altered thermal responsiveness, which may be related to sex-dependent changes in gene expression within the affected DRGs. Regardless, both sexes show similar increases in I/R-induced pain-like behaviors. CONCLUSIONS: Here, we illustrate a unique phenomenon wherein discrete, sex-dependent mechanisms of primary muscle afferent sensitization after ischemic injury to the periphery may underlie similar behavioral changes between the sexes. Furthermore, although the group III and IV muscle afferents are fully developed functionally, the differential mechanisms of sensitization manifest prior to sexual maturity. Hence, this study illustrates the pressing need for further exploration of sex differences in afferent function throughout the lifespan for use in developing appropriately targeted pain therapies.

EPIDEMIOLOGY STUDIES

Endometriosis increased the risk of bladder pain syndrome/interstitial cystitis: A population-based study.
Wu CC, Chung SD, Lin HC.
Neurourol Urodyn. 2018 Jan 10. doi: 10.1002/nau.23462.

OBJECTIVE: Previous studies have suggested an association between bladder pain syndrome/interstitial cystitis (BPS/IC) and endometriosis. However, no nation-wide population study has yet reported an association between them. In this study, we examined the risk of BPS/IC among subjects with endometriosis during a 3-year follow-up in Taiwan using a population-based dataset. STUDY DESIGN: This study comprised 9191 subjects with endometriosis, and 27,573 subjects randomly selected as controls. We individually followed-up each subject (n=36,764) for a 3-year period to identify subjects subsequently diagnosed with BPS/IC. A Cox proportional hazards regression model was employed to estimate the risk of subsequent BPS/IC following a diagnosis of endometriosis. RESULTS: Incidences of BPS/IC during the 3-year follow-up period was 0.2% and 0.05% for subjects with and without endometriosis, respectively. The hazard ratio for developing BPS/IC over a 3-year period for subjects with endometriosis compared to subjects without endometriosis was 4.43 (95% CI: 2.13-9.23). After adjusting for co-morbidities like diabetes, hypertension, coronary heart disease, obesity, hyperlipidemia, chronic pelvic pain, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, depression, panic disorder, migraines, sicca syndrome, allergies, endometriosis, asthma, tobacco use, and alcohol abuse, the Cox proportional hazards regressions revealed that the hazard ratio for BPS/IC among subjects with endometriosis was 3.74 (95% CI=1.76-7.94, $p<0.001$) compared to that in controls. CONCLUSIONS: This study provides epidemiological evidence of an association between endometriosis and a subsequent diagnosis of BPS/IC.

Migraine in young females with irritable bowel syndrome: still a challenge.

Georgescu D, Reisz D, Gurban DV, Georgescu LA, Ionita I, Ancusa OE, Lighezan D. Neuropsychiatr Dis Treat. 2017 Dec 20;14:21-28. doi: 10.2147/NDT.S144955. eCollection 2018.

Migraine without aura is frequently reported in female patients with irritable bowel syndrome (IBS), but knowledge about the relationship between these two conditions is still lacking. This study aimed to explore the particularities of migraine without aura in young female patients with IBS in order to establish a possible link between them. From a cohort of young female patients hospitalized with IBS in the Internal Medicine Department, 30 joined this pilot study, and they were assigned into two groups on the basis of presence or absence of migraine. In this sample, 15 patients have mild to moderate migraine without aura, with a recently taken normal brain scan, and 15 were without migraine. Diseases and conditions not related to migraine and other possible specific female comorbidities were ruled out. Patients undertook a thorough clinical examination in order to assess fibromyalgia (FM) and chronic pelvic pain (CPP), Questionnaires for migraine disability assessment (MIDAS) and generalized anxiety disorder (GAD) were performed. Laboratory testing of blood, urine, and stool were also performed. Optimized lymphocyte proliferation test for food allergy (FA) and a fecal microbiota (microbiological semiquantitative method) for dysbiosis (DB) assessment were performed. Based on the results, migraine-positive group displayed more severe comorbidities: FM (p=0.0002), FA (p=0.0006), CPP (p=0.026), higher scores of anxiety (GAD, p=0.0008), and more severe DB (p=0.0009). We noticed a strong positive correlation between MIDAS and GAD (r=0.83), a good positive correlation between MIDAS and DB (r=0.56), and a moderate positive correlation between MIDAS, FM, and FA (r=0.46 and 0.41). In conclusion, young female patients with IBS and migraine without aura displayed more severe associated issues - anxiety, intestinal DB, FM, FA, and CPP. The severity of migraine correlated well with anxiety range and DB magnitude and moderately with FM and FA.

Comorbidity of gastrointestinal disorders, migraine, and tension-type headache: A cross-sectional study in Iran.
Martami F, Ghorbani Z, Abolhasani M, Togha M, Meysamie A, Sharifi A, Razeghi Jahromi S. Neurol Sci. 2018 Jan;39(1):63-70. doi: 10.1007/s10072-017-3141-0.

