CUTTING EDGE

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This e-newsletter - published by the CPRA to keep the medical-scientific and patient communities abreast of research advances on Chronic Overlapping Pain Conditions (COPCs) - contains abstracts of studies on the epidemiology, pathophysiology and clinical management of COPCs published between June and August 2018. Prior issues are available on our website. To read the CPRA's White Paper, click here . Please direct any questions or comments to the CPRA's Director, Christin Veasley - cveasley@cpralliance.org.

In this Issue...

PATHOPHYSIOLOGY STUDIES

Insights into myalgic encephalomyelitis/chronic fatigue syndrome phenotypes through comprehensive metabolomics.

Nagy-Szakal D, Barupal DK, Lee B, Che X, Williams BL, Kahn EJR, Ukaigwe JE, Bateman L, Klimas NG, Komaroff AL, Levine S, Montoya JG, Peterson DL, Levin B, Hornig M, Fiehn O, Lipkin WI.

Sci Rep. 2018 Jul 3;8(1):10056. doi: 10.1038/s41598-018-28477-9.

The pathogenesis of ME/CFS, a disease characterized by fatigue, cognitive dysfunction, sleep disturbances, orthostatic intolerance, fever, irritable bowel syndrome (IBS), and lymphadenopathy, is poorly understood. We report biomarker discovery and topological analysis of plasma metabolomic, fecal bacterial metagenomic, and clinical data from 50 ME/CFS patients and 50 healthy controls. We confirm reports of altered plasma levels of choline, carnitine and complex lipid metabolites and demonstrate that patients with ME/CFS and IBS have increased plasma levels of ceramide. Integration of fecal metagenomic and plasma metabolomic data resulted in a stronger predictive model of ME/CFS (cross-validated AUC=0.836) than either metagenomic (cross-validated AUC=0.745) or metabolomic (cross-validated AUC=0.820) analysis alone. Our findings may provide insights into the pathogenesis of ME/CFS and its subtypes and suggest pathways for the development of diagnostic and therapeutic strategies.

Linaclotide attenuates visceral organ crosstalk: Role of guanylate cyclase-c activation in reversing bladder-colon cross-sensitization.
Mohammadi EN, Ligon CO, Silos-Santiago A, Ge P, Kurtz C, Higgins C, Hannig G, Greenwood-Van Meerverld B.
J Pharmacol Exp Ther. 2018 Aug;366(2):274-281. doi: 10.1124/jpet.118.248567.

Bladder pain syndrome (BPS) is poorly understood; however, there is a female predominance and comorbidity with irritable bowel syndrome(IBS). Here we test the hypothesis that linaclotide, a guanylate cyclase-C (GC-C) agonist approved for the treatment of IBS with constipation (IBS-C), may represent a novel therapeutic for BPS acting through a mechanism involving an inhibition of visceral organ cross-sensitization. We showed previously that infusion of dilute protamine sulfate (PS) into the bladder increased sensitivity and permeability in the bladder and colon. PS was infused into the bladder of female rats; sensitivity was assessed via application of von Frey filaments applied to the suprapubic area and the frequency of withdrawal responses was recorded. Colonic sensitivity was measured via visceromotor behavioral response to graded pressures of colorectal distension (CRD). Permeability was measured in vitro via transepithelial electrical resistance (TEER) and conductance (G). Linaclotide (3 μg/kg, p.o.) or vehicle was administered daily for 7 days prior to experiments. Rats treated with PS bladder infusion exhibited visceral hyperalgesia, as shown by a significantly higher response frequency to individual von Frey filaments and increased behavioral responses to CRD. Linaclotide attenuated bladder and colonic hyperalgesia to control levels. PS infusion into the bladder increased bladder and colon permeability measured as a decrease in TEER and increased G. Linaclotide significantly inhibited PS-induced colonic hyperpermeability while having no effect on bladder hyperpermeability. Our findings suggest a novel treatment paradigm for GC-C agonism in IBS-C and BPS mediated through a mechanism involving visceral organ crosstalk.

TRP channels as potential targets for sex-related differences in migraine pain.
Artero-Morales M, Gonzalez-Rodriguez S, Ferrer-Montiel A.
Front Mol Biosci. 2018 Aug 14;5:73. doi: 10.3389/fmolb.2018.00073. eCollection 2018.

Chronic pain is one of the most debilitating human diseases and represents a social and economic burden for our society. Great efforts are being made to understand the molecular and cellular mechanisms underlying the pathophysiology of pain transduction. It is particularly noteworthy that some types of chronic pain, such as migraine, display a remarkable sex dimorphism, being up to three times more prevalent in women than in men. This gender prevalence in migraine appears to be related to sex differences arising from both gonadal and genetic factors. Indeed, the functionality of the somatosensory, immune, and endothelial systems seems modulated by sex hormones, as well as by X-linked genes differentially expressed during development. Here, we review the current data on the modulation of the somatosensory system functionality by gonadal hormones. Although this is still an area that requires intense investigation, there is evidence suggesting a direct regulation of nociceptor activity by sex hormones at the transcriptional, translational, and functional levels. Data are being accumulated on the effect of sex hormones on TRP channels such as TRPV1 that make pivotal contributions to nociceptor excitability and sensitization in migraine and other chronic pain syndromes. These data suggest that modulation of TRP channels' expression and/or activity by gonadal hormones provide novel pathways for drug intervention that may be useful for targeting the sex dimorphism observed in migraine.

Sex and race differences in pain sensitization among patients with chronic low back pain.
Meints SM, Wang V, Edwards RR.
J Pain. 2018 Jul 17. pii: S1526-5900(18)30332-8. doi: 10.1016/j.jpain.2018.07.001.

