



CUTTING EDGE

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COPCs Research Advances



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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 in September and October 2017. Prior issues are available on our website, <http://www.cpralliance.org>. To read the CPRA's White Paper, click [here](#). Please direct any questions or comments to the CPRA's Director, Christin Veasley - cveasley@cpralliance.org.

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NATIONAL MULTICENTER STUDIES

[Effects of water avoidance stress on peripheral and central responses during bladder filling in the rat: A multidisciplinary approach to the study of urologic chronic pelvic pain syndrome \(MAPP\) research network study.](#)

Wang Z, Chang HH, Gao Y, Zhang R, Guo Y, Holschneider DP, Rodriguez LV.

PLoS One. 2017 Sep 8;12(9):e0182976. doi: 10.1371/journal.pone.0182976. eCollection 2017.

Stress plays a role in the exacerbation and possibly the development of functional lower urinary tract disorders. Chronic water avoidance stress (WAS) in rodents is a model with high construct and face validity to bladder hypersensitive syndromes, such as interstitial cystitis/bladder pain syndrome (IC/BPS), characterized by urinary frequency and bladder hyperalgesia and heightened stress responsiveness. Given the overlap of the brain circuits involved in stress, anxiety, and micturition, we evaluated the effects chronic stress has on

bladder function, as well as its effects on regional brain activation during bladder filling. Female Wistar-Kyoto rats were exposed to WAS (10 days) or sham paradigms. One day thereafter, cystometrograms were obtained during titrated bladder dilation, with visceromotor responses (VMR) recorded simultaneously. Cerebral perfusion was assessed during passive bladder distension (20-cmH₂O) following intravenous administration of [¹⁴C]-iodoantipyrine. Regional cerebral blood flow was quantified by autoradiography and analyzed in 3-dimensionally reconstructed brains with statistical parametric mapping. WAS animals compared to controls demonstrated a decreased pressure threshold and visceromotor threshold triggering the voiding phase. At 20-cmH₂O, VMR was significantly greater in WAS animals compared to controls. WAS animals showed greater activation in cortical regions of the central micturition circuit, including the posterior cingulate, anterior retrosplenial, somatosensory, posterior insula, orbital, and anterior secondary ("supplementary") motor cortices, as well as in the thalamus, anterior hypothalamus, parabrachial and Barrington nuclei, and striatum. Seed analysis showed increased functional connectivity of WAS compared to control animals of the posterior cingulate cortex to the pontine parabrachial nucleus; of the Barrington nucleus to the anterior dorsal midline and ventrobasilar thalamus and somatosensory and retrosplenial cortices; and of the posterior insula to anterior secondary motor cortex. Our findings show a visceral hypersensitivity during bladder filling in WAS animals, as well as increased engagement of portions of the micturition circuit responsive to urgency, viscerosensory perception and its relay to motor regions coordinating imminent bladder contraction. Results are consistent with recent findings in patients with interstitial cystitis, suggesting that WAS may serve as an animal model to elucidate the mechanisms leading to viscerosensitive brain phenotypes in humans with IC/BPS.

PATHOPHYSIOLOGY STUDIES

[Shared genetic risk between migraine and coronary artery disease: A genome-wide analysis of common variants.](#)

Winsvold BS, Bettella F, Witoelar A, Anttila V, Gormley P, Kurth T, Terwindt GM, Freilinger TM, Frei O, Shadrin A, Wang Y, Dale AM, van den Maagdenberg AMJM, Chasman DI, Nyholt DR, Palotie A, Andreassen OA, Zwart JA; International Headache Genetics Consortium. PLoS One. 2017 Sep 28;12(9):e0185663. doi: 10.1371/journal.pone.0185663. eCollection 2017.

Migraine is a recurrent pain condition traditionally viewed as a neurovascular disorder, but little is known of its vascular basis. In epidemiological studies migraine is associated with an increased risk of cardiovascular disease, including coronary artery disease (CAD), suggesting shared pathogenic mechanisms. This study aimed to determine the genetic overlap between migraine and CAD, and to identify shared genetic risk loci, utilizing a conditional false discovery rate approach and data from two large-scale genome-wide association studies (GWAS) of CAD (C4D, 15,420 cases, 15,062 controls; CARDIoGRAM, 22,233 cases, 64,762 controls) and one of migraine (22,120 cases, 91,284 controls). We found significant enrichment of genetic variants associated with CAD as a function of their association with migraine, which was replicated across two independent CAD GWAS studies. One shared risk locus in the PHACTR1 gene (conjunctive false discovery rate for index SNP rs9349379 < 3.90 x 10⁻⁵), which was also identified in previous studies, explained much of the enrichment. Two further loci (in KCNK5 and AS3MT) showed evidence for shared risk (conjunctive false discovery rate < 0.05). The index SNPs at two of the three loci had opposite effect directions in migraine and CAD. Our results confirm previous reports that migraine and CAD share genetic risk loci in excess of what would be expected by chance, and highlight one shared risk locus in PHACTR1. Understanding the biological mechanisms underpinning this shared risk is likely to improve our understanding of both disorders.