Migraine can be accompanied by some gastrointestinal (GI) disorders. In this study, we aimed to investigate the relationship between migraine and tension-type headache (TTH) and different lower and upper GI disorders as well as non-alcoholic fatty liver (NAFLD) and cholelithiasis. This cross-sectional study included 1574 overweight and obese participants who were referred to the Obesity Research Center of Sina Hospital, Tehran, Iran. The diagnosis of migraine and TTH was made by an expert neurologist based on the international classification of headache disorders-III β (ICHD III β). GI disorders, including irritable bowel syndrome (IBS), constipation, heartburn, dyspepsia, non-alcoholic fatty liver (NAFLD), and cholelithiasis, were diagnosed by a gastroenterology specialist. The overall mean age of participants was 37.44 ± 12.62. A total of 181 (11.5%) migraine sufferers (with and without aura) and 78 (5%) TTH subjects were diagnosed. After adjusting for potential confounders by multivariable regression models, migraine had significant association with IBS (OR = 5.16, 95% CI = 2.07-12.85, P = 0.000), constipation (OR = 3.96, 95% CI = 2.25-6.99, P = 0.000), dyspepsia (OR = 4.12, 95% CI = 2.63-6.45, P = 0.000), and heartburn (OR = 5.03, 95% CI 2.45-10.33, P = 0.000), while the association between migraine and NAFLD was marginally significant (OR = 2.03, 95% CI = 0.98-4.21, P = 0.055). Furthermore, the prevalence of NAFLD (OR = 2.93, 95% CI 1.29-6.65, P = 0.010) and dyspepsia (OR = 4.06, 95% CI = 2.24-7.34, P = 0.000) was significantly higher in TTH patients than the headache-free group. These findings show an association between GI disorders and primary headaches especially migraine and are, therefore, of value to the management of migraine and TTH. Further studies should investigate the etiology of the relationship between all subtypes of primary headaches and GI disorders.

Migraine and complex regional pain syndrome: A case-referent clinical study.
Woldeamanuel YW, Cooley C, Foley-Saldena K, Cowan RP.

Biomed Res Int. 2017;2017:5714673. doi: 10.1155/2017/5714673.

We studied clinical phenotype differences between migraineurs *with* CRPS (Mig + CRPS) and those without (Mig - CRPS). Mig + CRPS cases and Mig - CRPS referents aged ≥18 years were enrolled. Diagnosis was made in accordance with International Classification of Headache Disorders-3 beta (ICHD-3 beta) for migraine and Budapest Criteria for CRPS. Migraines both with and without aura were included. A total of 70 Mig + CRPS cases (13% males, mean age 48 years) and 80 Mig - CRPS referents (17% males, mean age 51 years) were included. 33% of Mig + CRPS and 38% of Mig - CRPS exhibited episodic migraine (EM) while 66% of Mig + CRPS and 62% of Mig - CRPS had chronic migraine (CM) (OR = 0.98, CI 0.36, 2.67). Median duration of CRPS was 3 years among EM + CRPS and 6 years among CM + CRPS cohort ($p < 0.02$). Mig + CRPS (57%) carried higher psychological and medical comorbidities compared to Mig - CRPS (6%) (OR 16.7, CI 10.2, 23.6). Higher migraine frequency was associated with longer CRPS duration. Migraineurs who developed CRPS had higher prevalence of psychological and medical disorders. Alleviating migraineurs' psychological and medical comorbidities may help lower CRPS occurrence.

Association between temporomandibular disorders, chronic diseases, and ophthalmologic and otolaryngologic disorders in Korean adults: A cross-sectional study.
Song HS, Shin JS, Lee J, Lee TJ, Kim MR, Cho JH, Kim KW, Park Y, Song HJ, Park SY, Kim S, Kim M, Ha IH.
PLoS One. 2018 Jan 31;13(1):e0191336. doi: 10.1371/journal.pone.0191336. eCollection 2018.

INTRODUCTION: Temporomandibular disorders (TMDs) are common musculoskeletal conditions in the maxillofacial area. Although strong relationships between TMDs and other pain and diseases exist, few studies have comprehensively assessed the association between chronic diseases, ophthalmologic and otolaryngologic disorders and TMD. METHODS: Of 25,534 individuals included in the fifth Korea National Health and Nutrition Examination Survey (2010-2012), 17,575 aged ≥20 years who completed survey items on TMD symptoms were included for cross-sectional analysis. Logistic regression analysis was performed to assess the association between chronic diseases, ophthalmologic and otolaryngologic disorders and examination findings, and TMD symptoms after adjusting for various confounding variables.RESULTS: Out of 17,575 participants, 2,059 (11.75%) reported experience of ≥1 TMD symptom(s). Compared to individuals without chronic disease, those with asthma (odds ratio (OR) 1.46; 95% confidence interval (CI) 1.09-1.96), migraine (1.44; 1.26-1.65), osteoarthritis (1.51; 1.20-1.89), thyroid dysfunction (1.49; 1.13-1.96), and depressive symptoms (1.51; 1.29-1.77) had higher ORs for TMD prevalence. Participants with tinnitus (1.97; 1.70-2.27), hearing difficulties (1.55; 1.29-1.87), dizziness (1.52; 1.27-1.82), rhinitis (1.46; 1.28-1.65), and xerophthalmia (1.82; 1.57-2.12) also displayed higher ORs for TMD prevalence. Patients diagnosed with chronic rhinosinusitis upon otolaryngologic examination exhibited an OR of 1.44 (95% CI 1.11-1.87) for TMD prevalence, while that for individuals with abnormal laryngoscopic results was 0.57 (95% CI 0.36-0.90). CONCLUSIONS: These findings imply that TMDs, chronic diseases, and ophthalmologic and otolaryngologic disorders hold various correlations, suggesting the need for multitarget approaches to effectively address this phenomenon.

Presence of comorbidities and prognosis of clinical symptoms in knee and/or hip osteoarthritis: A systematic review and meta-analysis.
Calders P, Van Ginckel A.
Semin Arthritis Rheum. 2017 Oct 31. pii: S0049-0172(17)30564-4. doi: 10.1016/j.semarthrit.2017.10.016.

