CUTTING EDGE

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About the Chronic Pain Research Alliance

NATIONAL STUDIES

Identification of Clusters of Individuals Relevant to Temporomandibular Disorders and Other Chronic Pain Conditions: The OPPERA Study.

Bair E, Gaynor S, Slade GD, Ohrbach R, Fillingim RB, Greenspan JD, Dubner R, Smith

SB, Diatchenko L, Maixner W
Pain. 2016 Feb 27. [Epub ahead of print]

Classification of most chronic pain disorders gives emphasis to anatomical location of the pain to distinguish one disorder from the other (e.g., back pain versus temporomandibular disorder [TMD]) or to define subtypes (e.g., TMD myalgia versus arthralgia). However, anatomic criteria overlook etiology, potentially hampering treatment decisions. The present study identified clusters of individuals using a comprehensive array of biopsychosocial measures. Data were collected from a case-control study of 1,031 chronic TMD cases and 3,247 TMD-free controls. Three subgroups were identified using supervised cluster analysis (referred to as the adaptive, pain-sensitive, and global symptoms clusters). Compared to the adaptive cluster, participants in the pain-sensitive cluster showed heightened sensitivity to experimental pain, and participants in the global symptoms cluster showed both greater pain sensitivity and greater psychological distress. Cluster membership was strongly associated with chronic TMD: 91.5% of TMD cases belonged to the pain-sensitive and global symptoms clusters whereas 41.2% of controls belonged to the adaptive cluster. TMD cases in the pain-sensitive and global symptoms clusters also showed greater pain intensity, jaw functional limitation, and more comorbid pain conditions. Similar results were obtained when the same methodology was applied to a smaller case-control study consisting of 199 chronic TMD cases and 201 TMD-free controls. During a median 3-year follow-up period of TMD-free individuals, participants in the global symptoms cluster had greater risk of developing first-onset TMD (hazard ratio=2.8) compared to participants in the other two clusters. Cross-cohort predictive modeling was used to demonstrate the reliability of the clusters.

Subjective Sleep Quality Deteriorates Prior to Development of Painful Temporomandibular Disorder.

Sanders AE, Akinkugbe AA, Bair E, Fillingim RB, Greenspan JD, Ohrbach R, Dubner R, Maixner W, Slade G
J Pain. In press.

There is good evidence that poor sleep quality increases risk of painful temporo-mandibular disorder (TMD). However little is known about the course of sleep quality in the months preceding TMD onset, and whether the relationship is mediated by heightened sensitivity to pain. The Pittsburgh Sleep Quality Index was administered at enrollment into the OPPERA prospective cohort study. Thereafter the Sleep Quality Numeric Rating Scale was administered every three months to 2,453 participants. Sensitivity to experimental pressure pain and pinprick pain stimuli was measured at baseline and repeated during follow-up of incident TMD cases (n=220) and matched TMD-free controls (n=193). Subjective sleep quality deteriorated progressively, but only in those who subsequently developed TMD. A Cox proportional hazards model showed that risk of TMD was greater among participants whose sleep quality worsened during follow-up (adjusted hazard ratio=1.73, 95% confidence limits: 1.29,2.32). This association was independent of baseline measures of sleep quality, psychological stress, somatic awareness, comorbid conditions, non-pain facial symptoms and demographics. Poor baseline sleep quality was not significantly associated with baseline

pain sensitivity or with subsequent change in pain sensitivity. Furthermore the relationship between sleep quality and TMD incidence was not mediated via baseline pain sensitivity nor change in pain sensitivity.

PATHOPHYSIOLOGY STUDIES

Pain and Sex Hormones: A Review of Current Understanding.
Maurer AJ, Lissounov A, Knezevic I, Candido KD, Knezevic NN
Pain Manag. 2016 Mar 17. [Epub ahead of print]

Multiple epidemiologic studies have demonstrated an increased prevalence for women in several chronic pain disorders. Clinical and experimental investigations have consistently demonstrated sex-specific differences in pain sensitivity and pain threshold. Even though the underlying mechanisms responsible for these differences have not yet been elucidated, the logical possibility of gonadal hormone influence on nociceptive processing has garnered recent attention. In this review, we evaluated the complex literature regarding gonadal hormones and their influence on pain perception. We reviewed the numerous functions of gonadal hormones, discussed the influence of these hormones on several common chronic pain syndromes (migraine, tension and cluster headaches, fibromyalgia, temporomandibular syndrome, rheumatoid arthritis and back pain, among others), and have attempted to draw conclusions from the available data.