[Headache exacerbates pain characteristics in temporomandibular disorders.](#)

Costa YM, Alves da Costa DR, de Lima Ferreira AP, Porporatti AL, Svensson P, Rodrigues Conti

AIMS: To evaluate the impact of headache in adults with masticatory myofascial pain (MMP) on the outcome variables clinical pain (ie, self-reported pain intensity and pressure pain sensitivity), sleep quality, and pain catastrophizing. METHODS: A total of 97 patients with MMP were diagnosed with co-existing headache (MMPH group, n = 50) or without headache (MMP group, n = 47) according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD). The outcome parameters were the Pittsburgh Sleep Quality Index (PSQI); the Catastrophizing Thoughts subscale of the Pain-Related Self-Statement Scale (PRSS-C); pressure pain thresholds (PPTs) of the masseter and anterior temporalis muscles; and self-reported facial pain intensity measured on a 0- to 10-cm visual analog scale (VAS). Student t test for independent samples ($\alpha = 1.2\%$) and factorial analysis of variance (ANOVA) ($\alpha = 5\%$) were used to analyze the data. RESULTS: The MMPH group showed significantly impaired sleep quality (mean \pm standard deviation [SD] PSQI score 9.1 ± 3.5) compared with the MMP group (7.2 ± 3.4 ; $P = .008$). Subscale scores on the PRSS-C were significantly higher in the MMPH (2.1 ± 1.2) than in the MMP group (1.6 ± 1.4 , uncorrected $P = .048$). Also, the PPTs (kgf/cm^2) of the masseter and anterior temporalis muscles were significantly lower in the MMPH group (1.52 ± 0.53 ; 1.29 ± 0.43 , respectively) than in the MMP group (2.09 ± 0.73 ; 1.70 ± 0.68 , respectively; $P < .001$), with no differences in self-reported facial pain intensity. Factorial analyses further indicated that chronic migraine was associated with poorer sleep quality ($P = .003$) and that tension-type headache patients had lower PPTs in the anterior temporalis muscle ($P = .041$) in comparison with non-headache patients. CONCLUSION: Co-existence of headache further exacerbates clinical characteristics in patients with painful TMD, which implies involvement of common mechanisms and pathways of vulnerability in these patients.

[The role of centralised pain in osteoarthritis.](#)

Clauw DJ, Hassett AL.

Clin Exp Rheumatol. 2017 Sep-Oct;35 Suppl 107(5):79-84.

The mechanisms underlying chronic pain states, including osteoarthritis, differ from those underlying acute pain. In chronic pain states, central nervous system (CNS) factors often play a particularly prominent role. In many individuals with chronic pain, pain can occur with minimal or no evidence of ongoing nociceptive input. Medical subspecialties have applied a wide-range of labels to these pain conditions including fibromyalgia, irritable bowel syndrome and interstitial cystitis to name just a few. These same CNS processes can augment or magnify pain when there is ongoing nociceptive input, as in conditions such as osteoarthritis or autoimmune disorders. The hallmark of these 'centrally driven' pain conditions is a diffuse hyperalgesic state identifiable through the use of experimental sensory testing, that has been corroborated by functional neuroimaging. Characteristic symptoms of these central pain conditions include multifocal pain, fatigue, poor sleep, memory complaints and frequent co-morbid mood and anxiety disorders. In contrast to acute and peripheral pain states that are responsive to non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, central pain conditions respond best to CNS neuromodulating agents, such as serotonin-norepinephrine reuptake inhibitors (SNRIs) and anticonvulsants. While osteoarthritis is generally considered a peripherally mediated pain state, a subset of these patients also manifests centrally driven pain characteristics. Thus, osteoarthritis can also be thought of as a "mixed" pain state and this requires a more tailored approach to treatment.

[Estradiol sensitizes the transient receptor potential Vanilloid 1 Receptor in pain responses.](#)

Payrits M, Saghy E, Cseko K, Pohoczky K, Bolcskei K, Ernszt D, Barabas K, Szolcsanyi J, Abraham IM, Helyes Z, Szoke E.

Endocrinology. 2017 Oct 1;158(10):3249-3258. doi: 10.1210/en.2017-00101.

Sex differences exist in chronic pain pathologies, and gonadal estradiol (E2) alters the pain sensation. The nociceptor transient receptor potential vanilloid 1 (TRPV1) receptor plays a

critical role in triggering pain. Here we examined the impact of E2 on the function of TRPV1 receptor in mice sensory neurons in vitro and in vivo. Both mechano- and thermonociceptive thresholds of the plantar surface of the paw of female mice were significantly lower in proestrus compared with the estrus phase. These thresholds were higher in ovariectomized (OVX) mice and significantly lower in sham-operated mice in proestrus compared with the sham-operated mice in estrus phase. This difference was absent in TRPV1 receptor-deficient mice. Furthermore, E2 potentiated the TRPV1 receptor activation-induced mechanical hyperalgesia in OVX mice. Long pretreatment (14 hours) with E2 induced a significant increase in TRPV1 receptor messenger RNA expression and abolished the capsaicin-induced TRPV1 receptor desensitization in primary sensory neurons. The short E2 incubation (10 minutes) also prevented the desensitization, which reverted after coadministration of E2 and the tropomyosin-related kinase A (TrkA) receptor inhibitor. Our study provides in vivo and in vitro evidence for E2-induced TRPV1 receptor upregulation and sensitization mediated by TrkAR via E2-induced genomic and nongenomic mechanisms. The sensitization and upregulation of TRPV1 receptor by E2 in sensory neurons may explain the greater pain sensitivity in female mice.

[The impact of the standard American diet in rats: Effects on behavior, physiology and recovery from inflammatory injury.](#)

Totsch SK, Quinn TL, Strath LJ, McMeekin LJ, Cowell RM, Gower BA, Sorge RE.
Scand J Pain. 2017 Sep 16. pii: S1877-8860(17)30181-7. doi: 10.1016/j.sjpain.2017.08.009.