OBJECTIVE: (i) To determine the association between the presence of comorbidities and severity of pain and physical dysfunction in people with knee and/or hip osteoarthritis; (ii) to explore associations between specific comorbidities (cardiac disease and/or hypertension, diabetes, depression, and back pain) and symptom severity. METHODS: Studies were identified through systematic searches in four electronic databases and grey literature, and,

subsequently, methodologically appraised. Eligible citations entailed cross-sectional or longitudinal studies as well as randomised controlled trials providing data of a direct association between comorbidity presence and the severity of self-reported and/or performance-based symptoms of pain and/or physical functioning, in people with knee and/or hip osteoarthritis. We performed random-effects meta-analysis if at least two citations of low-to-moderate risk of bias were available. The quality of the body of evidence was determined using Cochrane-recommended methods. RESULTS: Of all eligible citations (n = 26), 17 studies were entered in meta-analysis. Moderate quality evidence revealed an association between having ≥1 general comorbidity and worsening of pain (regression coefficient (95% confidence interval (CI)): 0.18 (95% CI: 0.14,0.22)) and/or performance-based physical functioning (0.20 (95% CI: 0.10,0.29)). The presence of cardiac disease and/or hypertension (self-reported: 0.08 (95% CI: 0.01,0.16); performance-based: 0.11 (95% CI: 0.02,0.20)), or back pain (self-reported: 0.12 (95% CI: 0.04,0.20)) predicted deteriorated physical functioning. Co-existing diabetes was associated with worse pain (0.10 (95% CI: 0.02,0.17)). Other findings were non-significant and/or the evidence of poor quality. CONCLUSIONS: Greater comorbidity burden contributes to worse pain and performance-based physical function in people with knee and/or hip osteoarthritis. Suffering comorbid cardiac disease including hypertension, back pain or diabetes may have differential effects on symptom severity.

Impact of moving from a widespread to multisite pain definition on other fibromyalgia symptoms.
Dean LE, Arnold L, Crofford L, Bennett R, Goldenberg D, Fitzcharles MA, Paiva ES, Staud R, Clauw D, Sarzi-Puttini P, Jones GT, Ayorinde A, Flub E, Beasley M, Macrfarlane GJ.
Arthritis Care Res (Hoboken). 2017 Dec;69(12):1878-1886. doi: 10.1002/acr.23214.

OBJECTIVE: To investigate whether associations between pain and the additional symptoms associated with fibromyalgia are different in persons with chronic widespread pain (CWP) compared to multisite pain (MSP), with or without joint areas. METHODS: Six studies were used: 1958 British birth cohort, Epidemiology of Functional Disorders, Kid Low Back Pain, Managing Unexplained Symptoms (Chronic Widespread Pain) in Primary Care: Involving Traditional and Accessible New Approaches, Study of Health and its Management, and Women's Health Study (WHEST; females). MSP was defined as the presence of pain in ≥8 body sites in adults (≥10 sites in children) indicated on 4-view body manikins, conducted first to include joints (positive joints) and second without (negative joints). The relationship between pain and fatigue, sleep disturbance, somatic symptoms, and mood impairment was assessed using logistic regression. Results are presented as odds ratios (ORs) with 95% confidence intervals (95% CIs). RESULTS: There were 34,818 participants across the study populations (adults age range 42-56 years, male 43-51% [excluding WHEST], and CWP prevalence 12-17%). Among those reporting MSP, the proportion reporting CWP ranged between 62% and 76%. Among those reporting the symptoms associated with fibromyalgia, there was an increased likelihood of reporting pain, the magnitude of which was similar regardless of the definition used. For example, within WHEST, reporting moderate/severe fatigue (Chalder fatigue scale 4-11) was associated with a >5-fold increase in likelihood of reporting pain (CWP OR 5.2 [95% CI 3.9-6.9], MSP-positive joints OR 6.5 [95% CI 5.0-8.6], and MSP-negative joints OR 6.5 [95% CI 4.7-9.0]). CONCLUSION: This large-scale study demonstrates that regardless of the pain definition used, the magnitude of association between pain and other associated symptoms of fibromyalgia is similar. This finding supports the continued collection of both when classifying fibromyalgia, but highlights the fact that pain may not require to follow the definition outlined within the 1990 American College of Rheumatology criteria.

Symptoms of central sensitization and comorbidity for juvenile fibromyalgia in childhood migraine: An observational study in a tertiary headache center.
De Tommaso M, Sciruicchio V, Delussi M, Vecchio E, Goffredo M, Simeone M, Barbaro MGF.
J Headache Pain. 2017 Dec;18(1):59. doi: 10.1186/s10194-017-0764-8.

BACKGROUND: Central sensitization is an important epiphenomenon of the adult migraine, clinically expressed by allodynia, pericranial tenderness and comorbidity for fibromyalgia in a relevant number of patients. This study aimed to evaluate the frequency and the clinical characteristics of allodynia, pericranial tenderness, and comorbidity for Juvenile Fibromialgia (JFM) in a cohort of migraine children selected in a tertiary headache center. METHODS: This was an observational cross-sectional study on 8-15 years old migraine patients. Allodynia was assessed by a questionnaire. Pericranial tenderness and comorbidity for JFM as well as their possible association with poor quality of life and migraine related disability, and with other clinical symptoms as anxiety, depression, sleep disorders and pain catastrophizing, were also evaluated. RESULTS: One hundred and fifty one patients were selected, including chronic migraine (n°47), migraine without aura (n° 92) and migraine with aura (n° 12) sufferers. Allodynia was reported in the 96,6% and pericranial tenderness was observed in the 68.8% of patients. Pericranial tenderness was more severe in patients with more frequent migraine and shorter sleep duration. Allodynia seemed associated with anxiety, pain catastrophizing and high disability scores. Comorbidity for JFM was present in the 0.03% of patients. These children presented with a severe depression and a significant reduction of quality of life as compared to the other patients. CONCLUSIONS: This study outlined a relevant presence of symptoms of central sensitization among children with migraine. Severe allodynia and comorbidity for JFM seemed to cause a general decline of quality of life, which would suggest the opportunity of a routine assessment of these clinical features.