Growing evidence suggests that chronic low back pain (CLBP) is associated with pain sensitization, and that there are sex and race disparities in CLBP. Given the sex and race differences in pain sensitization, this has been hypothesized as a mechanism contributing to

the sex and race disparities in CLBP. This study examined sex and race differences in pain sensitization among patients with CLBP, as well as the role of catastrophizing as a potential mediator of those differences. The study found that compared with men, women required less pressure to produce deep muscle pain and rated mechanical punctate pain as more painful. Compared with non-Hispanic white patients, black patients demonstrated greater pain sensitivity for measures of deep muscle hyperalgesia and mechanical punctate pain. Furthermore, catastrophizing partially mediated the race differences in deep muscle pain such that black participants endorsed greater pain catastrophizing, which partially accounted for their increased sensitivity to, and temporal summation of, deep muscle pain. Taken together, these results support the need to further examine the role of catastrophizing and pain sensitization in the context of sex and race disparities in the experience of CLBP. PERSPECTIVE: This study identifies sex and race differences in pain sensitization among patients with CLBP. Further, it recognizes the role of catastrophizing as a contributor to such race differences. More research is needed to further dissect these complex relationships.

An observational study of headaches in children and adolescents with functional abdominal pain: Relationship to mucosal inflammation and gastrointestinal and somatic symptoms.

Friesen C, Singh M, Singh V, Schurman JV.

Medicine (Baltimore). 2018 Jul;97(30):e11395. doi: 10.1097/MD.0000000000011395.

Headaches and abdominal pain are among the most common pediatric pain conditions. Mast cells have been implicated in the pathophysiology of migraines, as well as functional dyspepsia (FD) and irritable bowel syndrome (IBS). The primary aims of the current study were to assess headache prevalence in patients with FD and to assess the association between headaches and mucosal mast cells and eosinophils. An additional aim was to explore associations of headache with other symptoms. We conducted a cross-sectional retrospective chart review of 235 consecutive patients with chronic abdominal pain. All patients had completed a standardized questionnaire as part of their routine clinical evaluation. Both gastrointestinal and non-gastrointestinal somatic symptoms were included in the analysis. All patients diagnosed with FD had undergone upper endoscopy with biopsies obtained from the gastric antrum and duodenum and these specimens were utilized to assess eosinophil and mast cell densities, respectively. Overall, 86% of patients fulfilled Rome IV criteria for FD. Headache was reported by 73.8% of FD patients versus 45.2% of non-FD patients (p=0.001). Duodenal mast cell densities were significantly increased in those reporting headaches. Headache was not associated with any specific gastrointestinal symptoms but was associated with a wide array of non-gastrointestinal symptoms including fatigue, dizziness, muscle pain, joint pain, and chest pain. Headaches are common in children and adolescents with abdominal pain and, utilizing Rome IV criteria, are specifically associated with FD. In patients with FD, headaches are associated with increased duodenal mast cell density and a variety of somatic symptoms, all of which are possibly the result of mast cell activation.

Monoamine system disruption induces functional somatic syndromes associated symptomatology in mice.

Nagakura Y, Ohsaka N, Azuma R, Takahashi S, Takebayashi Y, Kawasaki S, Murae S, Miwa M, Saito H.

Physiol Behav. 2018 Oct 1;194:505-514. doi: 10.1016/j.physbeh.2018.07.007.

Functional somatic syndromes (FSS), a clinical condition manifesting a variety of unexplained somatic symptoms, has been proposed as an inclusive nosology encompassing individual syndromes such as fibromyalgia syndrome and irritable bowel syndrome. Accumulating evidence suggests that disturbance of the endogenous monoamine system could be involved in the aetiology of FSS. Therefore, the purpose of present study was to investigate whether the disturbance of the monoamine system would cause FSS-associated symptomatology in mice. The optimal dose of reserpine, an inducer of endogenous

monoamines reduction, was first explored in mice. General body condition (body weight, rectal temperature, and ptosis) and FSS-associated symptomatology (paw withdrawal threshold, small intestinal transit, and locomotor activity) were measured. The concentration of monoamines was measured in central and peripheral tissues. Mice dosed with reserpine (0.25 mg/kg s.c., once daily for 3 consecutive days) exhibited a decrease in paw withdrawal threshold, delay in small intestinal transit, and reduction of locomotor activity without deterioration of general body condition on day 5 after the first reserpine injection. The concentration of monoamines was decreased in the central nervous system and skeletal muscle, but not in the small intestine. A reserpine dose of 0.5 mg/kg or more caused deterioration of general body condition. In conclusion, the optimal protocol of reserpine treatment for inducing pain symptom without deterioration of general physical condition is 0.25 mg/kg s.c., once daily for 3 consecutive days in mice. This protocol causes not only pain but also FSS-associated symptomatology which are associated with disruption of the endogenous monoamine system. The reserpine-treated animal may be useful for the research of not only fibromyalgia syndrome but also FSS, especially for the research focusing on the hypothesis that FSS is associated with the disturbance of endogenous monoamine system.

The "Biology-First" Hypothesis: Functional disorders may begin and end with biology-A scoping review.
Enck P, Mazurak N.
Neurogastroenterol Motil. 2018 Jun 28:e13394. doi: 10.1111/nmo.13394.