BACKGROUND AND AIMS: Obesity is a significant health concern in the Western world and the presence of comorbid conditions suggests an interaction. The overlapping distributions of chronic pain populations and obesity suggests that an interaction may exist. Poor quality diet (high carbohydrates, saturated fats, omega-6 polyunsaturated fatty acids) can lead to increased adiposity which can activate immune cells independent of the activating effect of the diet components themselves. This dual action can contribute to chronic inflammation that may alter susceptibility to chronic pain and prolong recovery from injury. However, traditional examinations of diet focus on high-fat diets that often contain a single source of fat, that is not reflective of an American diet. Thus, we examined the impact of a novel human-relevant (high-carbohydrate) American diet on measures of pain and inflammation in rats, as well as the effect on recovery and immune cell activation. METHODS: We developed a novel, human-relevant Standard American Diet (SAD) to better model the kilocalorie levels and nutrient sources in an American population. Male and female rats were fed the SAD over the course of 20 weeks prior to persistent inflammatory pain induction with Complete Freund's Adjuvant (CFA). Mechanical and thermal sensitivity were measured weekly. Spontaneous pain, open field locomotion and blood glucose levels were measured during diet consumption. Body composition was assessed at 20 weeks. Following full recovery from CFA-induced hypersensitivity, blood was analyzed for inflammatory mediators and spinal cords were immunohistochemically processed for microglial markers. RESULTS: Chronic consumption of the SAD increased fat mass, decreased lean mass and reduce bone mineral density. SAD-fed rats had increased leptin levels and pro-inflammatory cytokines in peripheral blood serum. Following CFA administration, mechanical sensitivity was assessed and recovery was delayed significantly in SAD-fed animals. Sex differences in the impact of the SAD were also observed. The SAD increased body weight and common T-cell related inflammatory mediators in female, but not male, animals. In males, the SAD had a greater effect on bone mineral density and body composition. Long-term consumption of the SAD resulted in elevated microglial staining in the dorsal horn of the spinal cord, but no sex differences were observed. CONCLUSIONS: We demonstrate the negative effects of an American diet on physiology, behavior and recovery from injury. SAD consumption elevated pro-inflammatory mediators and increased microglial activation in the spinal cord. While there were sex differences in weight gain and inflammation, both sexes showed prolonged recovery from injury. IMPLICATIONS: These data suggest that poor quality diet may increase susceptibility to chronic pain due to persistent peripheral and central immune system activation. Furthermore, consumption of a diet that is high in carbohydrates and omega-6 polyunsaturated fatty acid is likely to lead to protracted recovery following trauma or surgical

procedures. These data suggest that recovery of a number of patients eating a poor quality diet may be expedited with a change in diet to one that is healthier.

EPIDEMIOLOGY STUDIES

[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.* 2017 Oct 11. doi: 10.1007/s10072-017-3141-0. [Epub ahead of print]

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.

[Clinical implications of associations between headache and gastrointestinal disorder: A study using the Hallym Smart Clinical Data Warehouse.](#)

Lee SH, Lee JJ, Kwon Y, Kim JH, Sohn JH.

Front Neurol. 2017 Oct 3;8:526. doi: 10.3389/fneur.2017.00526. eCollection 2017.

BACKGROUND: The brain and gastrointestinal (GI) tract are strongly connected *via* neural, endocrine, and immune pathways. Previous studies suggest that headaches, especially migraines, may be associated with various GI disorders. However, upper GI endoscopy in migraineurs has shown a low prevalence of abnormal findings. Also, the majority of studies have not demonstrated an association between *Helicobacter pylori* (HP) infection and migraine, although a pathogenic role for HP infection in migraines has been suggested. Further knowledge concerning the relation between headaches and GI disorders is important as it may have therapeutic consequences. Thus, we sought to investigate possible associations between GI disorders and common primary headaches, such as migraines and tension-type headaches (TTH), using the Smart Clinical Data Warehouse (CDW) over a period of 10 years. **METHODS:** We retrospectively investigated clinical data using a clinical data analytic solution called the Smart CDW from 2006 to 2016. In patients with migraines and TTH who visited a gastroenterology center, GI disorder diagnosis, upper GI endoscopy findings, and results of HP infection were collected and compared to clinical data from controls, who had health checkups without headache. The time interval between headache diagnosis and an examination at a gastroenterology center did not exceed 1 year. **RESULTS:** Patients were age- and sex-matched and eligible cases were

included in the migraine group (n=168), the TTH (n=168), and the control group (n=336). Among the GI disorders diagnosed by gastroenterologists, gastroesophageal reflux disorder was more prevalent in the migraine group, whereas gastric ulcers were more common in the migraine and TTH groups compared with controls ($p < 0.0001$). With regard to endoscopic findings, there were high numbers of erosive gastritis and chronic superficial gastritis cases in the migraine and TTH groups, respectively, and the severity of gastritis was significantly higher in patients with TTH compared with controls ($p < 0.001$). However, no differences were observed in the prevalence of HP infection between the groups. CONCLUSION: The observed association in this study may suggest that primary headache sufferers who experience migraines or TTH are more prone to GI disorders, which may have various clinical implications. Further research concerning the etiology of the association between headaches and GI disorders is warranted.

[What are the predictors of altered central pain modulation in chronic musculoskeletal pain populations? A systematic review.](#)

Clark J, Nijs J, Yeowell G, Goodwin PC.
Pain Physician. 2017 Sep;20(6):487-500.