Comorbidity of gynecological and non-gynecological diseases with adenomyosis and endometriosis.
Choi EJ, Cho SB, Lee SR, Lim YM, Jeong K, Moon HS, Chung H.
Obstet Gynecol Sci. 2017 Nov;60(6):579-586. doi: 10.5468/ogs.2017.60.6.579.

OBJECTIVE: Adenomyosis and endometriosis are relatively common gynecological diseases that exhibit many common features. This study identified gynecological and non-gynecological diseases that exhibited comorbidity with adenomyosis and endometriosis in Korean women. METHODS: We used Health Insurance Review and Assessment data from 2009 to 2011 and searched for adenomyosis and endometriosis (coded as N80.1 and D25 in International Classification of Disease, 10th revision [ICD-10], respectively). We selected records from patients who had independent disease occurrences in each year, and comorbidities were estimated using Fisher's exact test. We computed each year's similarities and combined 3 years' results using Fisher's *P*-value summation method. RESULTS: A total of 61,516 patients' data were collected during the study period. The prevalence of adenomyosis and endometriosis were similar each year: 12.4% and 9.3% in 2009, 12.5% and 9.4% in 2010 and 13.3% and 9.1% in 2011, respectively. Meta-analysis revealed that 31 ICD-10 codes were significantly related with adenomyosis, and 44 ICD-10 codes were related with endometriosis. Gynecological diseases, such as leiomyoma and benign ovarian tumor, were significantly related to adenomyosis and endometriosis. Non-gynecological diseases, such as anemia and hypercholesterolemia, were also related to adenomyosis and endometriosis. CONCLUSION: We must monitor for the presence of gynecological and non-gynecological diseases with co-morbidities during evaluations and follow-up of patients with adenomyosis or endometriosis.

Changes in healthcare spending after diagnosis of comorbidities among endometriosis patients: A difference-in-differences analysis.
Epstein AJ, Soliman AM, Davis M, Johnson SJ, Snabes MC, Surrey ES.
Adv Ther. 2017 Nov;34(11):2491-2502. doi: 10.1007/s12325-017-0630-8.

INTRODUCTION: We sought to characterize changes in healthcare spending associated with the onset of 22 endometriosis-related comorbidities. METHODS: Women aged 18-49 years with endometriosis (N = 180,278) were extracted from 2006-2015 de-identified Clinformatics® DataMart claims data. For 22 comorbidities, comorbidity patients were identified on the basis of having a first comorbidity diagnosis after their initial endometriosis diagnosis. Controls were identified on the basis of having

no comorbidity diagnosis and were matched 1:1 to comorbidity patients on demographics and baseline spending. Total medical and pharmacy spending was measured during 12 months before and after each patient's index date (first comorbidity diagnosis for comorbidity patients, and equal number of days after earliest endometriosis claim for controls). Pre-post spending differences were compared using difference-in-differences linear regression. Total and comorbidity-related cumulative spending per patient for all endometriosis patients were calculated annually for the 5 years following endometriosis diagnosis. RESULTS: The number of endometriosis patients with each comorbidity varied between 121 for endometrial cancer and 16,177 for fatigue. Healthcare spending increased significantly with the onset of eight comorbidities: breast cancer, ovarian cancer, pregnancy complications, systemic lupus erythematosus/rheumatoid arthritis/Sjogren's/multiple sclerosis, infertility, uterine fibroids, ovarian cyst, and headache [$p<0.001$ except for headache ($p = 0.045$)]. Spending decreased significantly for fatigue, cystitis/UTI, and eczema [$p < 0.001$ except for fatigue ($p = 0.048$)] and was not statistically different for the other 11 comorbidities. Difference-in-differences estimates were significantly higher for comorbidity patients for all comorbidities except eczema ($p \leq 0.003$). Mean 5-year total cumulative spending was $58,191 per endometriosis patient, of which between 11% and 23% was attributable to comorbidity-related medical claims. CONCLUSION: For all but one of the 22 comorbidities associated with endometriosis, comorbidity onset was associated with a relative increase in total healthcare spending.

Occurrence of chronic pelvic pain, abnormal uterine bleeding, and hysterectomy postprocedure among women who have undergone female sterilization procedures: A retrospective claims analysis of commercially insured women in the US.
Carney PI, Yao J, Lin J, Law A.
J Minim Invasive Gynecol. 2017 Nov 2. pii: S1553-4650(17)31265-7. doi: 10.1016/j.jmig.2017.10.029.

STUDY OBJECTIVE: To evaluate the frequency of chronic pelvic pain (CPP), abnormal uterine bleeding (AUB), and hysterectomy after hysteroscopic sterilization (HS) or laparoscopic sterilization (LS) in the United States. DESIGN: Retrospective cohort study (Canadian Task Force classification II-2). SETTING: Commercially insured women. PATIENTS: Women (aged 18-49 years) with claims for HS or LS from January 1, 2010 to December 31, 2012 were identified from the MarketScan Commercial database. Women were required to have 6 months of continuous coverage before (baseline) and 24 months after (follow-up) the procedure date. Women with ≥1 diagnosis for a pain condition (pain in pelvis/lower abdomen, low back pain, chronic headache, fibromyalgia) and/or AUB (excessive/frequent menstruation, irregular menstrual cycle, metorrhagia) during baseline were identified with International Classification of Diseases, Ninth Revision, Clinical Modification codes. INTERVENTIONS: HS/LS. MEASUREMENTS AND MAIN RESULTS: Outcome measurements were proportions of women with CPP, AUB, and hysterectomy during follow-up. Among the study population 10 224 women underwent HS, whereas 8051 underwent LS. During baseline 23.3% and 26.9% of women with HS and LS, respectively, had a pre-existing pain diagnosis. Among both HS and LS study cohorts, greater proportions of women with a pre-existing pain condition versus those without had CPP in the 24 months afterward (HS cohort: 19.8% vs 9.3%, $p<.001$; LS cohort: 23.8% vs 11.4%, $p<.001$). During baseline 11.7% and 6.4% of women with HS and LS, respectively, had pre-existing AUB. Among cohorts, greater proportions of women with pre-existing AUB versus those without had AUB in the 24 months afterward (HS cohort: 21.2% vs 7.3%, $p<.001$; LS cohort: 15.9% vs 6.4%, $p<.001$). Among women who underwent HS and LS, pre-existing pain and AUB were associated with higher rates of hysterectomy post procedure. Multivariable regression results showed similar direction of findings. CONCLUSION: Among women who underwent HS and LS, pre-existing pain conditions and AUB were associated with higher rates of CPP and AUB post procedure, respectively, and both pre-existing conditions were associated with a greater frequency of subsequent hysterectomy.