While it is generally accepted that gastrointestinal infections can cause functional disturbances in the upper and lower gastrointestinal tract-known as postinfectious irritable bowel syndrome (PI-IBS) and functional dyspepsia (PI-FD)-it has still not been widely recognized that such an infection can also initiate functional non-intestinal diseases, and that non-intestinal infections can provoke both intestinal and non-intestinal functional disturbances. We conducted a scoping review of the respective literature and-on the basis of these data-hypothesize that medically unexplained functional symptoms and syndromes following an infection may have a biological (genetic, endocrine, microbiological) origin, and that psychological and social factors, which may contribute to the disease "phenotype," are secondary to this biological cause. If this holds true, then the search for psychological and social theories and factors to explain why one patient develops a chronic functional disorder while another does not is-at least for postinfectious states-misleading and detracts from exploring and identifying the true origins of these essentially biological disorders. The biopsychosocial model may, as the term implies, always begin with biology, also for functional (somatoform) disorders.

EPIDEMIOLOGY STUDIES

Pain and self-rated health among middle-aged and older Canadians: an analysis of the Canadian community health survey-healthy aging.
Chireh B, D'Arcy C.
BMC Public Health. 2018 Aug 13;18(1):1006. doi: 10.1186/s12889-018-5912-9.

BACKGROUND: Pain is an important health problem adversely affecting functionality and quality of life. Though self- rated health (SRH) is a major predictor of mortality, its relationship with pain is not well understood. We explore 1) how pain and age interact to influence SRH, and 2) provincial variations in SRH across Canada. METHODS: We analyzed cross-sectional data from Statistics Canada's Canadian Community Health Survey-Healthy Aging (n-30,685), which targeted those 45 years and older and was conducted from 2008 to 12-01 to 2009-11-30. The response rate was 74.4%. The topics covered included socio-demographics, well-being and chronic diseases. We performed both bivariate and multivariate analyses between each predictor and SRH; unadjusted and adjusted odds ratios and 95% confidence intervals are reported. Two-level logistic regression mixed model was

used to account for provincial differences. An intraclass correlation coefficient was also computed. RESULTS: Slightly more than half of respondents (56.40%) were female. In bivariate analyses, those experiencing pain had an odds ratio of 0.20. Which means that the odds of reporting good self-rated health are 4 to 5 times lower for those with pain, compare to the odds of reporting good self-rated health among those without pain (p<0.001). In multivariate analyses the highly educated, female gender, the never married or single and households with high yearly income were predictors of good health (p<0.001). Those who reported depressive symptoms, the lonely, the obese, daily smokers and/or the stressed were less likely to rate their health as good (p<0.001). The influence of pain on SRH was stronger among younger age groups (45-54 years) compared to older age groups (75-84 years, with an odds ration of 3.53 [p<0.001] versus 3.14 [p<0.001]). CONCLUSIONS: Pain, among other determinants, is associated with SRH. Individuals in rating their health may consider a variety of factors, some of which may not be apparent to health providers. We found that those who reported depressive symptoms, were daily smokers, the obese, the lonely, and/or having a stressful life were less likely to rate their health as good. No significant provincial variations in SRH in Canada was observed in this study.

Prevalence of self-reported chronic pain among adolescents: evidence from 42 countries and regions.
Gobina I, Villberg J, Valimaa R, Tynjala J, Whitehead R, Cosma A, Brooks F, Cavallo F, Ng K, Gaspar de Matos M, Villerusa A.
Eur J Pain. 2018 Aug 11. doi: 10.1002/ejp.1306.

BACKGROUND: Reports of the overall chronic pain prevalence and its associated demographic characteristics among adolescents vary greatly across existing studies. Using internationally comparable data, the present study investigates age, sex and country-level effects in the prevalence of chronic single-site and multi-site pain among adolescents during the last six months preceding the survey. METHODS: Data (n = 214,283) from the 2013/2014 Health Behaviour in School-aged Children (HBSC) study were used including nationally representative samples of 11-, 13- and 15-year-olds from general schools in 42 participating countries. Multilevel logistic regression analyses were used. RESULTS: The overall proportion of adolescents reporting chronic weekly pain during the last six months was high (44.2%). On average, in comparison with different specific localized types of single-site pain the prevalence of multi-site pain was more common varying from 13.2% in Armenia to 33.8% in Israel. Adolescent age and sex were strong predictors for reporting pain, but significantly different demographic patterns were found in the cross-country analyses. The most consistent findings indicate that multi-site pain was more prevalent among girls across all countries and that the prevalence increased with age. CONCLUSIONS: Internationally comparable data suggest that self-reported chronic pain among adolescents is highly prevalent, but different age and sex patterns across countries exist. Adolescents with chronic pain is not a homogenous group. Chronic pain co-occurrence and differences in chronic pain characteristics should be addressed in both clinical and public health practice for effective adolescent chronic pain management and prevention.

The trajectories of the number of pain sites and their associated factors in older adults: Results from the Korean Longitudinal Study of Ageing.
Lee J, Jang SN, Cho SI.
Gerontology. 2018 Jul 3:1-9. doi: 10.1159/000490051.

BACKGROUND: The aging of the population will result in an increase in demand for pain management. Pain adversely affects physical and mental functioning in older adults and accounts for a considerable proportion of all medical expenses. OBJECTIVES: This study was performed to investigate the patterns of changes in the trajectories of the number of pain sites in older adults and the factors that affect these patterns according to gender. METHODS: Data were extracted for subjects that participated in the Korean Longitudinal Study of Ageing from 2006 to 2014. The study population consisted of 2,839 individuals (1,190

men and 1,649 women) ≥60 years old. A group-based trajectory model was used to determine the optimal number of subgroups and the trajectories of the number of pain sites according to gender. A multinomial regression analysis was conducted to identify factors that affect the probability of inclusion in each trajectory group. RESULTS: The trajectories of the number of pain sites were consistent in both genders. Almost all women had one or more pain symptom, and a greater number of pain sites than men. Older age, longest-duration occupation requiring manual labor, lack of physical activity, depressive symptoms, and poor self-rated health were associated with a greater number of pain sites in both genders. A lower level of education, married status, and experience of injury were associated with the number of pain sites in men but not in women, while household income and chronic diseases were associated with the number of pain sites only in women. CONCLUSIONS: The pain status at the early stage is predictive of future pain. In this study, we identified gender differences in the trends of the number of pain sites and associated factors. Further comprehensive studies on pain intensity and duration are required.