BACKGROUND: Altered central pain modulation is the predominant pain mechanism in a proportion of chronic musculoskeletal pain disorders and is associated with poor outcomes. Although existing studies predict poor outcomes such as persistent pain and disability, to date there is little consensus on what factors specifically predict altered central pain modulation. OBJECTIVES: To review the existing literature on the predictive factors specifically for altered central pain modulation in musculoskeletal pain populations. STUDY DESIGN: This is a systematic review in accordance with supplemented PRISMA guidelines. METHODS: A systematic search was performed by 2 mutually blinded reviewers. Relevant articles were screened by title and abstract from Medline, Embase, PubMed, CINAHL, and Web of Science electronic databases. Alternative sources were also sought to locate missed potential articles. Eligibility included studies published in English, adults aged 18 to 65, musculoskeletal pain, baseline measurements taken at the pre-morbid or acute stage, > 3-month follow-up time after pain onset, and primary outcome measures specific to altered central pain modulation. Studies were excluded where there were concurrent diseases or they were non-predictive studies. Risk of bias was assessed using the quality in prognostic studies (QUIPS) tool. Study design, demographics, musculoskeletal region, inclusion/exclusion criteria, measurement timelines, predictor and primary outcome measures, and results were extracted. Data were synthesized qualitatively and strength of evidence was scored using the grading of recommendations, assessment, development, and evaluations (GRADE) scoring system. RESULTS: Nine eligible articles were located, in various musculoskeletal populations (whiplash, n = 2; widespread pain, n = 5; temporomandibular disorder, n = 2). Moderate evidence was found for 2 predictive factors of altered central pain modulation: 1) high sensory sensitivity (using genetic testing or quantitative sensory tests), and 2) psychological factors (somatization and poor self-expectation of recovery), at a pre-morbid or acute stage baseline. LIMITATIONS: At the times of the article publications, the current definitions and clinical guidelines for identifying altered central pain modulation were not yet available. Careful interpretation of the information provided using current knowledge and published guidelines was necessary to extract information specific to altered central pain modulation in some of the studies, avoiding unwarranted assumptions. CONCLUSIONS: Premorbid and acute stage high sensory sensitivity and/or somatization are the strongest predictors of altered central pain modulation in chronic musculoskeletal pain to date. This is the first systematic review specifically targeting altered central pain modulation as the primary outcome in musculoskeletal pain populations. Early identification of people at risk of developing chronic pain with altered central pain modulation may guide clinicians in appropriate management, diminishing the burden of persistent pain on patients and health care providers alike. Systematic Review Registration no.: PROSPERO 2015:CRD42015032394.

[Fibromyalgia among patients with chronic migraine and chronic tension-type headache: A](#)

[multicenter prospective cross-sectional study.](#)

Cho SJ, Sohn JH, Bae JS, Chu MK.

Headache. 2017 Sep 22. doi: 10.1111/head.13191. [Epub ahead of print]

OBJECTIVES: To investigate the frequency and impact of fibromyalgia among patients with chronic migraine (CM) and chronic tension-type headache (CTTH). **BACKGROUND:** Fibromyalgia (FM) is a common comorbidity in patients with chronic headaches. CM and CTTH are the two common types of chronic headaches. **METHODS:** We conducted a cross-sectional study in neurology outpatient clinics of four university hospitals and selected first-visit 136 patients with CM and 35 patients with CTTH. FM was assessed based on the 2010 American College of Rheumatology diagnostic criteria. **RESULTS:** The frequency of FM was significantly higher among patients with CM when compared to those with CTTH (91/136 [66.9%] vs 9/35 [25.7%], $p < 0.001$). Logistic regression analyses revealed an increased odds ratio (OR) for FM for patients with CM when compared to those with CTTH after adjustment for age, sex, anxiety, depression, and insomnia (OR=3.6, 95% confidence interval = 1.1-11.4). Furthermore, CM patients with FM had higher scores in FM Impact Questionnaire compared to CTTH patients with FM (51.5 +/- 16.3 vs 43.7 +/- 18.7, $p=0.015$). Comorbidity of FM was associated with increased frequency of photophobia, phonophobia, anxiety, depression, and insomnia among patients with CM. Such association was not noted among patients with CTTH. **CONCLUSION:** FM based on 2010 American College of Rheumatology diagnostic criteria was more prevalent among patients with CM than those with CTTH. Some clinical features and comorbidities of CM varied with the presence of FM.

[The prevalence of pain and analgesia use in the Australian population: Findings from the 2011 to 2012 Australian National Health Survey.](#)

Miller A, Sanderson K, Bruno R, Breslin M, Neil AL.

Pharmacoepidemiol Drug Saf. 2017 Sep 12. doi: 10.1002/pds.4301. [Epub ahead of print]

BACKGROUND: Opioid analgesic use and associated adverse events have increased over the last 15 years, including in Australia. Whether this is associated with increased chronic pain prevalence in the Australian population is unknown. This study aimed to estimate (1) the prevalence of chronic pain and analgesia use in the Australian population by age and sex; (2) the severity of pain in the population with chronic pain by sex; and (3) the distribution of recent pain severity in those using analgesia by age and sex. **METHODS:** This study used cross-sectional, nationally representative data collected by the Australian Bureau of Statistics 2011 to 2012 National Health Survey. A total of $n = 20\,426$ participants were included with an overall response rate of 84.8%. Weighting procedures were applied to obtain population estimates, confidence intervals, and when testing for statistical significance. **RESULTS:** The prevalence of chronic and reoccurring pain (over a 6-month period) was 15.4% (2.75 million) for Australians aged ≥ 15 years. Prevalence increased with age for both sexes. Significantly more females reported moderate-to-very severe pain overall ($P < 0.001$), and within most age groups. Recent use of opioid analgesia was reported by 12.0% of males and 13.4% of females with chronic pain. **CONCLUSION:** Chronic pain and opioid analgesic use are important public health issues in Australia. Study estimates of chronic pain and recent pain were no greater than earlier estimates. The acknowledged increase of opioid use in the literature thus appears consistent with changing treatment and/or prescribing patterns over time. Sex differences regarding pain prevalence, severity, and opioid use were apparent.