Changes in Functional Connectivity of Pain Modulatory Systems in Women with Primary Dysmenorrhea.
Wei SY, Chao HT, Tu CH, Li WC, Low I, Chuang CY, Chen LF, Hsieh JC
Pain. 2016 Jan;157(1):92-102. doi: 10.1097/j.pain.0000000000000340.

Menstrual pain is the most prevalent gynecological complaint, and is usually without organic cause (termed primary dysmenorrhea, PDM). The high comorbidity in the later life of PDM with many functional pain disorders (associated with central dysfunction of pain inhibition, e.g., fibromyalgia) suggests possible maladaptive functionality of pain modulatory systems already occurred in young PDM women, making them vulnerable to functional pain disorders. Periaqueductal gray (PAG) matter functions as a critical hub in the neuraxis of pain modulatory systems; therefore, we investigated the functional connectivity of PAG in PDM. Forty-six PDM subjects and 49 controls received resting-state functional magnetic resonance imaging during menstruation and periovulatory phases. The PAG of PDM subjects exhibited adaptive/reactive hyperconnectivity with the sensorimotor cortex during painful menstruation, whereas it exhibited maladaptive hypoconnectivity with the dorsolateral prefrontal cortex and default mode network (involving the ventromedial prefrontal cortex, posterior cingulate cortex, or posterior parietal cortex) during menstruation or periovulatory phase. We propose that the maladaptive descending pain modulatory systems in PDM may underpin the central susceptibility to subsequent development of various functional disorders later in life. This hypothesis is corroborated by the growing body of

evidence that hypoconnectivity between PAG and default mode network is a coterminal to many functional pain disorders.

Concomitant Migraine and Temporomandibular Disorders are Associated with Higher Heat Pain Hyperalgesia and Cephalic Cutaneous Allodynia.

Chaves TC, Dach F, Florencio LL, Carvalho GF, Goncalves MC, Bigal ME, Speciali JG, Bevilaqua-Grossi D
Clin J Pain. 2016 Feb 22. [Epub ahead of print]

OBJECTIVES: To assess differences in the levels of hyperalgesia and cutaneous allodynia (CA) among women with migraine and/or temporomandibular disorders (TMD). METHODS: Eighty women participated in the study. Mean ages for the control group, TMD group, migrainegroup, and migraine+TMD group were 26.15 (95% confidence interval [CI] 28.73-23.57), 31.65 (95% CI 37.82-25.48), 35.05 (95% CI 40.37-29.73), and 34.20 (95% CI 37.99-30.41) years, respectively. The 12-item Allodynia Symptom Checklist (ASC-12) was administered to assess CA. All participants underwent the Quantitative Sensory Test in order to obtain cold- and heat-pain thresholds (CPT and HPT). Mechanical pain thresholds were assessed using Semmes-Weinstein monofilaments. One-way ANOVA and chi-square tests were used for statistical analysis. Alpha was set at the.05 level for statistical significance. RESULTS: For all sites evaluated, CPT mean values were significantly lower in the TMD, migraine, and TMD+migraine groups than in the control group. However, HPT mean values in the extracephalic region were significantly smaller only for the TMD+migraine group compared with the control group (41.94Â°C, 95%CI 40.54-43.34 vs. 44.79Â°C, 95%CI 43.45-46.12, P=0.03). Mechanical hyperalgesia in orofacial and neck sites was significantly lower in the TMD and TMD+migraine groups than in the control group. Mean total ASC-12 score in the TMD+migraine group was significantly higher than in the migraine group (9.53, 95% CI 7.45-11.60 vs. 6.95, 95% CI 5.35-8.55, P=0.02). CONCLUSION: More pronounced levels of hyperalgesia and CA were found in patients with both TMD and migraine. Thus, it is suggested that the concomitant presence of TMD and migraine may be related to intensification of central sensitization.

Impact of Migraine on Fibromyalgia Symptoms.

Giamberardino MA, Affaitati G, Martelletti P, Tana C, Negro A, Lapenna D, Curto M, Schiavone C, Stellin L, Cipollone F, Costantini R
J Headache Pain. 2015 Dec;17(1):28. doi: 10.1186/s10194-016-0619-8.