Identifying natural subgroups of migraine based on comorbidity and concomitant condition profiles: Results of the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study.
Lipton RB, Fanning KM, Buse DC, Martin VT, Reed ML, Manack Adams A, Goadsby PJ.
Headache. 2018 Jul;58(7):933-947. doi: 10.1111/head.13342.

OBJECTIVE: To identify natural subgroups of people with migraine based on profiles of comorbidities and concomitant conditions, hereafter referred to as comorbidities. BACKGROUND: Migraine is a heterogeneous disease. Identifying natural subgroups (endophenotypes) may facilitate biological and genetic characterization and the development of personalized treatment. METHODS: The Chronic Migraine Epidemiology and Outcomes Study is a prospective web-based survey study designed to characterize the course of migraine and related comorbidities in a systematic US sample of people with migraine. Respondents were asked if they ever had a specific comorbidity and, if present, whether the comorbidity was confirmed/diagnosed by a "doctor"; 62 comorbidities were available for analysis. Latent class analysis (LCA) modeling determined the optimal number of classes and a parsimonious set of comorbidities. RESULTS: Of the 12,810 respondents with migraine, 11,837 reported one or more comorbidity and were included in this analysis. After statistical analysis and clinical judgment reduced the number of comorbidities, we selected an 8-class model based on 22 comorbidities. Each class had a distinct pattern summarized as follows: Class 1, Most Comorbidities; Class 2, Respiratory/Psychiatric; Class 3, Respiratory/Pain; Class 4, Respiratory; Class 5, Psychiatric; Class 6, Cardiovascular; Class 7, Pain; Class 8, Fewest Comorbidities. The distribution of individuals across models was variable, with one-third of respondents in Class 8 (Fewest Comorbidities) and <10% in Class 1 (Most Comorbidities). Demographic and headache characteristics, not used in assigning class membership, varied across classes. For example, comparing Class 1 (Most Comorbidities) and Class 8 (Fewest Comorbidities), Class 1 had a greater proportion of individuals with severe disability (Migraine Disability Assessment grade IV; 48.1% vs 22.3% of overall individuals) and higher rates of allodynia (67.6% vs 47.0%), medication overuse (36.4% vs 15.0%), chronic migraine (23.1% vs 9.1%), and aura (40.1% vs 28.8%). CONCLUSIONS: LCA modeling identified 8 natural subgroups of persons with migraine based on comorbidity profiles. These classes show differences in demographic and headache features not used to form the classes. Subsequent research will assess prognostic and biologic differences among the classes.

Systemic diseases and other painful conditions in patients with temporomandibular disorders and migraine.
Contreras EFR, Fenandes G, Ongaro PCJ, Campi LB, Goncalves DAG.
Braz Oral Res. 2018 Jul 23;32:e77. doi: 10.1590/1807-3107BOR-2018.vol32.0077.

Temporomandibular disorders (TMD) are a highly prevalent, painful musculoskeletal condition affecting the masticatory system, and are frequently associated with migraines (M) and other diseases. This study aimed to investigate the association between painful TMD and

M with other painful conditions and systemic diseases, such as cervicalgia, body pain (BP), ear-nose-throat disorders, musculoskeletal disorders, diabetes, cardiopulmonary diseases and gastritis/peptic ulcer. METHODS: This was a cross-sectional study conducted in a sample of 352 individuals. Participants were stratified into three groups according to the presence of painful TMD and M: controls [individuals free of TMD and any headache (HA)]; TMD only (presence of painful TMD, but free of any HA); and TMD+M (presence of painful TMD and M). TMD was classified according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) - Axis I. Nonspecific physical symptoms (NSPS) were assessed by RDC/TMD - Axis II. The International Classification of Headache Disorders - II criteria, second edition, were applied to identify and classify primary HA. Other painful conditions and systemic diseases were assessed by volunteers' self-report. The prevalence of all assessed conditions was higher in the TMD+M group. Multiple regression models showed that cervicalgia was associated with the TMD only group ($p<0.05$), whereas gender($p<0.05$), cervicalgia ($p<0.05$), BP ($p<0.05$) and NSPS ($p<0.05$) were significantly associated with the TMD+M group. Our results suggest that individuals with a comorbidity (TMD associated with M) have a more severe condition than those presenting only painful TMD.

Tinnitus as a comorbidity to temporomandibular disorders - a systematic review.
Skog C, Fjellner J, Ekberg E, Haggman-Henrikson B.
J Oral Rehabil. 2018 Aug 20. doi: 10.1111/joor.12710.

