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LEADERSHIP 301

Adults Living with IC/BPS May Qualify

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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 October 2016 and January 2017. Past 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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About the Chronic Pain Research Alliance

FEATURED EDITORIAL

Individual differences in pain: Understanding the mosaic that makes pain personal.
Fillingim RB.
Pain. 2016 Nov 24. [Epub ahead of print]

The experience of pain is characterized by tremendous inter-individual variability. Multiple biological and psychosocial variables contribute to these individual differences in pain, including demographic variables, genetic factors, and psychosocial processes. For

example, sex, age and ethnic group differences in the prevalence of chronic pain conditions have been widely reported. Moreover, these demographic factors have been associated with responses to experimentally-induced pain. Similarly, both genetic and psychosocial factors contribute to clinical and experimental pain responses. Importantly, these different biopsychosocial influences interact with each other in complex ways to sculpt the experience of pain. Some genetic associations with pain have been found to vary across sex and ethnic group. Moreover, genetic factors also interact with psychosocial factors, including stress and pain catastrophizing, to influence pain. The individual and combined influences of these biological and psychosocial variables results in a unique mosaic of factors that contributes pain in each individual. Understanding these mosaics is critically important in order to provide optimal pain treatment, and future research to further elucidate the nature of these biopsychosocial interactions is needed in order to provide more informed and personalized pain care.

NATIONAL MULTICENTER STUDIES

Temporal change in headache and its contribution to the risk of developing first-onset temporomandibular disorder in the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study.
Tchivileva IE, Ohrbach R, Fillingim RB, Greenspan JD, Maixner W, Slade GD.
Pain. 2017 Jan;158(1):120-129.

While cross-sectional studies have demonstrated an association between headache and temporomandibular disorder (TMD), whether headache can predict the onset of TMD is unknown. The aims of this study were to evaluate the contribution of headache to the risk of developing TMD and describe patterns of change in headache types over time. An initially TMD-free cohort of 2410 persons with low frequency of headache completed quarterly questionnaires assessing TMD and headache symptoms over a median 3.0-year follow-up period. First-onset TMD was confirmed by clinical examination in 199 participants. Baseline reports of migraine (hazard ratio [HR] = 1.67, 95% confidence interval [CI]: 1.06-2.62) or mixed headache types (HR = 4.11, 95% CI: 1.47-11.46), or headache frequency (HR = 2.13, 95% CI: 1.31-3.48) predicted increased risk of developing TMD. In addition, headache dynamics across the follow-up period before the TMD onset were evaluated in a nested case-control study where 248 incident TMD cases were matched to 191 TMD-free controls. Both headache prevalence and frequency increased across the observation period among those who developed TMD but not among controls. Patients with TMD were more likely to experience worsening in the headachetype compared with that by controls, eg, prevalence of definite migraine among TMD cases increased 10-fold. Among all headache types experienced by patients with TMD before the TMD onset, migraine had the highest odds of progression relative to remission (odds ratio = 2.8, 95% CI: 1.6-4.8), whereas for controls this ratio was significant only for the tension-type headache (odds ratio = 2.1, 95% CI: 1.2-3.9). The important clinical implication of these findings is that adequate treatment of migraine may reduce the risk for developing TMD.

Brain white matter changes associated with urological chronic pelvic pain syndrome: multisite neuroimaging from a MAPP case-control study.
Huang L, Kutch JJ, Ellingson BM, Martucci KT, Harris RE, Clauw DJ, Mackey S, Mayer EA, Schaeffer AJ, Apkarian AV, Farmer MA.
Pain. 2016 Dec;157(12):2782-2791.

Clinical phenotyping of urological chronic pelvic pain syndromes (UCPPSs) in men and women have focused on end organ abnormalities to identify putative clinical subtypes. Initial evidence of abnormal brain function and structure in male pelvic pain has necessitated large-scale, multisite investigations into potential UCPPS brain biomarkers. We present the

first evidence of regional white matter (axonal) abnormalities in men and women with UCPPS, compared with positive (irritable bowel syndrome, IBS) and healthy controls. Epidemiological and neuroimaging data were collected from participants with UCPPS (n = 52), IBS (n = 39), and healthy sex- and age-matched controls (n = 61). White matter microstructure, measured as fractional anisotropy (FA), was examined by diffusion tensor imaging. Group differences in regional FA positively correlated with pain severity, including segments of the right corticospinal tract and right anterior thalamic radiation. Increased corticospinal FA was specific and sensitive to UCPPS, positively correlated with pain severity, and reflected sensory (not affective) features of pain. Reduced anterior thalamic radiation FA distinguished patients with IBS from those with UCPPS and controls, suggesting greater microstructural divergence from normal tract organization. Findings confirm that regional white matter abnormalities characterize UCPPS and can distinguish between visceral diagnoses, suggesting that regional axonal microstructure is either altered with ongoing pain or predisposes its development.