[Pain problems for patients with mild and moderate chronic obstructive pulmonary disease - a community-based study in Shanghai.](#)

Xiao T, Zhou X, He Y, Chen Y, Qiu H, Zhang S, Wei X, Wu K, Ruan X, Wang N, Fu C.

J Pain Res. 2017 Sep 15;10:2247-2252. doi: 10.2147/JPR.S141940. eCollection 2017.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a great public health burden worldwide. Few studies have focused on pain problems in patients with mild and moderate COPD in Chinese community settings. **METHODS:** A cross-sectional study of 283 patients with mild and moderate COPD was conducted in six communities that were randomly sampled in

Pudong New Area of Shanghai, China, in 2016. A face-to-face interview was conducted to collect data on personal characteristics and health conditions. The short form McGill Pain Questionnaire and the COPD assessment test (CAT) were applied to evaluate pain problems and health status, respectively. RESULTS: Among 283 subjects, more than one third (37%) had pain problems indicated by the present pain intensity (PPI) scale. COPD patients aged <65 years with exacerbation in the past 12 months or a CAT score of ≥ 10 had a significantly higher score in affective dimension. Female sex, COPD severity, and length of disease were significantly related to higher scores of the sensory dimension. Those with moderate COPD or a CAT score of ≥ 10 had significantly higher scores of visual analog scale than those with mild COPD or a CAT score <10. Patients with moderate COPD had a higher rank of PPI than those with mild COPD. CONCLUSION: Pain was common in patients with mild and moderate COPD in the community settings of Shanghai, China. Severity of COPD and CAT score were significantly related to the prevalence of pain. Intervention measures should be developed to improve pain problems for COPD patients.

[Chronic prostatitis and comorbid non-urological overlapping pain conditions: A co-twin control study.](#)

Gasperi M, Krieger JN, Forsberg C, Goldberg J, Buchwald D, Afari N.
J Psychosom Res. 2017 Nov;102:29-33. doi: 10.1016/j.jpsychores.2017.09.005.

OBJECTIVES: Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is characterized by pain and voiding symptoms in the absence of an obvious infection or other cause. CP/CPPS frequently occurs with non-urological chronic overlapping pain conditions (COPCs) of unknown etiology. We conducted a co-twin control study in men discordant for chronic prostatitis (CP), an overarching diagnosis of which approximately 90% is CP/CPPS. The primary aim was to investigate the contribution of familial factors, including shared genetic and common environmental factors, to the comorbidity of CP and COPCs. METHODS: Data from 6824 male twins in the Vietnam Era Twin Registry were examined to evaluate the association between self-reported lifetime physician diagnosis of CP with COPCs including fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, temporomandibular disorder, tension headaches, and migraine headaches. Random effects logistic regression models were used and within-pair analyses evaluated confounding effects of familial factors on the associations. RESULTS: There were significant associations between CP and all 6 examined COPCs. After adjusting for shared familial influences in within twin pair analyses, the associations for all COPCs diminished but remained significant. Familial confounding was strongest for the association of CP with fibromyalgia and temporomandibular disorder and smallest for irritable bowel syndrome. CONCLUSIONS: CP and COPCs are highly comorbid. These associations can be partially explained by familial factors. The mechanisms underlying these relationships are likely diverse and multifactorial. Future longitudinal research can help to further elucidate specific genetic and environmental mechanisms and determine potentially causal relationships between CP and its comorbidities.

[Pattern and severity of multimorbidity among patients attending primary care settings in Odisha, India.](#)

Pati S, Swain S, Metsemakers J, Knottnerus JA, van den Akker M.
PLoS One. 2017 Sep 14;12(9):e0183966. doi: 10.1371/journal.pone.0183966. eCollection 2017.

Multimorbidity is increasingly the primary concern of healthcare systems globally with substantial implications for patient outcomes and resource cost. A critical knowledge gap exists as to the magnitude of multimorbidity in primary care practice in low and middle income countries with available information limited to prevalence. In India, primary care forms the bulk of the health care delivery being provided through both public (community health center) and private general practice setting. We undertook a study to identify multimorbidity patterns and relate these patterns to severity among primary care attendees in Odisha state of India. A total of 1649 patients attending 40 primary care facilities were interviewed using a structured multimorbidity assessment questionnaire. Multimorbidity

patterns (dyad and triad) were identified for 21 chronic conditions, functional limitation was assessed as a proxy measure of severity and the mean severity score for each pattern, was determined after adjusting for age. The leading dyads in younger age group i.e. 18-29 years were acid peptic disease with arthritis/ chronic back ache/tuberculosis /chronic lung disease, while older age groups had more frequent combinations of hypertension + arthritis/ chronic lung disease/vision difficulty, and arthritis + chronic back ache. The triad of acid peptic disease + arthritis + chronic backache was common in men in all age groups. Tuberculosis and lung diseases were associated with significantly higher age-adjusted mean severity score (poorer functional ability). Among men, arthritis, chronic backache, chronic lung disease and vision impairment were observed to have highest severity) whereas women reported higher severity for combinations of hypertension, chronic back ache and arthritis. Given the paucity of studies on multimorbidity patterns in low and middle income countries, future studies should seek to assess the reproducibility of our findings in other populations and settings. Another task is the potential implications of different multimorbidity clusters for designing care protocols, as currently the protocols are disease specific, hardly taking comorbidity into account.