The aim of this systematic review was to evaluate the prevalence of tinnitus in patients with temporomandibular disorders (TMD) and the possible effects of TMD treatment on tinnitus symptoms. A search of the PubMed, Web of Science, and Cochrane databases from inception of each database up to January 2017 found 222 articles. After independent screening of abstracts by two of the authors, we assessed 46 articles in full text. The inclusion and exclusion criteria reduced these to 25 articles of which 22 studies reported prevalence based on 13,358 patients and 33,876 controls, and eight studies reported effect of TMD treatment on tinnitus based on 536 patients and 18 controls. The prevalence of tinnitus in patients with TMD varied from 3.7% to 70% (median 42.3%) whereas the prevalence in control groups without TMD varied between 1.7% and 26% (median 12%). The eight treatment studies, indicated that treatment of TMD symptoms may have a beneficial effect on severity of tinnitus. However, only one treatment study included a control group, meaning that the overall level of evidence is low. The finding that tinnitus is more common in patients with TMD means that it can be regarded as a comorbidity to TMD. However, in view of the lack of evidence currently available, further well-designed and randomized studies with control groups are needed to investigate whether possible mechanisms common to tinnitus and TMD do exist and whether TMD treatment can be justified to try to alleviate tinnitus in patients with TMD and comorbidity of tinnitus. This article is protected by copyright. All rights reserved.

Prevalence of temporomandibular disorders in patients with Hashimoto thyroiditis.
Grozdinska A, Hofmann E, Schmid M, Hirschfelder U.
J Orofac Orthop. 2018 Jul;79(4):277-288. doi: 10.1007/s00056-018-0140-6.

OBJECTIVES: Autoimmune thyroid disease (AITD), also known as Hashimoto thyroiditis (HT), is a degenerative inflammatory disease with high prevalence among women and has been associated with fibromyalgia and widespread chronic pain. The goal was to determine the frequency of temporomandibular disorders (TMD) in patients with HT. METHODS: In all, 119 women (age 19-60 years) were divided into a study (52 women diagnosed with HT) and a control (67 healthy individuals, of which 15 were excluded) group. Serum concentrations of thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), anti-thyroglobulin (Tg) and anti-thyroid peroxidase (TPO) antibody levels were measured. The temporomandibular jaw and muscles were examined using the German Society of Functional Diagnostics and Therapy guidelines. The Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) was used to assess TMD. Standardized questionnaires, incorporating epidemiological criteria, state and treatment of the thyroid

disease, Helkimo Index (HI), and Fonseca Anamnestic Index (FAI), were filled out by all patients. RESULTS: The two groups did not differ in terms of demographic parameters or mandibular jaw mobility. Significantly higher levels of anti-TPO and anti-Tg were attested in all subjects of the HT group. Markedly elevated prevalence of TMD was found in the HT group. Muscle painand stiffness were found in 45 (86.5%) subjects of the HT group ($p<0.001$), of whom 33 (63.4%) also had disc displacement with reposition ($p<0.001$). Whereas 50% of the control group showed no TMD symptoms, all subjects in the HT group had symptoms. CONCLUSIONS: A significantly elevated prevalence of TMD was found in patients with HT. Thus, patients with TMD who do not respond to therapy should be referred for thyroid diagnostic workup.

Risk of developing comorbidities among women with endometriosis: A retrospective matched cohort study.
Surrey ES, Soliman AM, Johnson SJ, Davis M, Castelli-Haley J, Snabes MC.
J Womens Health (Larchmt). 2018 Aug 2. doi: 10.1089/jwh.2017.6432.

BACKGROUND: Endometriosis has been associated with higher rates of various chronic conditions, but its epidemiological data are fragmented and dated. We sought to compare the incidence of developing commonly occurring comorbidities among patients with and without endometriosis in a large, contemporary patient cohort that reflects real-world clinical practice. MATERIALS AND METHODS: A cohort of women aged 18-49 with incident endometriosis was extracted from the 2006-2015 de-identified Clinformatics® DataMart commercial insurance claims database (OptumInsight, Eden Prairie, MN). Endometriosis was identified by International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis code 617.x on ≥1 inpatient or emergency department claim or ≥2 outpatient claims. Nonendometriosis control patients were exactly matched 4:1 to cases based on state, insurance plan type, and age (±1 year). Based on a literature review and expert consultation, 22 comorbidities were identified for analysis. The risk of developing a comorbidity post-index date was analyzed with stratified Cox proportional hazards models. RESULTS: There were 26,961 cases and 107,844 controls. Mean age was 36 years. The adjusted risk of developing a comorbid condition among endometriosis cases was statistically significantly higher than the matched controls for all 22 comorbidities ($p<0.001$) and was at least twice as large for nine comorbidities (infertility/subfertility, ovarian cyst, uterine fibroids, pelvic inflammatory disorder, interstitial cystitis, irritable bowel syndrome, constipation/dyschezia, ovarian cancer, and endometrial cancer). CONCLUSION: The incidence of developing many comorbidities was significantly higher among endometriosis patients compared with matched women without endometriosis. Additional research is needed to establish the implications for healthcare resource use.

Fibromyalgia in migraine: a retrospective cohort study.
Whealy M, Nanda S, Vincent A, Mandrekar J, Cutrer FM.
J Headache Pain. 2018 Jul 31;19(1):61. doi: 10.1186/s10194-018-0892-9.

BACKGROUND: Migraine is a common and disabling disorder. Fibromyalgia has been shown to be commonly comorbid in patients with migraine and can intensify disability. The aim of this study was to determine if patients with co-morbid fibromyalgia and migraine report more depressive symptoms, have more headache related disability, or report higher intensity of headache as compared to patients with migraine only. Cases of comorbid fibromyalgia and migraine were identified using a prospectively maintained headache database at Mayo Clinic Rochester. One-hundred and fifty seven cases and 471 controls were identified using this database and the Mayo Clinic electronic medical record. FINDINGS: Depressive symptoms as assessed by PHQ-9, intensity of headache, and migraine related disability as assessed by MIDAS were primary measures used to compare migraine patients with comorbid fibromyalgia versus those without. Patients with comorbid fibromyalgia reported significantly higher PHQ-9 scores (OR 1.08, $p<0.0001$) and headache intensity scores (OR 1.149, $p=0.007$). There was no significant difference in migraine related disability (OR 1.002, $p=0.075$). Patients with fibromyalgia were more

likely to score in a higher category of depression severity (OR 1.467, p<0.0001) and more likely to score in a higher category of migraine related disability (OR 1.23, p=0.004). CONCLUSION: Patients with comorbid fibromyalgia and migraine report more depressive symptoms, higher headache intensity, and are more likely to have severe headache related disability as compared to controls with fibromyalgia. Clinicians who care for patients with migraine may consider screening for comorbid fibromyalgia particularly in patients with moderate to severe depressive symptoms, high headache intensity and/or high headache related disability. This is the first matched study to look at these characteristics, and it replicates previous findings from unmatched studies.