PATHOPHYSIOLOGY STUDIES

Gut microbiota, bacterial translocation, and interactions with diet: Pathophysiological links between major depressive disorder and non-communicable medical comorbidities.
Slyepchenko A, Maes M, Jacka FN, Köhler CA, Barichello T, McIntyre RS, Berk M, Grande I, Foster JA, Vieta E, Carvalho AF.
Psychother Psychosom. 2017;86(1):31-46.

BACKGROUND: Persistent low-grade immune-inflammatory processes, oxidative and nitrosative stress (O&NS), and hypothalamic-pituitary-adrenal axis activation are integral to the pathophysiology of major depressive disorder (MDD). The microbiome, intestinal compositional changes, and resultant bacterial translocation add a new element to the bidirectional interactions of the gut-brain axis; new evidence implicates these pathways in the patho-aetiology of MDD. In addition, abnormalities in the gut-brain axis are associated with several chronic non-communicable disorders, which frequently co-occur in individuals with MDD, including but not limited to irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS), obesity, and type 2 diabetes mellitus (T2DM). METHODS: We searched the PubMed/MEDLINE database up until May 1, 2016 for studies which investigated intestinal dysbiosis and bacterial translocation (the 'leaky gut') in the pathophysiology of MDD and co-occurring somatic comorbidities with an emphasis on IBS, CFS, obesity, and T2DM. RESULTS: The composition of the gut microbiota is influenced by several genetic and environmental factors (e.g. diet). Several lines of evidence indicate that gut-microbiota-diet interactions play a significant pathophysiological role in MDD and related medical comorbidities. Gut dysbiosis and the leaky gut may influence several pathways implicated in the biology of MDD, including but not limited to immune activation, O&NS, and neuroplasticity cascades. However, methodological inconsistencies and limitations limit comparisons across studies. CONCLUSIONS: Intestinal dysbiosis and the leaky gut may constitute a key pathophysiological link between MDD and its medical comorbidities. This emerging literature opens relevant preventative and therapeutic perspectives.

Are epigenetic factors implicated in chronic widespread pain?
Burri A, Marinova Z, Robinson MD, Kuhnel B, Waldenberger M, Wahl S, Kunze S, Gieger C, Livshits G, Williams F.
PLoS One. 2016 Nov 10;11(11):e0165548. doi: 10.1371/journal.pone.0165548.

Background: Chronic widespread musculoskeletal pain (CWP) is the cardinal symptom of fibromyalgia and affects about 12% of the general population. Familial aggregation of CWP has been repeatedly demonstrated with estimated heritabilities of around 50%, indicating a genetic susceptibility. The objective of the study was to explore genome-wide disease-differentially methylated positions (DMPs) for chronic widespread pain (CWP) in a sample of

unrelated individuals and a subsample of discordant monozygotic (MZ) twins. Methodology/Principle Findings: A total of N = 281 twin individuals from the Twins UK registry, including N = 33 MZ twins discordant for self-reported CWP, were part of the discovery sample. The replication sample included 729 men and 756 women from a subsample of the KORA S4 survey-an independent population-based cohort from Southern Germany. Epigenome-wide analysis of DNA methylation was conducted using the Illumina Infinium HumanMethylation 450 DNA BeadChip in both the discovery and replication sample. Of our 40 main loci that were carried forward for replication, three CPGs reached significant p-values in the replication sample, including malate dehydrogenase 2 (*MDH2*; p-value 0.017), tetranectin (*CLEC3B*; p-value 0.039), and heat shock protein beta-6 (*HSPB6*; p-value 0.016). The associations between the collagen type I, alpha 2 chain (*COL1A2*) and monoamine oxidase B (*MAOB)* observed in the discovery sample-both of which have been previously reported to be biological candidates for pain-could not be replicated. Conclusion/Significance: Our results may serve as a starting point to encourage further investigation in large and independent population-based cohorts of DNA methylation and other epigenetic changes as possible disease mechanisms in CWP. Ultimately, understanding the key mechanisms underlying CWP may lead to new treatments and inform clinical practice.

Sex-based differences in brain alterations across chronic pain conditions.
Gupta A, Mayer EA, Fling C, Labus JS, Naliboff BD, Hong JY, Kilpatrick LA.
J Neurosci Res. 2017 Jan 2;95(1-2):604-616. doi: 10.1002/jnr.23856.

Common brain mechanisms are thought to play a significant role across a multitude of chronic pain syndromes. In addition, there is strong evidence for the existence of sex differences in the prevalence of chronic pain and in the neurobiology of pain. Thus, it is important to consider sex when developing general principals of pain neurobiology. The goal of the current Mini-Review is to evaluate what is known about sex-specific brain alterations across multiple chronic pain populations. A total of 15 sex difference and 143 single-sex articles were identified from among 412 chronic pain neuroimaging articles. Results from sex difference studies indicate more prominent primary sensorimotor structural and functional alterations in female chronic pain patients compared with male chronic pain patients: differences in the nature and degree of insula alterations, with greater insula reactivity in male patients; differences in the degree of anterior cingulate structural alterations; and differences in emotional-arousal reactivity. Qualitative comparisons of male-specific and female-specific studies appear to be consistent with the results from sex difference studies. Given these differences, mixed-sex studies of chronic pain risk creating biased data or missing important information and single-sex studies have limited generalizability. The advent of large-scale neuroimaging databases will likely aid in building a more comprehensive understanding of sex differences and commonalities in brain mechanisms underlying chronic pain.