[Clinical, psychological features and quality of life of fibromyalgia patients: A cross-sectional study of Chinese sample.](#)

Zhang Y, Liang D, Jiang R, Ji X, Wang Y, Zhu J, Zhang J, Huang F.

Clin Rheumatol. 2017 Oct 13. doi: 10.1007/s10067-017-3872-6. [Epub ahead of print]

This study aimed to determine the clinical, psychological features, and quality of life in Chinese fibromyalgia (FM) patients who fulfilled the American College of Rheumatology (ACR) 2010 FM classification criteria at initial diagnosis. A cross-sectional study was carried out in the Chinese People's Liberation Army (PLA) General Hospital. A hundred and seven Chinese FM patients (86 females, 21 males) were included. Eighty-six patients completed the questionnaires. Descriptive, differences, and correlation analyses were performed. The results showed that Chinese FM patients started their diseases at a median age of 37 years, with a male-to-female ratio of 1:4.1. Most patients were diagnosed about 2 years after symptoms onset. Nearly 60 % (59.81%) patients had less than college education, 58.88% did not have a full-time job, and 41.12% had low-back pain. Out of 86 patients, 58 (67.4%) had anxiety and 75 (87.2%) had depression. FM patients had poor quality of life in each aspect and deficient social support. The level of pain for the past 7 days was strongly correlated with patient global impression of severity (PGI-S; $r = 0.651$, $p < 0.001$) and patient global impression of bother (PGI-B; $r = 0.628$, $p < 0.001$). PGI-B was correlated with seven subscales of short-form health survey (SF-36). The study demonstrated the clinical, psychological features of Chinese patients. The diagnosis was delayed for about 2 years. Most of the patients had anxiety and depression, had poor quality of life, and lacked proper social support. PGI-B might be a simple measurement to evaluate patients' quality of life.

[Military sexual trauma in female veterans is associated with chronic pain conditions.](#)

Cichowski SB, Rogers RG, Clark EA, Murata E, Murata A, Murata G.

Mil Med. 2017 Sep;182(9):e1895-e1899. doi: 10.7205/MILMED-D-16-00393.

INTRODUCTION: Little is known about the impact of MST on chronic pain conditions among female Veterans. The primary objective of this study was to compare the prevalence of chronic pain conditions among U.S. female veterans with a history of military sexual trauma (MST) to those without a history of MST. We anticipated that female Veterans with a history of MST would have higher associations with chronic pain conditions than the female Veterans without a history of MST. MATERIALS AND METHODS: This was a large-scale, retrospective study using the Veterans' Health Administration Corporate Data Warehouse with institutional approval (15-H175). International Classification of Diseases, 9th Revision codes from the outpatient visits, outpatient problem lists, and inpatient discharge diagnoses were used to identify chronic pain diagnoses. Baseline demographic data including date of birth, self-identified race/ethnicity, and body mass index were obtained. Significant findings in the univariate analysis were then placed into a multivariable logistic regression model to

adjust the effect of each predictor for the presence of others. Significance was set at $p < 0.01$ because of multiple comparisons made. RESULTS: For the entire cohort (516,950 women), 28.9% (149,540) were diagnosed with headaches, 18.3% (94,393) with chronic pelvic pain, 14.4% (74,216) with chronic back pain, 10.5% (54,302) with nonspecific joint pain, 9% (48,509) with fibromyalgia, 6.2% (32,037) with generalized abdominal pain, 4.2% (21,911) with irritable bowel syndrome, and 3.2% (16,309) with dyspareunia. Most women had more than one chronic pain diagnosis. At baseline, women with a history of MST were younger (63.3 ± 15.9 vs. 67.4 ± 17.9 years $p < 0.001$), heavier (29.5 ± 6.2 vs. 28.8 ± 6.1 kg/m^2 $p < 0.001$), smokers (49.3 vs. 38.8% $p < 0.001$), and more likely to be non-Hispanic white (56.3 vs. 52.3% $p < 0.001$) than women without a history of MST. Women with a history of MST had more pain diagnoses than those without the history of MST (all $p < 0.001$). The adjusted odds ratio of women with history of MST presenting with any pain condition compared to a women without a history of MST was 1.26 (95% confidence interval 1.24-1.28). In the multivariable model there remained an association between MST and chronic pain conditions including irritable bowel syndrome, chronic pelvic pain, back pain, chronic joint pain, fibromyalgia, dyspareunia, chronic abdominal pain, and headaches after adjusting for baseline differences in age, body mass index, smoking, and ethnicity. Importantly, drug abuse, and overdose were also associated with MST. CONCLUSION: A history of MST is associated with chronic pain diagnoses. Weaknesses of this study are those applicable to analyses of any retrospective database study. Specifically, the data are limited by the accuracy of physician coding and reporting. The strength of this study is that it represents a comprehensive, retrospective evaluation of potential sources for chronic pain within the female veteran population. In summary, we found that female veteran survivors of MST face an increased burden of chronic pain, including a broad range of pain conditions independent of the psychological effects of MST.