Concomitant fibromyalgia complicating chronic inflammatory arthritis: a systematic review and meta-analysis.
Duffield SJ, Miller N, Zhao S, Goodson NJ.
Rheumatology (Oxford). 2018 Aug 1;57(8):1453-1460. doi: 10.1093/rheumatology/key112.

OBJECTIVES: This systematic review and meta-analysis will describe the prevalence of concomitant FM in adults with inflammatory arthritis and quantify the impact of FM on DAS. METHODS: Cochrane library, MEDLINE, Psychinfo, PubMed, Scopus and Web of Science were searched using key terms and predefined exclusion criteria. As appropriate, proportional and pairwise meta-analysis methods were used to pool results. RESULTS: Forty articles were identified. In RA the prevalence of FM ranged from 4.9 to 52.4% (21% pooled). In axSpA the range was 4.11-25.2% (13% pooled in AS only). In PsA the range was 9.6-27.2% (18% pooled). The presence of concomitant FM was related to higher DAS in patients with RA and AS (DAS28 mean difference 1.24, 95% CI: 1.10, 1.37 in RA; BASDAI mean difference 2.22, 95% CI: 1.86, 2.58 in AS). Concomitant FM was also associated with higher DAS in existing PsA studies. Self-reported, rather than objective, components of DAS appear to be raised in the presence of FM (e.g. tender joint count and Visual Analogue Scale (VAS) pain scores). CONCLUSION: FM is common in RA, AxSpA and PsA. Comorbid FM appears to amplify DAS and could therefore influence management of these rheumatic conditions.

Functional GI disorders are prevalent among pediatric patients with persistent asthma.
Colman RJ, Rosario NBS, Gutierrez Bonilla A, Benavidez Alvarez G, Benavidez Alvarez J, Uy VP, Pina PR, Rubin DH.
J Dig Dis. 2018 Aug 9. doi: 10.1111/1751-2980.12653.

AIM: Functional gastrointestinal disorders (such as functional abdominal pain, irritable bowel syndrome and functional dyspepsia) are a common cause of chronic GI symptoms in children. Prior studies demonstrated a high comorbidity of functional GI disorders (FGIDs) among patients with asthma. However, data exploring specific disease characteristics within the US populations are scarce. This study aimed to assess the prevalence and comorbidities of FGIDs among pediatric asthma patients at a university-affiliated urban community hospital. METHODS: This prospective, cross-sectional study assessed FGID prevalence, asthma control, and symptoms of anxiety among pediatric patients with persistent asthma. The validated diagnostic pediatric ROME-III questionnaire was used to assess FGIDs. The Asthma Control Test assessed asthma control. The Beck Anxiety Index assessed symptoms of anxiety. Higher BAI scores corresponded with increased anxiety. RESULTS: Among 110 enrolled patients, eighteen (16%) met diagnostic criteria for FGIDs, 10 of which were consistent with a functional abdominal pain disorder. Patients with FGIDs had a significantly lower mean ACT score (M=11.5±4.9) compared to patients without FGIDs (M=14.8±5.3) (P=0.03;Cohen's d=0.6). FGID patients had significantly higher anxiety scores (M=34±11) than those without FGIDs (M=14±13)(P<0.01). Asthma control predicted presence of an FGID (OR=0.9 95%CI[0.80-0.99];P=0.03). However, after adjusting for anxiety, asthma control no longer predicted FGID presence (aOR=0.9 95%CI[0.83-1.05]). CONCLUSIONS: This study suggests a high prevalence of functional GI disorders among patients with persistent asthma. Moreover, patients with FGIDs had poor asthma control and increased anxiety. Clinicians should consider FGIDs in patients with poor asthma control and assess for anxiety as indicated.

The proportion of women with central sensitivity syndrome in gynecology outpatient clinics.
Vij M, Davies A, Dua A, Freeman R.
Int Urogynecol J. 2018 Jul 4. doi: 10.1007/s00192-018-3709-0.

INTRODUCTION AND HYPOTHESIS: Patients in gynecology outpatient clinics (GOPDs) may present with symptoms that do not correlate well with the observed pathology and are usually labelled as having a functional disorder or medically unexplained symptoms (MUS). Underlying central sensitivity syndrome (CSS) with central sensitization (CS) as a potential mechanism may be responsible for some of their symptoms. The aim of this study is to identify the proportion of women with central sensitivity syndrome attending GOPDs. METHODS: This was a prospective study. All women attending a GOPD included in the study were asked to complete a validated Central Sensitization Inventory (CSI). The responses were graded on a Likert scale from 0 (never) to 4 (always). The total score ranges from 0 to 100. For screening purposes, a single CSI cutoff score of 40 was used to identify the group of women who may have central sensitization syndrome. RESULTS: Three hundred twenty-six women participated in the study. Overall, 123 (37%) women achieved a score above 40. This could be interpreted as these patients having increased risk of underlying central sensitization. Of these, 43 had a previously confirmed diagnosis of migraine, 55 (44%) depression, 39 (31.7%) anxiety, 11 fibromyalgia (FM), 34 irritable bowel syndrome (IBS) and 16 chronic fatigue syndrome (CFS/ME). CONCLUSIONS: Managing patients and their expectations in gynecological outpatient departments when symptoms are inconsistent with observable pathological findings is challenging. This is further complicated when patients have a concomitant central sensitivity syndrome, which can also influence the surgical outcome. Identifying these patients is a key factor for appropriate management.