Sex differences in neuroimmunity and pain.
Rosen S, Ham B, Mogil JS.
J Neurosci Res. 2017 Jan 2;95(1-2):500-508. doi: 10.1002/jnr.23831.

Differences in the prevalence of chronic pain in women vs. men are well known, and decades of laboratory experimentation have demonstrated that women are more sensitive to pain than are men. Attention has thus shifted to investigating mechanisms underlying such differences. Recent evidence suggests that neuroimmune modulation of pain may represent an important cause of sex differences. The current review examines the evidence for gonadal hormone modulation of the immune system, immune system modulation of pain, and interactions that might help to explain sex differences in pain.

Anatomical and functional correlates of persistent pain in Parkinson's disease.
Polli A, Weis L, Biundo R, Thacker M, Turolla A, Koutsikos K, Chaudhuri KR, Antonini A.
Mov Disord. 2016 Dec;31(12):1854-1864. doi: 10.1002/mds.26826.

BACKGROUND: The pathophysiology of pain in Parkinson's disease (PD) is still poorly understood, although it is conceivable that supraspinal mechanisms may be responsible for pain generation and maintenance. METHODS: We examined brain functional and anatomical changes associated with persistent pain in 40 PD patients, 20 with persistent pain and 20 without pain. We also examined 15 pain-free healthy participants of similar age, gender, and cognitive state as a control group. We assessed pain by the King's Parkinson's Pain Scale, the Visual Analogue Scale for pain, and the Leeds Assessment for Neuropathic Symptoms and Sign. All patients underwent structural, diffusion tensor imaging, and resting-state functional MRI. We compared clinical characteristics, whole-brain cortical thickness, subcortical volumes, diffusion tensor imaging scalar measures, and functional connectivity by network based statistics.
RESULTS: The group with PD and persistent pain showed significant thinning in the bilateral temporal pole, left-medial orbitofrontal cortex, bilateral superior and left-inferior parietal areas, pars orbicularis, and right superior frontal, posterior cingulated, and precentral cortex. There were no significant subcortical volume and white matter differences between PD subgroups. Functional MRI showed a decrease of brain activity in the left frontal inferior orbital in PD patients with persistent pain, with greater activity bilaterally in the cerebellum and in the right inferior temporal areas. Only PD patients with persistent pain showed an accumbens-hippocampus disconnection without white matter and subcortical alterations.
CONCLUSIONS: We showed that persistent pain in PD is associated with supraspinal structural and functional changes. We also highlighted the contribution of frontal, prefrontal, and insular areas in nociceptive modulation and accumbens-hippocampus disconnection.

EPIDEMIOLOGY STUDIES

Increased risk of a suicide event in patients with primary fibromyalgia and in fibromyalgia patients with concomitant comorbidities: A nationwide population-based cohort study.
Lan CC, Tseng CH, Chen JH, Lan JL, Wang YC, Tsay GJ, Hsu CY.
Medicine (Baltimore). 2016 Nov;95(44):e5187.

An increased risk of suicide ideation and death has been reported in patients with fibromyalgia. This study aimed to evaluate the risk of a suicide event in patients with primary fibromyalgia and in fibromyalgia patients with comorbidities. We used the Longitudinal Health Insurance Database, a subset of the national insurance claim dataset, which enrolled 1 million Taiwanese people from 2000 to 2005, to identify 95,150 patients with incident fibromyalgia (ICD-9-CM 729.0-729.1) and 190,299 reference subjects matched by sex, age, and index date of diagnosis. The risk of a suicide event (ICD-9-CM, External-Cause Codes 950-959) was analyzed with a Cox proportional hazards model. Stratification analysis was performed by separating fibromyalgia patients and reference subjects with respect to each comorbidity to determine the risk of suicide in fibromyalgia patients with or without comorbidity relative to subjects who had neither fibromyalgia nor comorbidity. In this Taiwanese dataset, there were 347 suicide events in patients with fibromyalgia (4.16 per 10 person-years) and 424 in matched reference subjects (2.63 per 10 person-years) with a significant crude hazard ratio (HR) of 1.58 (95% confidence interval [CI] 1.38-1.83) and an adjusted HR of 1.38 (95% CI 1.17-1.71) for fibromyalgia patients relative to the matched reference subjects. According to the 2 by 2 stratification analysis, we found that fibromyalgia patients without comorbidity had an independent but mild risk of a suicide event with adjusted HRs ranging from 1.33 to 1.69 relative to subjects with neither fibromyalgia nor comorbidity. Meanwhile, fibromyalgia patients with comorbidity led to a markedly enhanced risk of a suicide event relative to the matched reference subjects, with adjusted HRs ranging from 1.51 to 8.23. Our analysis confirmed a mild-to-moderate risk of a suicide event in patients with primary fibromyalgia. Attention should be paid to the

prevention of suicide in fibromyalgia patients with concomitant comorbidities.