Background: Fibromyalgia (FMS) and high frequency episodic/chronic migraine (M) very frequently co-occur, suggesting common pathophysiological mechanisms; both conditions display generalized somatic hyperalgesia. In FMS-M comorbidity we assessed if: migraine attacks trigger FMS symptoms. Methods: Female patients with fibromyalgia (n=40), high frequency episodic migraine (M1, n=41), chronic migraine (M2, n=40), FMS + M1 (n=42) and FMS + M2 (n=40) underwent recording of: electrical pain thresholds in skin, subcutis and muscle and pressure pain thresholds in control sites, pressure pain thresholds in tender points (TePs), number of monthly migraine attacks and fibromyalgia flares (3 month diary). Migraine and FMS parameters were evaluated

before and after migraine prophylaxis, or no prophylaxis, for 3 months with calcium channel blockers, in two further FMS + M1 groups (n=49, n=39). One way ANOVA was applied to test trends among groups, Student's t-test for paired samples was used to compare pre and post treatment values. Results: The lowest electrical and pressure thresholds at all sites and tissues were found in FMS + M2, following by FMS + M1, FMS, M2 and M1 (trend: p,0.0001). FMS monthly flares were progressively higher in FMS, FMS + M1 and FMS + M2 (p<0.0001); most flares (86-87%) occurred within 12 hours from a migraine attack in comorbid patients (p<0.0001). Effective migraine prophylaxis vs no prophylaxis also produced a significant improvement of FMS symptoms (decreased monthly flares, increased pain thresholds, 0.0001<0.003). Conclusions: Comorbidity between fibromyalgia and migraine involves heightened somatic hyperalgesia compared to one condition only. Increased migraine frequently, with shift towards chronicity, enhances both hyperalgesia and spontaneous FMS pain, which is reversed by effective migraine prophylaxis. These results suggest different levels of central sensitization in patients with migraine, fibromyalgia or both conditions and a role for migraine as a triggering factor for FMS.

Establishing Clinically Relevant Severity Levels for the Central Sensitization Inventory.

Neblett R, Hartzell MM, Mayer TG, Cohen H, Gatchel RJ.
Pain Pract. 2016 Mar 15. doi: 10.1111/papr.12440.

OBJECTIVES: The aim of this study was to create and validate severity levels for the central sensitization inventory (CSI), a valid and reliable patient-reported outcome instrument designed to identify patients whose presenting symptoms may be related to a central sensitivity syndrome (CSS; eg, fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome), with a proposed common etiology of central sensitization (CS). METHODS: Based on CSI score means and standard deviations from previously published subject samples, the following CSI severity levels were established: subclinical = 0 to 29; mild = 30 to 39; moderate = 40 to 49; severe = 50 to 59; and extreme = 60 to 100. The concurrent validity of the CSI severity levels was then confirmed in a separate chronic pain patient sample (58% with a CSS diagnosis and 42% without) by demonstrating associations between CSI scores and (1) the number of physician-diagnosed CSSs; (2) CSI score distributions in both CSS and non-CSS patient samples; (3) patient-reported history of CSSs; and (4) patient-reported psychosocial measures, which are known to be associated with CSSs. RESULTS: Compared to the non-CSS patient subsample, the score distribution of the CSS patient subsample was skewed toward the higher severity ranges. CSI mean scores moved into higher severity levels as the number of individual CSS diagnoses increased. Patients who scored in the extreme CSI severity level were more likely to report previous diagnoses of fibromyalgia, chronic fatigue syndrome, temporomandibular jointdisorder, tension/migraine headaches, and anxiety or panic attacks (P < 0.01). CSI severity levels were also associated with patient-reported depressive symptoms, perceived disability, sleep disturbance, and pain intensity (P ≤ 0.02). CONCLUSION: This study provides support for these CSI severity levels as a guideline for healthcare providers and researchers in interpreting CSI scores and evaluating treatment responsiveness.

Liposome-Based Intravesical Therapy Targeting Nerve Growth Factor (NGF) Ameliorates Bladder Hypersensitivity in Rats with Experimental Colitis.