Painful bladder symptoms related to somatic syndromes in a convenience sample of community women with overactive bladder symptoms.
Kowalik CG, Cohn JA, Delpe S, Kaufman MR, Wein A, Dmochowski RR, Reynolds WS.
J Urol. 2018 Jul 11. pii: S0022-5347(18)43483-0. doi: 10.1016/j.juro.2018.06.070.

PURPOSE: Herein we aim to investigate the relationship between painful bladder filling and urinary urgency with somatic and chronic pain symptoms in women with overactive bladder (OAB) without an interstitial cystitis/bladder pain syndrome (IC/BPS) diagnosis. MATERIALS AND METHODS: Women meeting OAB criteria based on symptoms were recruited through the community (n=183, 83.9%) or Urology clinic (n=35, 16.1%) to complete validated questionnaires assessing urinary symptoms, somatic symptoms, and pain syndromes. Participants were categorized into 3 groups, (1) Neither (2) Either or (3) Both, based on their report of painful urinary urgency and/or painful bladder filling. Multivariable regression analyses were performed to determine factors predictive of having either or both painful urgency and/or painful filling. RESULTS: Of 218 women with OAB, 46% (n=101) had neither painful bladder filling nor urinary urgency, 43% (n=94) had either, and 11% (n=23) had both. Controlling for age, women with either or both urologic pain symptoms were more likely to have irritable bowel syndrome, chronic pelvic pain, and temporomandibular disorder compared to women in the neither group. Additionally, these women had higher pain intensity and somatic symptoms scores than women with neither symptom. CONCLUSIONS: The majority of women with OAB, without a diagnosis of IC/BPS, reported either painful urgency, painful filling, or both. Experiencing painful urgency and/or filling was associated with increased somatic symptom burden and pain intensity. These findings support the hypothesis that OAB and IC/BPS diagnoses may represent a continuum of bladder hypersensitivity.

Risk of urinary tract carcinoma among subjects with bladder pain syndrome/interstitial cystitis: A nationwide population-based study.
Wu MP, Luo HL, Weng SF, Ho CH, Chancellor MB, Chuang YC.
Biomed Res Int. 2018 Jun 28;2018:7495081. doi: 10.1155/2018/7495081. eCollection 2018.

OBJECTIVE: To investigate the subsequent risks of urinary tract cancers among individuals with bladder pain syndrome/interstitial cystitis (BPS/IC), and gender differences, as well as the effect of associated comorbidity using a population-based administrative database in Taiwan. PATIENTS AND METHODS: BPS/IC subjects (10192) and their age- and sex-matched non-BPS/IC control subjects (30576), who had no previous upper urinary tract cancer (UUC), bladder cancer (BC), and prostate cancer (PC), subsequently developed these disorders from the recruited date between 2002 and 2008 and the end of follow-up 2011. A Cox proportional hazards regression model was constructed to estimate the risk of subsequent UUC, BC, and PC following a diagnosis of IC/BPS. The effect of associated comorbidities was measured by Charlson Comorbidity Index (CCI). The risk of outcomes was assessed with Kaplan-Meier curves. RESULTS: In the BPS/IC subjects, 37 (0.36%) received a diagnosis of BC, and 22 (0.22%) received a diagnosis of UUC; both were significantly higher than the control group, 19 (0.06%) for BC and 30 (0.10%) for UUC. Cox proportional analysis revealed that the adjusted HR for BC and UUC during the follow-up period for patients with IC/BPS was 5.44 (95% CI: 3.10-9.54) and 1.97 (95% CI: 1.13-3.45) than that of comparison subjects. The HRs went up to 5.66 (95% CI: 3.21-9.99) and 2.01 (95% CI: 1.14-3.55) after adjusted by Comorbidity Index (CCI). The male BPS/IC patients have a higher adjusted HR for BC; however, female patients have a higher adjusted HR for both BC and UUC. The adjusted HR for PC has no difference between BPS/IC and control group. CONCLUSION: Patients with BPS/IC are at risk of developing BC in both males and females, and UUC in females. This result reminds physicians to evaluate the potential risk of subsequent development of BC and UUC among individuals with BPS/IC.

The impact of fibromyalgia syndrome and the role of comorbidity with mood and post-traumatic stress disorder in worsening the quality of life.
Carta MG, Moro MF, Pinna FL, Testa G, Cacace E, Ruggiero V, Piras M, Romano F, Minerba L, Machado S, Friere RC, Nardi AE, Sancassiani F.
Int J Soc Psychiatry. 2018 Aug 27:20764018795211. doi: 10.1177/0020764018795211.