Are persons with fibromyalgia or other musculoskeletal pain more likely to report hearing loss? A HUNT study.
Stranden M, Solvin H, Fors EA, Getz L, Helvik A.
BMC Musculoskelet Disord. 2016 Nov 16;17(1):477.

Background: Leading theories about the pathogenesis of fibromyalgia focus on central nervous dysregulation or sensitization, which can cause altered perception. There is growing evidence that fibromyalgia involves altered perception not only of pain, but also other sensory stimuli. On this basis, we investigated whether individuals with fibromyalgia are more likely to report subjective loss of hearing, adjusted for audiometrically measured loss of hearing, compared to persons without any musculoskeletal pain disorders. In addition, we studied persons with other musculoskeletal pain than fibromyalgia and persons who did not have any musculoskeletal pain. Methods: The study includes 44,494 persons from the second health survey in Nord-Trøndelag (HUNT2) who had undergone audiometry and answered a comprehensive questionnaire that mapped fibromyalgia, musculoskeletal pain at various sites and subjective hearing loss. Respondents with other musculoskeletal pain problems than fibromyalgia were divided into two groups with respectively localized and widespread musculoskeletal pain. Data were analyzed with logistic regression models adjusting for age, education, anxiety, depression and hearing thresholds. Results: In adjusted analysis, individuals with fibromyalgia had increased likelihood to report subjective hearing loss, compared to persons without fibromyalgia or other musculoskeletal pain (OR 4.578, 95% CI 3.622-5.787 and OR 4.523, 95% CI 3.077-6.647 in women and men). Furthermore, people with local and widespread musculoskeletal pain not diagnosed with fibromyalgia, also had increased likelihood to report subjective hearing loss, compared to people with no musculoskeletal pain. This relationship was greater for widespread pain than for localized pain (OR 1.915, 95% CI 1.627-2.255, and 1.796, 95% CI 1.590-2.029, in women and men with local musculoskeletal pain, and OR 3.073, 95% CI 2.668-3.539, OR 3.618, 95% CI 3.225-4.058, in women and men with widespread pain, respectively). Conclusions: Our findings are consistent with the hypothesis that fibromyalgia is related to a general dysregulation of the central nervous system. The same might also be the case for other local and, in particular, other widespread, musculoskeletal pain.

Comorbidity in allergic asthma and allergic rhinitis: functional somatic syndromes.
Tsiakiris G, Neely G, Lind N, Nordin S.
Psychol Health Med. 2016 Dec 30:1-6. [Epub ahead of print]

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.

Association between temporomandibular disorders and pain in other regions of the body.
Bonato LL, Quinelato V, De Felipe Cordeiro PC, De Sousa EB, Tesch R, Casado PL.

J Oral Rehabil. 2017 Jan;44(1):9-15. doi: 10.1111/joor.12457.

The pain from temporomandibular disorder (TMD) is often associated with physical symptoms of other chronic pain disorders and comorbidities, such as generalised muscle and joint pain. However, this association is not widely studied. To evaluate the prevalence of comorbid pain in joints, specifically in the knees, hips, ankles, shoulders, wrists and elbows, in individuals with and without TMD. We evaluated 337 patients from a public hospital in the city of Rio de Janeiro, Brazil. The Research Diagnostic Criteria for TMD questionnaire were used for the diagnosis of TMD. To assess the presence of other joint pain, the patients were asked to answer questions considering: the presence of pain in the knee, hip, ankle, shoulder, wrist and elbow joints and time duration of pain. Individuals with TMD are 5·5 times more likely to present with other joint pain compared with those without the disorder. TMD muscle disorders were most associated with a higher number of pain at the other locations. There was a significant association between the presence of pain at the other locations, muscle ($P < 0{\cdot}001$) and joint disorders ($P = <0{\cdot}001$), as well as age advance, in TMD participants, showed to be a covariate factor for pain at the other locations. Individuals with TMD showed a high prevalence of pain in other joints of the body when compared with individuals without the disorder, and knee pain was the most prevalent pain complaint.