Comorbidity increases the risk of relapse in multiple sclerosis: A prospective study.

Kowalec K, McKay KA, Patten SB, Fisk JD, Evans C, Tremlett H, Marrie RA; CIHR Team in Epidemiology and Impact of Comorbidity on Multiple Sclerosis (ECoMS).
Neurology. 2017 Dec 12;89(24):2455-2461. doi: 10.1212/WNL.0000000000004716.

OBJECTIVE: To evaluate the association between comorbidity and relapse rate in individuals with multiple sclerosis (MS). METHODS: We recruited individuals with prevalent relapsing-onset MS from 4 Canadian MS Clinics to participate in a 2-year prospective multicenter cohort study involving cross-sectional assessment of comorbidities and relapses. Comorbidities were recorded using questionnaires, and relapses were captured from medical records at each visit. The association between comorbidities at baseline and relapse rate over the subsequent 2-year follow-up period was examined using Poisson regression, adjusting for age, sex, disability, disease duration, and treatment status. RESULTS: Of 885 participants, 678 (76.6%) were women, averaging age 48.2 years at baseline. Anxiety (40.2%), depression (21.1%), hypertension (17.7%), migraine (18.1%), and hyperlipidemia (11.9%) were the most prevalent comorbidities. The frequency of participants experiencing relapses remained constant at 14.9% and 13.2% in years 1 and 2 post-baseline. After adjustment, participants reporting ≥3 baseline comorbidities (relative to none) had a higher relapse rate over the subsequent 2 years (adjusted rate ratio 1.45, 95% confidence interval [CI] 1.00-2.08). Migraine and hyperlipidemia were associated with increased relapse rate (adjusted rate ratio 1.38; 95% CI 1.01-1.89 and 1.67; 95% CI 1.07-2.61, respectively). CONCLUSIONS: Individuals with migraine, hyperlipidemia, or a high comorbidity burden (3 or more conditions) had an increased relapse rate over 2 years. These findings have potential implications for understanding the pathophysiology of MS relapses, and suggest that closer monitoring of individuals with specific or multiple comorbidities may be needed. Future research is needed to understand if the presence of comorbidity warrants a tailored approach to MS management.

Hip symptoms, physical performance, and health status in older adults with chronic low back pain: A preliminary investigation.
Hicks GE, Sions JM, Velasco TO.
Arch Phys Med Rehabil. 2017 Oct 27. pii: S0003-9993(17)31288-1. doi: 10.1016/j.apmr.2017.10.006.

OBJECTIVES: To determine (1) whether there are differences in the prevalence of clinical hip symptoms between older adults with and without chronic low back pain (CLBP); and (2) whether coexisting hip symptoms are associated with worse physical performance and poorer health-related quality of life (HRQOL). DESIGN: Case-control study.
SETTING: Individuals participated in a standardized evaluation in a clinical laboratory.
PARTICIPANTS: Clinical hip symptoms, which are proposed predictors of radiographic hip osteoarthritis according to American College of Rheumatology guidelines, were evaluated in a volunteer sample of community-dwelling older adults with CLBP (n=54; aged 60-85y) and in age- and sex-matched healthy controls (n=54). INTERVENTIONS: Not applicable. MAIN OUTCOME MEASURES: Physical performance was measured by the repeated chair rise test and stair-climbing test. HRQOL was measured by the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36). RESULTS: Hip joint pain, morning stiffness, and pain with hip internal rotation were more common among older adults with CLBP (P<.05). Participants with CLBP and coexisting hip symptoms had worse physical performance than individuals without CLBP or hip symptoms (P<.0001). Additionally, the presence of coexisting hip symptoms was associated with worse HRQOL, particularly in the domains of social functioning, mental health, and role limitations attributable to emotional problems as measured by the SF-36 (P<.01). CONCLUSIONS: Given our limited understanding of CLBP among older adults, there is a definitive need to systematically explore coexisting pain conditions that may contribute to worse outcomes. Based on these data, future longitudinal studies should explore whether coexisting hip symptoms are associated with a worse prognosis in older adults with CLBP.

Screening for adult ADHD in patients with fibromyalgia syndrome.
Van Rensburg R, Meyer HP, Hitchcock SA, Schuler CE.

Pain Med. 2017 Nov 1. doi: 10.1093/pm/pnx275.