BACKGROUND: The aim is to measure the association between fibromyalgia syndrome (FMS) and post-traumatic stress disorder (PTSD), mood and anxiety disorders using reliable psychiatric diagnoses according to Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV) and with a case-control design. METHODS: Case-control study with cases (71 consecutive female patients with FMS) and controls (284 subjects without FMS), randomly drawn after a gender- and age-matching technique from the database of an epidemiological survey. Psychiatric diagnoses were conducted according to DSM-IV and carried out by clinical staff using a structured interview (Advanced Neuropsychiatric Tools and Assessment Schedule). QoL was measured by Short Form Health Survey (SF-12). RESULTS: The lifetime prevalence of major depressive disorder (MDD: 43.7% vs 8.1%, p<0.0001), bipolar disorder (BD; 21.1% vs 0.7%, p<0.0001), PTSD (8.4% vs 1.4%, p<0.0001) and panic disorder (28.2% vs 5.6%, p<0.001) was higher in people with FMS than in controls. People with FMS showed a poorer QoL than controls on the SF-12 (26.43 +/- 6.04 vs 37.45 +/- 5.80, p<0.0001). Those with comorbidity with MDD and BD showed a mean SF-12 score of 24.75 =/- 6.31 versus 29.52 +/- 4.84 (n=25) of people with FMS without any mood disorder (p=0.002). The attributable burden of FMS in worsening QoL was found comparable to that of serious chronic diseases such as multiple sclerosis. CONCLUSION: FMS is a disorder that 'in itself' can have a devastating impact on an individual's life. The frequency of the association with major depressive and bipolar disorders increases the impact on the QoL of people with FMS. One of the causes of this association appears to be the extreme vulnerability to chronic stress that this disorder involves. The findings have important clinical significance: the physician must interpret in the right dimension and with dignity the suffering of the people with FMS.

CLINICAL STUDIES

The complex interplay between gastrointestinal and psychiatric symptoms in irritable bowel syndrome: A longitudinal assessment.

Stasi C, Caserta A, Nisita C, Cortopassi S, Fani B, Salvadori S, Pancetti A, Bertani L, Gambaccini D, de Bortoli N, Dell'Osso L, Blandizzi C, Marchi S, Bellini M.
J Gastroenterol Hepatol. 2018 Jul 3. doi: 10.1111/jgh.14375.

AIMS: The aims of this study were to better define the relationship between irritable bowel syndrome (IBS) and psychiatric disorders and to examine the efficacy of paroxetine in the treatment of IBS patients. METHODS: One hundred fifty subjects with diagnosis of IBS (Roma III criteria) and relative sub-classification (constipated, diarrhea, and mixed) were assessed for psychopathological features and gastrointestinal symptoms using IBS Symptom Severity Score and were consecutively enrolled. Fifty patients assumed paroxetine for 16 weeks and were longitudinally evaluated. RESULTS: The entire sample had a moderate/severe gastrointestinal symptomatology (IBS-SSS 285.1 ± 98.6). The IBS subtypes were diarrhea (47.3%), constipated (32%), and mixed (20.7%). Panic disorder was found in 17.4% and major depressive episode in 14.7%. More than 50% of the patients showed "psychopathological features." This group showed more severe gastrointestinal symptoms and worse quality of life than the group without any psychiatric comorbidity (44%). Psychiatric patients also showed a significant impairment of physical state, subjective feeling of well-being, and leisure activities when compared with no psychiatric patients. When the IBS-SSS > 300 group was subgrouped in psychiatric (67.2%) and no psychiatric (32.8%), we found significant differences in all clinician-administered and self-reported scales with more severe psychopathological features in psychiatric group ($P < 0.01$). Among the patients treated with paroxetine, 34 (68%) completed the longitudinal evaluation showing a significant improvement of both psychiatric and gastrointestinal symptoms. CONCLUSIONS: This study confirms a high presence of psychiatric comorbidities, emphasizing the need for psychiatric screening in all patients with IBS; moreover, the longitudinal evaluation of patients treated with paroxetine showed a significant improvement of both psychiatric and gastrointestinal symptoms.

Sleep and migraine: Assessment and treatment of comorbid sleep disorders.
Rains JC.
Headache. 2018 Jul;58(7):1074-1091. doi: 10.1111/head.13357

The relationship of sleep and migraine is unequivocal and familiarity with the nature and magnitude of these associations may inform clinical practice. Recent prospective, longitudinal, and time-series analysis has begun to unravel the magnitude and temporal patterns of sleep and migraine. Prospective evidence has shown that sleep variables can trigger acute migraine, precede and predict new onset headache by several years, and indeed, sleep disturbance and snoring are risk factors for chronification. The presence of a sleep disorder is associated with more frequent and severe migraine and portends a poorer headache prognosis. Interestingly, the disorders linked to migraine are quite varied, including insomnia, snoring and obstructive sleep apnea, restless legs, circadian rhythm disorders, narcolepsy, and others. Insomnia is by far the most common sleep disorder in headache patients. In fact, the majority of patients with chronic migraine presenting for treatment have insomnia. Despite a rapidly expanding literature, very few controlled treatment studies have been published to guide clinical practice. This paper focuses on clinical assessment and treatment of sleep disorders. An algorithm is presented for sleep disorders management in the migraine patient, which highlights major sleep disorders and psychiatric comorbidity. Diagnostic procedures are recommended that are conducive to clinical practice. Suggested tools include the sleep history, screening mnemonics, prediction equation, and sleep diary. New developments in treatment have produced abbreviated and cost-effective therapies for insomnia and obstructive sleep apnea that may reach a larger population. Revisions in the diagnostic manuals for sleep and headache disorders enhance recognition of sleep-related headache. Recommendations include behavioral sleep regulation, shown in recent controlled trials to decrease migraine frequency, management for sleep apnea headache, cognitive behavioral therapy (CBT) for insomnia abbreviated for the physician practice setting, sleep-related headache trigger, and others. There is no empirical evidence that sleep evaluation

should delay or supersede usual headache care. Rather, sleep management is complimentary to standard headache practice.

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.

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