The association between symptomatic and diagnostic depression and pain among the elderly population in South Korea.
Lee W, Hong K, Lim SS, Kim DH, Yoon JH.
J Nerv Ment Dis. 2017 Jan 14. doi: 10.1097/NMD.0000000000000633. [Epub ahead of print]

The exact nature of pain (amount or severity) associated with depression in the elderly population has not been studied extensively yet. We investigated the association between the characteristics of pain and both symptomatic and diagnostic depression using data from the 2012 Korean Longitudinal Study of Aging (2164 men, 2066 women). Symptomatic depression was identified as a score of 12 or higher on the 10-item Center for Epidemiologic Studies-Depression Scale. Odds ratios with a 95% confidence interval was calculated for depression using multiple logistic regression models after adjusting for age, sex, socioeconomic status, health behavioral factors, and chronic diseases. The fully adjusted odds ratio (95% confidence interval) for symptomatic/diagnostic depression were "1" = 2.09 (1.62-2.49)/1.71 (1.03-2.86), "2" = 1.88 (1.42-2.49)/1.82 (1.05-3.13), and ">3" = 2.27 (1.71-3.01)/3.21 (1.94-5.32), and 1.86 (1.48-2.33)/1.57 (1.00-2.49) for mild, 1.74 (1.22-2.48)/2.10 (1.11-3.98) for moderate, and 5.41 (3.77-7.77)/7.34 (4.15-12.99) for severe of pain. The results indicated a significant association between the number of sites and severity of pain and the prevalence of depression in the Korean elderly.

Patient-reported outcomes and opioid use in outpatients with chronic pain.
Witkin LR, Zylberger D, Mehta N, Hindenlang M, Johnson C, Kean J, Horn SD, Inturrisi CE.
J Pain. 2017 Jan 11. pii: S1526-5900(17)30002-0. doi: 10.1016/j.jpain.2016.12.018. [Epub ahead of print]

The Weill Cornell Medical College (WCMC) Pain Registry database contains patient characteristics, treatments, and outcomes for a prospective cohort of 1159 chronic pain patients who were seen at the WCMC Pain Medicine outpatient clinic from 7/08/2011 to 12/10/2014. Patients aged 45-64 comprised 43% followed by age >=65 at 37%. Fifty-eight percent were female. Average pain intensity (Brief Pain Inventory) was reported as mild by 22.3% of patients, moderate by 34.7%, and severe by 43.0%. For each pain intensity category, patient's report of average percent pain relief and health state (EQ-5D) was inversely related to average pain intensity category, while measures of pain interference, number of worst pain locations, and physical and psychological distress were directly related to pain intensity category. Seventy-seven percent of patients received an opioid at one or more clinic encounters. Median daily opioid dose in morphine equivalents (MEQs) was 55

with a range from 2 to 1145 MEQs. Regression analysis revealed that being male was associated with greater likelihood of an opioid ordered and higher average dosage than being female. The registry can identify patient characteristics and treatments that provide new insights into chronic pain management.
PERSPECTIVE: This article describes results of analyses of patient-reported outcomes and patient-related electronic health record data collected under standard of care from a prospective cohort of chronic pain outpatients at a NYC pain management clinic. The registry provides an opportunity to learn how to improve individualized chronic pain management.

DSM-5 insomnia and short sleep: Comorbidity landscape and racial disparities.
Kalmbach DA, Pillai V, Arnedt JT, Drake CL.
Sleep. 2016 Dec 1;39(12):2101-2111. doi: 10.5665/sleep.6306.

STUDY OBJECTIVES: We estimated rates of cardiometabolic disease, pain conditions, and psychiatric illness associated with Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) insomnia disorder (current and in remission) and habitual short sleep (fewer than 6 h), and examined the roles of insomnia and short sleep in racial disparities in disease burden between black and non-Hispanic white Americans. METHODS: This epidemiological survey study was cross-sectional. The community-based sample consisted of 3,911 subjects (46.0 y ± 13.3; 65.4% female; 25.0% black) across six sleep groups based on DSM-5 insomnia classification (*never* vs. *remitted* vs. *current*) and self-reported habitual sleep duration (*normal* vs. *short*). Vascular events, cardiometabolic disease, pain conditions, and psychiatric symptoms were self-reported. RESULTS: Short sleeping insomniacs were at elevated risk for myocardial infarction, stroke, treated hypertension, diabetes, chronic pain, back pain, depression, and anxiety, independent of sex, age, and obesity. Morbidity profiles for insomniacs with normal sleep duration and former insomniacs, irrespective of sleep duration, were similar with elevations in treated hypertension, chronic pain, depression, and anxiety. Regarding racial disparities, cardiometabolic and psychiatric illness burden was greater for blacks, who were more likely to have short sleep and the short sleep insomnia phenotype. Evidence suggested that health disparities may be attributable in part to race-related differences in sleep. CONCLUSIONS: Insomnia disorder with short sleep is the most severe phenotype of insomnia and comorbid with many cardiometabolic and psychiatric illnesses, whereas morbidity profiles are highly similar between insomniacs with normal sleep duration and former insomniacs. Short sleep endemic to black Americans increases risk for the short sleep insomnia phenotype and likely contributes to racial disparities in cardiometabolic disease and psychiatric illness.