[Gender differences in variables associated with sleep quality in chronic tension type headache.](#)

Cigarán-Méndez M, Fernández-Muñoz JJ, Navarro-Pardo E, Jiménez-Antona C, Parás-Bravo P, Alburquerque-Sendín F, Fernández-De-Las-Peñas C.
Women Health. 2017 Sep 18. doi: 10.1080/03630242.2017.1372845. [Epub ahead of print]

We aimed to evaluate gender differences in the relationships between headache features, sleep quality, anxiety, depressive symptoms and burden of headache in 193 patients (73% women) with chronic tension type headache (CTTH). Sleep quality was assessed with the Pittsburgh Sleep Quality Index. Headache features were collected with a four-week diary. The Hospital Anxiety and Depression Scale was used to assess anxiety/depressive symptoms. Headache Disability Inventory was used to evaluate the burden of headache. In men with CTTH, sleep quality was positive correlated with headache frequency ($r = 0.310$; $P = 0.018$), emotional ($r = 0.518$; $P < 0.001$) and physical ($r = 0.468$; $P < 0.001$) burden of headache, and depressive symptoms ($r = 0.564$; $P < 0.001$). In women, positive correlations were observed between sleep quality and headache intensity ($r = 0.282$; $P < 0.001$), headache frequency ($r = 0.195$; $P = 0.021$), emotional burden ($r = 0.249$; $P = 0.004$) and depressive symptoms ($r = 0.382$; $P < 0.001$). The results of stepwise regression analyses revealed that depressive symptoms and emotional burden of headache explained 37.2% of the variance in sleep quality in men ($P < 0.001$), whereas depressive symptoms and headache intensity explained 17.4% of the variance in sleep quality in women ($P < 0.001$) with CTTH. Gender differences associated with poor sleep should be considered for proper management of individuals with CTTH.

[Gender differences in sleep disorders in the US military.](#)

Foster SN, Hansen SL, Capener DC, Matsangas P, Mysliwiec V.
Sleep Health. 2017 Oct;3(5):336-341. doi: 10.1016/j.sleh.2017.07.015.

OBJECTIVES: The purpose of this study is to compare sleep disorders between male and female military personnel. Comorbid behavioral health disorders and chronic pain were also studied in relation to sleep disorders. DESIGN: We conducted a retrospective review of

military personnel who underwent a sleep medicine evaluation and an in-laboratory attended polysomnography. Initial sleep questionnaires, demographics, polysomnographic variables, and comorbid disorders of interest were reviewed and compared for each sex. SETTING: All patients were referred to the Wilford Hall Ambulatory Surgical Center Sleep Disorders Center for evaluation of sleep disturbance. PARTICIPANTS: Our cohort consisted of 209 military personnel with 51.7% men. The cohort was relatively young with a mean age of 34.3 years. Men had a significantly higher body mass index at 29.4 vs 27.3 in women. RESULTS: Insomnia was diagnosed in 72 women and 41 men ($P < .001$), whereas obstructive sleep apnea (OSA) was diagnosed in 92 men and 50 women ($P < .001$). Depression and anxiety were more common in women. Women had an average of 1.76 ± 1.36 comorbid conditions compared with 1.08 ± 1.19 in men. In patients diagnosed with both insomnia and OSA, women were more likely to have post-traumatic stress disorder, depression, and anxiety. Neither the Epworth Sleepiness Scale (12.8 ± 4.88) nor the Insomnia Severity Index (16.9 ± 5.33) differed between sexes. CONCLUSIONS: Gender-related differences in sleep disorders are present in active-duty personnel. Behavioral health disorders were frequent comorbid disorders, and women diagnosed with both insomnia and OSA manifested greater psychiatric comorbidity. The frequent association between sleep and behavioral health disorders in military personnel requires further study.

[Indexes of anxiety, depression and disability in patients with myofascial pain, with and without the additional diagnosis of migraine.](#)

Poluha RL, Silva RS, Conti PCR, Mitirattanakul S, Merrill R.

Rev Dor. 2017 July/Sept; 18(3)

BACKGROUND AND OBJECTIVES: The aim of this study was to compare anxiety, depression and disability indexes in patients with myofascial pain with and without additional diagnosis of migraine. METHODS: We included 203 patients of the Orofacial Pain Clinic of the University of California, Los Angeles, USA. Patients were over 18 years of age, both genders, with a primary diagnosis of myofascial pain. The patients were also evaluated for the presence of migraine according to the criteria of the International Headache Society. The sample was divided into two groups: 120 patients with only myofascial pain (Group 1) and 83 patients with myofascial pain and with an additional diagnosis of migraine (Group 2). The Beck Anxiety Inventory, Beck Depression Inventory and Migraine Disability Assessment questionnaires were applied. The Mann-Whitney test was used to compare the groups at a significance level of 5%. RESULTS: Patients in group 1 presented significantly higher indexes in the Beck Anxiety Inventory ($p=0.005$), Beck Depression Inventory ($p=0.025$) and number of days lost and/or impaired (56.4 days) than those in group 2. The Migraine Disability Assessment Questionnaire scores for groups 1 and 2 were, respectively, 48% and 24.1% for grade I; 9.2% and 3.6% for grade II; 8.2% and 22.9% for grade III; and, 34.7% and 49.4% for grade IV. CONCLUSION: Patients with myofascial pain and migraine had significantly higher anxiety, depression and disability indexes ($p < 0.05$), as well as moderate and severe disability levels considerably higher than those with only myofascial pain.