OBJECTIVE: Fibromyalgia syndrome (FMS) is a common chronic pain disorder associated with altered activity of neurotransmitters involved in pain sensitivity such as dopamine, serotonin, and noradrenaline. FMS may significantly impact an individual's functioning due to the presence of chronic pain, fatigue, and cognitive impairment. Dyscognition may be more disabling than the chronic pain but is mostly under-recognized. This study aimed to assess the potential co-occurrence of FMS and adult attention deficit hyperactivity disorder (ADHD), a chronic neurodevelopmental disorder also associated with impaired cognition and dopaminergic function. METHODS: In a cross-sectional observational study, 123 previously confirmed FMS patients were screened for adult ADHD using the World Health Organization Adult ADHD Self Report scale v1.1. The Revised Fibromyalgia Impact Questionnaire (FIQ-R) was used to assess the impact of FMS. Cognitive assessment was based on self-report in accordance with the 2011 modified American College of Rheumatology criteria and the FIQ-R, respectively. RESULTS: Of the 123 participants, 44.72% (n=55) screened positive for adult ADHD. Participants with both FMS and a positive adult ADHD screening test scored higher on the FIQ-R score (64.74, SD=17.66, vs 54.10, SD=17.10). Self-reported cognitive impairment was rated higher in the combined group (odds ratio = 10.61, 95% confidence interval; 3.77-29.86, p<0.01). CONCLUSIONS: These results indicate that the co-occurrence of adult ADHD in FMS may be highly prevalent and may also significantly impact the morbidity of FMS. Patients with FMS should be assessed for the presence of adult ADHD.

Comorbidity in allergic asthma and allergic rhinitis: Functional somatic syndromes.
Tsiakiris G, Neely G, Lind N, Nordin S.
Psychol Health Med. 2017 Dec;22(10):1163-1168. doi: 10.1080/13548506.2016.1276606.

Based on the concept of central sensitisation, the present study tested the hypothesis of comorbidity in allergic asthma and allergic rhinitis with diagnoses of functional somatic syndromes (FSSs), including fibromyalgia, irritable bowel syndrome and migraine. Data were used from the population-based Västerbotten Environmental Health Study (n = 3406). The participants consisted of 164 individuals with allergic asthma and 298 individuals with allergic rhinitis as well as 2876 individuals without allergic or non-allergic asthma, allergic rhinitis or atopic dermatitis. Diagnoses were based on self-reports of having been diagnosed by a physician. Odds ratios (ORs) were calculated from binary logistic regression analysis, both crude and adjusted for age and education. The adjusted ORs (1.87-4.00) for all FSSs differed significantly from unity for both allergic asthma and rhinitis. The results provide support for the hypothesis of comorbidity in allergic asthma and rhinitis with FSSs. Since central sensitisation is likely to underlie FSSs, the present findings raises the question as to whether central sensitisation may also be involved in allergic asthma and rhinitis.

Previous mental disorders and subsequent onset of chronic back or neck pain: Findings from 19 countries.
Viana MC, Lim CCW, Garcia Pereira F, Aguilar-Gaxiola S, Alonso J, Bruffaerts R, de Jonge P, Calds-de-Almeida JM, O'Neill S, Stein DJ, Al-Hamzawi A, Benjet C, Cardoso G, Florescu S, de Girolamo G, Haro JM, Hu C, Kovess-Masfety V, Levinson D, Piazza M, Posada-Villa J, Rabczendo D, Kessler RC, Scott KM.
J Pain. 2018 Jan;19(1):99-110. doi: 10.1016/j.jpain.2017.08.011.

Associations between depression/anxiety and pain are well established, but its directionality is not clear. We examined the associations between temporally previous mental disorders and subsequent self-reported chronic back/neck pain onset, and investigated the variation in the strength of associations according to timing of events during the life course, and according to gender. Data were from population-based household surveys conducted in 19 countries (n=52,095). Lifetime prevalence and age of onset of 16 mental disorders according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, and the occurrence and age of onset of back/neck pain were assessed using the Composite International Diagnostic Interview. Survival analyses estimated the

associations between first onset of mental disorders and subsequent back/neck pain onset. All mental disorders were positively associated with back/neck pain in bivariate analyses; most (12 of 16) remained so after adjusting for psychiatric comorbidity, with a clear dose-response relationship between number of mental disorders and subsequent pain. Early-onset disorders were stronger predictors of pain; when adjusting for psychiatric comorbidity, this remained the case for depression/dysthymia. No gender differences were observed. In conclusion, individuals with mental disorder, beyond depression and anxiety, are at higher risk of developing subsequent back/neck pain, stressing the importance of early detection of mental disorders, and highlight the need of assessing back/neck pain in mental health clinical settings. PERSPECTIVE: Previous mental disorders according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition are positively associated with subsequent back/neck pain onset, with a clear dose-response relationship between number of mental disorders and subsequent pain. Earlier-onset mental disorders are stronger predictors of subsequent pain onset, compared with later-onset disorders.

How are socio-demographic and psycho-social factors associated with the prevalence and chronicity of severe pain in 14 different body sites? A cross-sectional population-based survey.

Dorner TE, Stein KV, Hahne J, Wepner F, Friedrich M, Mittendorder-Rutz E.
Wien Klin Wochesnschr. 2018 Jan;130(1-2):14-22. doi: 10.1007/s00508-017-1223-x.

BACKGROUND: Severe pain and chronic pain have a high impact on individuals and society. Body location of pain is important with regard to perception, articulation, and underlying biological, mental or social causes of pain. METHODS: A cross-sectional survey was performed in the general Austrian population with 15,474 personally interviewed subjects aged 15 years and older. RESULTS: The 1-year period prevalence of severe pain in any body site was 38.6% and of chronic pain 24.9%. In all, 8.1% had pain in at least three body sites. Subjects aged 65 years and older (52.2%), those with low education (43.4%), unemployed subjects (50.4%), retired subjects (52.4%), those with anxiety/depression (67.7%), and subjects with lack of social support (49.6%) were sub-populations with high pain prevalence. In multivariate analyses, depression/anxiety was associated with prevalence and chronicity of severe pain in all body sites (range of ORs 1.89-5.01), while such associations were found for lack of social support (range of ORs 1.33-1.65), female sex (range of ORs 1.38-2.34), higher age (range of ORs 1.09-1.18 for 5 year intervals), as well as low educational (range of ORs 1.47-2.06 primary vs. tertiary education) and unemployment status (range of ORs 1.50-2.62) in most body sites. Being born in non-EU or EFTA states was associated with pain in many body sites (range of ORs 1.38-2.10). CONCLUSIONS: Psychosocial factors are associated with pain presence in similar ways irrespective of location. Regarding socio-demographic factors, differences towards the magnitude and the direction in the association with pain frequency and chronicity in different body sites emerged.