The association between headaches and temporomandibular disorders is cofounded by bruxism and somatic complaints.
van der Meer HA, Speksnijder CM, Engelbert R, Lobbezoo F, Nijhuis-van der Sanden MW, Visscher CM.
Clin J Pain. 2016 Dec 19. doi: 10.1097/AJP.0000000000000470. [Epub ahead of print]

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. METHODS: Several subtypes of headaches were diagnosed: self-reported headache, (probable) migraine, (probable) tension-type headache (TTH), and secondary headache attributed to TMD. The presence of TMD was subdivided into two subtypes: painful TMD and function-related TMD. The associations between the subtypes of TMD and headaches were evaluated by single regression models. Subsequently, to study the influence of possible confounding factors on this association, the regression models were extended with age, gender, bruxism, stress, depression, and somatic complaints. 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 complaints. For probable migraine, both somatic complaints and bruxism confounded the initial association found with painful TMD. DISCUSSION: The findings of this study imply there is a central working mechanism overlapping TMD and headache. Healthcare providers should not look at these disorders separately, but rather at the bigger picture to appreciate the complex nature of the diagnostic and therapeutic process.

Chronic symptoms in a representative sample of community-dwelling older people: a cross-sectional study in Switzerland.
Henchoz Y, Büla C, Guessous I, Rodondi N, Goy R, Demont M, Santos-Eggimann B.
BMJ Open. 2017 Jan 17;7(1):e014485. doi: 10.1136/bmjopen-2016-014485.

OBJECTIVES: The burden of multiple diagnoses is well documented in older people, but less is known about chronic symptoms, many of which are even not brought to medical attention. This study aimed to determine the prevalence of chronic symptoms, their relationships with disability in basic activities of daily living (BADL) and quality of life (QoL), and their public health impact. DESIGN: A large cross-sectional population-based study. SETTING: Community in 2 regions of French-speaking Switzerland. PARTICIPANTS: Community-dwelling older adults aged 68 years and older in 2011 (N=5300). OUTCOMES: Disability in BADL defined as difficulty or help needed with any of dressing, bathing, eating, getting in/out of bed or an arm chair, and using the toilet. Overall QoL dichotomised as favourable (ie, excellent or very good) or unfavourable (ie, good, fair or poor). Disturbance by any of the following 14 chronic symptoms for at least 6 months: joint pain, back pain, chest pain, dyspnoea, persistent cough, swollen legs, memory gaps, difficulty concentrating, difficulty making decisions, dizziness/vertigo, skin problems, stomach/intestine problems, urinary incontinence and impaired sexual life. RESULTS: Only 17.1% of participants did not report being disturbed by any of these chronic symptoms. Weighted prevalence ranged from 3.1% (chest pain) to 47.7% (joint pain). Most chronic symptoms were significantly associated with disability in BADL or unfavourable QoL, with substantial gender differences. The number of chronic symptoms was significantly associated with disability in BADL and unfavourable QoL, with gradients suggesting dose-response relationships. Joint pain and back pain had the highest population attributable fractions. CONCLUSIONS: Chronic symptoms are highly prevalent in older people, and are associated with disability in BADL and unfavourable QoL, particularly when multiple chronic symptoms co-occur. Owing to their high public health impact, musculoskeletal chronic symptoms represent good targets for preventive interventions.

Comorbidities that cause pain and the contributors to pain in individuals with chronic obstructive pulmonary disease.
Chen YW, Camp PG, Coxson HO, Road JD, Guenette JA, Hunt MA, Reid WD.
Arch Phys Med Rehabil. 2016 Nov 17. pii: S0003-9993(16)31237-0. doi: 10.1016/j.apmr.2016.10.016. [Epub ahead of print]

OBJECTIVE: To determine comorbidities that cause pain and the potential contributors to pain in individuals with COPD. DESIGN: Prospective cross-sectional survey study. SETTING: Pulmonary rehabilitation programs of six centers. PARTICIPANTS: A convenience sample of individuals with COPD who attended pulmonary rehabilitation programs (n=137). In total, 100 (73%) returned the survey packages. Of those responders, 96 (70%) participants were included in the analyses. INTERVENTIONS: Not applicable. MAIN OUTCOME MEASURES: Pain was measured using the Brief Pain Inventory (BPI). The "health conditions that might contribute to pain and medication record" form asked about comorbidities that cause pain stated in lay terms. The health conditions that cause pain were then validated by health professionals. Demographics, fatigue, dyspnea, quality of life, and self-efficacy were also measured using questionnaires. RESULTS: Pain was reported in 71% of participants (68 of

96). Low back pain was the most common location (41%). Arthritis (75%), back problems (47%) and muscle cramps (46%) were the most common comorbidities that cause pain. Lower self-efficacy, renting rather than home ownership increased the likelihood of pain ($p < 0.05$). Pain severity and BFI scores contributed to pain interference scores ($p < 0.05$). CONCLUSION: Pain was highly prevalent in pulmonary rehabilitation program participants with COPD. The most common causes of pain were musculoskeletal conditions. Pain severity and higher levels of fatigue contributed to how pain interfered with daily aspects of living. The assessment and management of pain needs to be addressed within the overall care of individuals with COPD.