[Prior mental disorders and subsequent onset of chronic back or neck pain: Findings from 19 countries.](#)

Viana MC, Lim CCW, Pereira FG, Aguilar-Gaxiola S, Alonso J, Bruffaerts R, de Jonge P, Caldas-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, Rabcenko D, Kessler RC, Scott KM.

J Pain. 2017 Oct 11. pii: S1526-5900(17)30732-0. doi: 10.1016/j.jpain.2017.08.011. [Epub ahead of print]

Associations between depression/anxiety and pain are well established, but its directionality is not clear. We examined the associations between temporally prior mental disorders and subsequent self-reported chronic back/neck pain onset, and investigated the variation in the strength of associations by timing of events during the life course, and by gender. Data were from population-based household surveys conducted in 19

countries (n=52,095). Lifetime prevalence and age-of-onset of 16 DSM-IV mental disorders, 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 (12/16) 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: Prior DSM-IV mental disorders 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 to later onset disorders.

CLINICAL STUDIES

[Pain management in rheumatology research, training, and practice.](#)

Borenstein DG, Hassett AL, Pisetsky D.

Clin Exp Rheumatol. 2017 Sep-Oct;35 Suppl 107(5):2-7.

The Pain Management Task Force of the American College of Rheumatology published a report in 2010 highlighting pain management as a fundamental aspect of clinical practice, training and research. In the interim, the consideration of pain as a focus of attention of rheumatologists and rheumatology health professionals has become even more challenging than in 2010 because of the epidemic of opiate addiction and overdose death. The characterisation of categories of pain by mechanism (e.g., inflammation, joint degeneration, abnormalities of central pain processing) can help guide treatment. However, such categorisation can overlook the overlap of these processes and their interaction to create mixed pain states. Further complicating the assessment of pain, outcome measures in rheumatic disease often assess the degree of pain indirectly while concentrating on the quantification of inflammation. Non-inflammatory pain often persists despite treatment, highlighting the need for alternative analgesic therapies. Recommended therapies include acetaminophen, nonsteroidal anti-inflammatory drugs, and stimulators of the pain inhibitory pathway. Each of these non-opioid therapies has incomplete efficacy and potential toxicities that can limit their utility. Non-pharmacologic therapies can show efficacy that rivals or surpasses pharmacologic therapies in the control of pain and improving function in a variety of rheumatic disorders including chronic low back pain and fibromyalgia. A limitation of the use of these therapies is inadequate training and appreciation of their benefits. Furthermore, the supply of trained practitioners to provide non-pharmacological care and support patient efforts for self-management is often limited. Together, these considerations suggest the importance of a renewed effort to implement task force recommendations.

[A somatization comorbidity phenotype impacts response to therapy in rheumatoid arthritis: post-hoc results from the certolizumab pegol phase 4 PREDICT trial.](#)

Curtis JR, Herrem C, Ndlovu 'N, O'Brien C, Yazici Y.

Arthritis Res Ther. 2017 Sep 29;19(1):215. doi: 10.1186/s13075-017-1412-z.

BACKGROUND: Comorbidities may contribute to disease activity and treatment response in rheumatoid arthritis (RA) patients. We defined a somatization comorbidity phenotype (SCP) and examined its influence on response to certolizumab pegol (CZP) using data from the PREDICT trial. METHODS: Patients in PREDICT were randomized to the patient-reported Routine Assessment of Patient Index Data 3 (RAPID3) or physician-based Clinical Disease

Activity Index (CDAI) for treatment response assessment. Post-hoc analyses identified patients with the SCP, which included diagnosis of depression, fibromyalgia/myalgias, and/or use of medications indicated for treatment of depression, anxiety, or neuropathic pain. The effect of the SCP on RAPID3 or CDAI response at week 12 and low disease activity (LDA; Disease Activity Score in 28 joints based on erythrocyte sedimentation rate ≤ 3.2) at week 52, in week-12 responders, was analyzed using non-parametric analysis of covariance (ANCOVA). RESULTS: At baseline, 43% (313/733) of patients met the SCP classification. Patients with the SCP were 9% more likely to withdraw from the trial. American College of Rheumatology 20% (ACR20), ACR50, and ACR70 responses were 5-14% lower among those with the SCP, and 11% more patients reported adverse events (AEs). Patients without SCP in the CDAI arm were twice as likely to achieve LDA at week 52 compared with those with SCP (32% versus 16%). No differentiation by SCP was observed in the RAPID3 arm (pooled result 21.5%). CONCLUSIONS: We operationalized a potentially important somatization comorbidity phenotype in a trial setting that was associated with a substantially lower likelihood of treatment response and a higher frequency of AEs. Including large numbers of patients with this phenotype in RA trials may reduce the measured clinical effectiveness of a new molecule.

[Longitudinal outcomes associated with significant other responses to chronic fatigue and pain.](#)

Schmaling KB, Fales JL, McPherson S.

J Health Psychol. 2017 Sep 1:1359105317731824. doi: 10.1177/1359105317731824.

This study investigated significant others' behavior associated with fatigue, pain, and mental health outcomes among 68 individuals with chronic fatigue (43% also had fibromyalgia) over 18 months. More negative significant others' responses were associated with more pain, poorer physical and mental health, and more fatigue-related symptoms over time. More fibromyalgia tender points covaried with more solicitous significant others' responses over time. Better mental health covaried with more distracting significant others' responses over time. The results are discussed in terms of theoretical models of the role of perceived significant others' responses on patient outcomes and recommendations for future research.

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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