CLINICAL STUDIES

AAPT diagnostic criteria for chronic abdominal, pelvic, and urogenital pain: Irritable bowel syndrome.

Zhou Q, Wesselmann U, Walker L, Lee L. Zeltzer L, Verne GN.
J Pain. 2017 Oct 24. pii: S1526-5900(17)30737-X. doi: 10.1016/j.jpain.2017.10.002.

In conjunction with the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks public-private partnership with the U.S. Food and Drug Administration and the American Pain Society, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks-American Pain Society Pain Taxonomy (AAPT) initiative strove to develop the characteristics of a diagnostic system useful for clinical and research purposes across disciplines and types of chronic pain conditions. After the establishment of these characteristics, a working group of clinicians and

clinical and basic scientists with expertise in abdominal, pelvic, and urogenital pain began generating core diagnostic criteria and defining the related extraintestinal somatic pain and other symptoms experienced by patients. Systematic diagnostic criteria for several common abdominal, pelvic, and urogenital pain conditions are in development. In this report, we present the proposed AAPT criteria for irritable bowel syndrome (IBS), the most common chronic, noncancer abdominal pain condition. A systematic review and synthesis was conducted to complement the Rome IV Diagnostic Criteria for IBS. Future efforts will subject these proposed AAPT criteria to systematic empirical evaluation of their feasibility, reliability, and validity. The AAPT IBS criteria are part of an evidence-based classification system that provides a consistent vocabulary regarding diagnostic criteria, common features, comorbidities, consequences, and putative mechanisms of the disorder. A similar approach is being applied to other chronic and often debilitating abdominal, pelvic, and urogenital pain conditions. PERSPECTIVE: The AAPT's goal is to develop an evidence-based taxonomy for chronic pain on the basis of a consistently applied multidimensional framework, and encourage experts to apply this taxonomy to specific chronic pain conditions. In this report, the taxonomy is applied to IBS, a chronic abdominal pain condition.

Assessment and manifestation of central sensitisation across different chronic pain conditions.
Arendt-Nielsen L, Morlion B, Perrot S, Dahan A, Dickenson A, Kress HG, Wells C, Bouhassira D, Mohr Drewes A.
Eur J Pain. 2018 Feb;22(2):216-241. doi: 10.1002/ejp.1140.

Different neuroplastic processes can occur along the nociceptive pathways and may be important in the transition from acute to chronic pain and for diagnosis and development of optimal management strategies. The neuroplastic processes may result in gain (sensitisation) or loss (desensitisation) of function in relation to the incoming nociceptive signals. Such processes play important roles in chronic pain, and although the clinical manifestations differ across condition processes, they share some common mechanistic features. The fundamental understanding and quantitative assessment of particularly some of the central sensitisation mechanisms can be translated from preclinical studies into the clinic. The clinical perspectives are implementation of such novel information into diagnostics, mechanistic phenotyping, prevention, personalised treatment, and drug development. The aims of this paper are to introduce and discuss (1) some common fundamental central pain mechanisms, (2) how they may translate into the clinical signs and symptoms across different chronic pain conditions, (3) how to evaluate gain and loss of function using quantitative pain assessment tools, and (4) the implications for optimising prevention and management of pain. The chronic pain conditions selected for the paper are neuropathic pain in general, musculoskeletal pain (chronic low back pain and osteoarthritic pain in particular), and visceral pain (irritable bowel syndrome in particular). The translational mechanisms addressed are local and widespread sensitisation, central summation, and descending pain modulation. SIGNIFICANCE: Central sensitisation is an important manifestation involved in many different chronic pain conditions. Central sensitisation can be different to assess and evaluate as the manifestations vary from pain condition to pain condition. Understanding central sensitisation may promote better profiling and diagnosis of pain patients and development of new regimes for mechanism based therapy. Some of the mechanisms underlying central sensitisation can be translated from animals to humans providing new options in development of therapies and profiling drugs under development.

A systematic review of atypical antipsychotics in chronic pain management: Olanzapine demonstrates potential in central sensitization, fibromyalgia, and headache/migraine.
Jimenez XF, Sundararajan T, Covington EC.
Clin J Pain. 2017 Oct 26. doi: 10.1097/AJP.0000000000000567.

INTRODUCTION: Many psychopharmacologic agents are used as primary or adjunct agents in pain management. Atypical antipsychotics (AAs) have also been used as adjuncts in pain

management regimens in a variety of manners; however, their efficacy in this capacity is unclear. METHODS: A systematic review of all studies examining AA use for pain was conducted. Three literature databases were utilized to search for word combinations of "pain" and a variety of commonly-prescribed AAs (olanzapine, quetiapine, risperidone, aripiprazole, ziprasidone, clozapine, paliperidone, iloperidone, lurasidone). Articles chosen for review included retrospective analyses, randomized control trials, and case series/reports. A PRISMA diagram illustrates the study selection process. RESULTS: Olanzapine, quetiapine, risperidone, aripiprazole, and ziprasidone are the only AAs with published studies in pain syndromes. Of these, olanzapine and quetiapine have the most combined studies (11 and 6, respectively). Olanzapine shows preliminary and consistent efficacy in fibromyalgia and headache/migraine, although only one study was a randomized controlled trial with Level I evidence of efficacy. Other AAs (quetiapine included) fail to demonstrate efficacy in pain syndromes and/or lack robust study designs. CONCLUSIONS: Few studies have been conducted to evaluate the analgesic effects of AAs. The collective findings of multiple studies evaluating olanzapine in pain syndromes suggest a high yet preliminary level of evidence of efficacy, warranting prospective studies in various pain syndrome contexts. Pharmacological mechanisms of AA action are elaborated, and the findings of this review are discussed. Risk and benefits of using AAs in chronic pain are elaborated, and investigational implications and future directions are explored.