The presence of respiratory disorders in individuals with low back pain: A systematic review.
Beeckmans N, Vermeersch A, Lysens R, Van Wambeke P, Goossens N, Thys T, Brumagne S, Janssens L.
Man Ther. 2016 Dec;26:77-86. doi: 10.1016/j.math.2016.07.011.

BACKGROUND: Inspiratory muscles, such as the diaphragm, play a key role in both respiration and spinal control. Therefore, diaphragm dysfunctions are often related to low back pain (LBP). However, few is known on the association between the presence of LBP and the presence of respiratory disorders (RD). OBJECTIVES: To perform a systematic review on the relation between RD and LBP. STUDY DESIGN: Systematic review. METHODS: Two reviewers searched on PubMed/MEDLINE for studies concerning LBP and RD, from 1950 up to January 2016. The search string consisted of the following key words: low back pain, dyspnea, respiratory problems, lung diseases, comorbidity, pulmonary disease, chronic obstructive, smoking, asthma, allergy, sinusitis, respiratory tract infection and hyperventilation. The aim was to evaluate a potential correlation, co-occurrence or causality between RD and LBP. RESULTS: A total of 16 articles were included. A significant correlation between the presence of LBP and the presence of RD such as dyspnea, asthma, different forms of allergy, and respiratory infections was found. No correlation was found between Chronic Obstructive Pulmonary Disease (COPD) and LBP, and no articles were found on the correlation between hyperventilation and LBP. CONCLUSIONS: This is the first study providing an overview of the literature on the relation between LBP and RD. Immunological, biomechanical, psychosocial and socio-economic factors might explain this correlation. Smoking is likely to contribute. Future studies must reveal the causative relationship. LEVEL OF EVIDENCE: Therapy, level 2a.

Prevalence of irritable bowel syndrome (IBS), migraine and co-existing IBS-migraine in medical students.
Perveen I, Parvin R, Saha M, Bari MS, Huda MN, Ghosh MK.
J Clin Diagn Res. 2016 Nov;10(11):OC09-OC13. doi: 10.7860/JCDR/2016/20900.8832.

Irritable Bowel Syndrome (IBS) and migraine frequently co-exist. Stress is a major contributing factor for both. Our medical students are subjected to stress related to the implicit responsibility of courses. But the prevalence of IBS, migraine and co-existing migraine in medical students is not known. AIM: To estimate the prevalence of migraine, IBS and co-existing IBS and migraine among medical students. A Cross-Sectional Survey. MATERIALS AND METHODS: Self-reported questionnaire based study, was conducted in which migraine was defined according to International Headache Society (IHS) criteria while IBS by both Asian criteria and Rome III criteria. Both preclinical (n=142) and clinical students (n=151) of four medical colleges (government and private) of Dhaka and Sylhet district participated in the study. Statistical Analysis: Student's t-test and chi-square test were used to compare the distributions of continuous data and categorical data respectively with significance level set at 0.05 or less. RESULTS: Among the 293 students (mean age 21.09 ± 2.24 years) volunteered in the study (Males= 177), 14 (4.8%, 11 males, 3 females, $p = 0.175$) met the criteria for IBS with comparable prevalence among preclinical and clinical (4.2% vs. 5.3%, $p = 0.787$) students from both private and government institutions (2.1% vs. 7.2%, $p = 0.055$). IBS-D was the most prevalent subtype ($n = 8$, $M = 6$) and abdominal pain relieved by

defecation (n = 11), was the most prevalent symptom. Fifty percent (n = 7) of IBS patients considered their bowel habit as normal. Among the 221 (75.4%) students with headache, only 51 (17.4%, 20 males and 31 females, p = 0.001) were diagnosed of migraine, with comparable prevalence among preclinical and clinical students (16.2% vs. 18.5%, p = 0.645). Only 17 (33%) subjects with migraine had accompanying aura. Common triggers were stress (n = 43), lack of sleep (n = 42), and daily life events. Twelve (23.5%) subjects with migraine had migraine-associated frequent disability. Only two female students with IBS-D (14.3%) had concomitant IBS and migraine. CONCLUSION: IBS and concomitant migraine - IBS prevalence was found to be low in our medical students, but migraine prevalence corresponds to other countries as well as in medical students.

CLINICAL STUDIES

Comorbidities of chronic facial pain and obstructive sleep apnea.
Olmos SR.
Curr Opin Pulm Med. 2016 Nov;22(6):570-5.

PURPOSE OF REVIEW: This article explains the high comorbidity of craniofacial pain (chronic face pain, temporomandibular disorders, and primary headaches) with obstructive sleep breathing disorders and obstructive sleep apnea (OSA). It is recommended that physicians treating OSA should be aware of the concurrent chronic pain that affects the quality of sleep, and also dentists treating chronic pain be aware of a sleep breathing origin so that proper reciprocal referrals be made for optimal patient treatment outcome. RECENT FINDINGS: These comorbid relationships are not limited to adults. The most recent literature demonstrates that children diagnosed with primary headaches are highly comorbid with OSA and frequently have chronic facial pain complaints. SUMMARY: It is recommended that patients who seek care for the symptoms of sleep-related breathing disorders (OSA), or patients seeking care for chronic head and face pain be screened with intake forms that include questions of both to insure optimal treatment outcomes for either chief complaint.

Painful temporomandibular disorders and central sensitization: Implications for management a pilot study.
Campi LB, Jordani PC, Tenan HL, Camparis CM, Gonçalves DA.
Int J Oral Maxillofac Surg. 2017 Jan;46(1):104-110. doi: 10.1016/j.ijom.2016.07.005.

The objective was to investigate the presence of cutaneous allodynia and hyperalgesia in the trigeminal and extra-trigeminal areas, as a surrogate for central sensitization (CS), in women with a painful temporomandibular disorder (TMD) and without other painful conditions. Painful TMDs, depression, and non-specific physical symptoms (NSPS) were classified according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD). The amount of pain in the trigeminal and extra-trigeminal areas was determined using a visual analogue scale (0-100mm) after the application of a vibrotactile stimulus and assessment of the pressure pain threshold (PPT). Statistical tests (Fisher's, χ^2, and Mann-Whitney) were performed, with a significance level of 5%. The sample comprised 45 women (mean age 37.5 years; 16 with a painful TMD) who were free of any headache, fibromyalgia, or other painful condition. Painful TMD was associated with higher pain sensitivity and lower PPT values in the trigeminal ($P<0.01$) and extra-trigeminal regions ($P<0.01$). The presence of depression contributed significantly to increased pain sensitivity. The presence of hyperalgesia and allodynia in both the trigeminal and extra-trigeminal regions among women with a painful TMD indicated the presence of CS. Changes involving the central nervous system should be considered during the evaluation and management of patients with a painful TMD.

Sex differences in the efficacy of psychological therapies for the management of chronic and recurrent pain in children and adolescents: A systematic review and meta-analysis.
Boerner KE, Eccleston C, Chambers CT, Keogh E.
Pain. 2016 Dec 15. doi: 10.1097/j.pain.0000000000000803. [Epub ahead of print]

Sex differences in chronic pain are reported to emerge during adolescence, although it is unclear if this includes responses to treatment. We conducted a meta-analysis to examine whether sex differences were present on outcome variables at pre-treatment, and whether the efficacy of psychological therapies for pediatric chronic pain differs between boys and girls at post-treatment and follow-up time points. Searches were conducted, extending two existing Cochrane reviews of randomized-controlled trials examining the efficacy of psychological therapies for chronic and recurrent pain in children and adolescents. Forty-six articles were eligible for inclusion, and data were extracted regarding pain, disability, anxiety, and depression in boys and girls at pre-treatment, post-treatment, and follow-up time points. No published study reported outcome data separately by sex, so authors of all studies were contacted and 17 studies provided data. Twice as many girls (n =1760) were enrolled into clinical trials of psychological therapies for pediatric chronic pain than boys (n = 828). Girls reported higher depression and anxiety at pre-treatment than boys. Girls with headache also reported significantly greater pre-treatment pain severity. Treatment gains were consistent across the sexes. One exception was for post-treatment disability in children with non-headache pain conditions; girls exhibited a significant effect of treatment relative to control condition (SMD= -0.50[-0.80,-0.20], $p < .01$), but no such effect was observed for boys (SMD= -0.08[-0.44,0.28], $p = .66$). Future research should examine whether mechanisms of treatment efficacy differ between boys and girls, and consider the impact of pre-treatment sex differences on response to treatment.

Sex differences in the epidemiology, clinical features, and pathophysiology of migraine.
Vetvik KG, MacGregor EA.
Lancet Neurol. 2017 Jan;16(1):76-87. doi: 10.1016/S1474-4422(16)30293-9.

Migraine is two to three times more prevalent in women than men, and women report a longer attack duration, increased risk of headache recurrence, greater disability, and a longer period of time required to recover. Conditions recognised to be comorbid with migraine include asthma, anxiety, depression, and other chronic pain conditions, and these comorbidities add to the amount of disability in both sexes. Migraine-specifically migraine with aura-has been identified as a risk factor for vascular disorders, particularly in women, but because of the scarcity of data, the comparative risk in men has yet to be established. There is evidence implicating the role of female sex hormones as a major factor in determining migraine risk and characteristics, which accounts for sex differences, but there is also evidence to support underlying genetic variance. Although migraine is often recognised in women, it is underdiagnosed in men, resulting in suboptimal management and less participation of men in clinical trials.

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.

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