Clinical characteristics of fibromyalgia in a chronic pain population.
Gostine M, Davis F, Roberts BA, Risko R, Asmus M, Cappelleri JC, Sadosky A.
Pain Pract. 2018 Jan;18(1):67-78. doi: 10.1111/papr.12583.

OBJECTIVE: To compare fibromyalgia (FM) characteristics among patients identified in a community-based chronic pain cohort based on traditional International Classification of Diagnoses 9th revision (ICD-9) diagnostic coding, with that of patients identified using a novel predictive model. METHODS: This retrospective study used data collected from July 1999 to February 17, 2015, in multiple chronic pain clinics in the United States. Patients were assigned to the FM case group based on specific inclusion criteria using ICD-9 codes or, separately, from results of a novel FM predictive model that was developed using random forest and logistic regression techniques. Propensity scoring (1:1) matched FM patients (cases) to nonmalignant chronic pain patients without FM (controls). Patient-reported measures (e.g., pain, fatigue, quality of sleep) and clinical characteristics (i.e., comorbidities, procedures, and regions of pain) were outcomes for analysis. RESULTS: Nine ICD-9 clinical modification diagnoses had odds ratios with large effect sizes (Cohen's $d > 0.8$), demonstrating the magnitude of the difference between the FM and matched non-FM cohorts: chronic pain syndrome, latex allergy, muscle spasm, fasciitis, cervicalgia, thoracic pain, shoulder pain, arthritis, and cervical disorders (all $P < 0.0001$). Six diagnoses were found to have a moderate effect size (Cohen's $0.5 < d > 0.8$): cystitis, cervical degeneration, anxiety, joint pain, lumbago, and cervical radiculitis. CONCLUSIONS: The identification of multiple comorbidities, diagnoses, and musculoskeletal procedures that were significantly associated with FM may facilitate differentiation of FM patients from other conditions characterized by chronic widespread pain. Predictive modeling may enhance identification of FM patients who may otherwise go undiagnosed.

Clinical course and prognostic factors across different musculoskeletal pain sites: A secondary analysis of individual patient data from randomized clinical trials.
Green DJ, Lewis M, Manswell G, Artus M, Dziedzic KS, Hay EM, Foster NE, van der Windt DA.
Eur J Pain. 2018 Jan 22. doi: 10.1002/ejp.1190.

BACKGROUND: Previous research has identified similar prognostic factors in patients with musculoskeletal (MSK) conditions regardless of pain presentation, generating opportunities for management based on prognosis rather than specific pain presentation. METHODS: Data from seven RCTs (2,483 participants) evaluating a range of primary care interventions for different MSK pain conditions were used to investigate the course of symptoms and explore similarities and differences in predictors of outcome. The value of pain site for predicting

changes in pain and function was investigated and compared with that of age, gender, social class, pain duration, widespread pain, and level of anxiety/depression. RESULTS: Over the initial three months of follow-up, changes in mean pain intensity reflected an improvement, with little change occurring after this period. Participants with knee pain due to osteoarthritis (OA) showed poorer long-term outcome (mean difference in pain reduction at 12 months -1.85, 95% CI -2.12 to -1.57, compared to low back pain). Increasing age, manual work, longer pain duration, widespread pain, and increasing anxiety/depression scores were significantly associated with poorer outcome regardless of pain site. Testing of interactions showed some variation between pain sites, particularly for knee OA, where age, manual work and pain duration were most strongly associated with outcome. CONCLUSIONS: Despite some differences in prognostic factors for trial participants with knee OA who were older and had more chronic conditions, similarity of outcome predictors across regional MSK pain sites provides evidence to support targeting of treatment based on prognostic factors rather than site of pain.

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 Dec;37(12):2035-2042. 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 role of cannabinoids in pain control: the good, the bad, and the ugly.
Pergolizzi JV Jr, Lequang JA, Taylor R Jr, Raffa RB, Colucci D; NEMA Research Group.
Minerva Anestesiol. 2018 Jan 16. doi: 10.23736/S0375-9393.18.12287-5.

Cannabinoids appear to possess many potential medical uses, which may extend to pain control. A narrative review of the literature has found a variety of studies testing botanical and synthetic cannabinoids in different pain syndromes (acute pain, cancer pain, chronic noncancer pain, fibromyalgia pain, migraine, neuropathic pain, visceral pain, and others). Results from these studies are mixed; cannabinoids appear to be most effective in controlling neuropathic pain, allodynia, medication-rebound headache, and chronic noncancer pain, but do not seem to offer any advantage over nonopioid analgesics for acute pain. Cannabinoids seem to work no better than placebo for visceral pain and conferred only modest analgesic effect in cancer pain. Cannabinoids do many good things-they appear to be effective in treating certain types of pain without the issues of tolerance associated with opioids. Negatively, marijuana currently has a very murky legal status all over the world-laws regulating its use are inconsistent and in flux. Thus, both patients and prescribers may be unsure about whether or not it is an appropriate

form of pain control. Cannabinoid-based analgesia has been linked to potential memory deficits and cognitive impairment. A great deal more remains to be elucidated about cannabinoids which may emerge to play an important role in the treatment of neuropathic and possibly other painful conditions. There remains a great deal more to learn about the role of cannabinoids in pain management.

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.