Kawamorita N, Yoshikawa S, Kashyap M, Tyagi P, Arai Y, Chancellor MB, Yoshimura N
J Urol. 2016 Jan 9. pii: S0022-5347(16)00009-4. doi: 10.1016/j.juro.2015.12.090.

PURPOSE: Pelvic organ cross sensitization is considered to contribute to overlapping symptoms in chronic pelvic pain syndrome. Nerve growth factor over expression in the bladder is reportedly involved in the symptom development of bladder pain syndrome/interstitial cystitis. We examined whether a reduction of over expressed nerve growth factor in the bladder by intravesical treatment with liposome and oligonucleotide conjugates would ameliorate bladder hypersensitivity in a rat colitis model. MATERIALS AND METHODS: Adult female rats were divided into 1) a control group, 2) a colitis-oligonucleotide group with intracolonic TNBS (2,4,6,trinitrobenzen sulfonic acid) enema and intravesical liposome-oligonucleotide treatments, 2) a colitis-saline group with intracolonic TNBS and intravesical saline treatments, 4) a sham oligonucleotide group with intravesical liposome-oligonucleotide treatment without colitis and 5) a sham-saline group with intravesical saline treatment without colitis. Liposomes conjugated with nerve growth factor antisense oligonucleotide or saline solution were instilled in the bladder and 24 hours later colitis was induced by TNBS enema. Effects of nerve growth factor antisense treatment were evaluated by pain behavior, cystometry, molecular analyses and immunohistochemistry 10 days after TNBS treatment. RESULTS: In colitis-oligonucleotide rats nerve growth factor antisense treatment ameliorated pain behavior and decreased a reduction in the intercontraction interval in response to acetic acid stimulation as well as nerve growth factor expression in the bladder mucosa. All were enhanced in colitis-saline rats compared to sham rats. CONCLUSIONS: Nerve growth factor over expression in the bladder mucosa and bladder hypersensitivity induced after colitis were decreased by intravesical application of liposome-oligonucleotide targeting nerve growth factor. This suggests that local antinerve growth factor therapy could be effective treatment of bladder symptoms in chronic pelvic pain syndrome.

The (Putative) Pathological Impact of Fibromyalgia on the Orofacial System.

[article in Dutch]
de Baat C, Gerritsen AE, de Baat-Ananta M, de Baat P
Ned Tijdschr Tandhellkd. 2016 Mar;123(3):148-53. doi: 10.5177/ntvt.2016.03.15240.

Fibromyalgia is a syndrome without apparent aetiology, characterised by pain, fatigue, memory disorders, mood disorders, and sleep disturbances. The syndrome is considered to be one of the rheumatic diseases. In the general population, the prevalence varies from 2 to 8%, with a women-men ratio of about 2:1. Suspicion of fibromyalgia arises when a patient has pain at multiple locations that cannot be attributed to trauma or inflammation, and when the pain is especially musculoskeletal. Primary management includes explaining the syndrome and offering reassurance. In addition, one can also attempt to increase mobility, avoid overloading, and improve physical condition and the level of activity, and to activate problem-solving skills. Subsequently, behavioural therapy and pharmacotherapy may be considered. The most important manifestations of fibromyalgia in the orofacial and occlusal system seem to be

temporomandibular dysfunction, headache, xerostomia, hyposalivation, burning mouth and dysgeusia. However, with respect to the precise relation of fibromyalgia with the orofacial system, much needs to be elucidated.

Microbes, molecular mimicry and molecules of mood and motivation.
Morris JA, Broughton SJ, Wessels Q
Med Hypotheses. 2016 Feb;87:40-3. doi: 10.1016/j.mehy.2015.12.011.

The hypothesis proposed is that functional disorders, such as irritable bowel syndrome, chronic fatigue syndrome and anorexia nervosa are caused by auto-antibodies to neuronal proteins induced by molecular mimicry with microbial antigens. The age incidence of these conditions, the marked female excess, increase with economic and technological advance, precipitation by infection, and the paucity of histological changes are all consistent with the hypothesis. It can be tested directly using human sera to search for cross reaction with brain proteins in model systems such as Drosophila melanogaster. The conditions might be amenable to treatment using pooled immunoglobulin. Identification and elimination from the microbial flora of the bacteria that express the cross reacting antigens should be possible.

EPIDEMIOLOGY STUDIES

Somatic Comorbidity in Women with Overactive Bladder Syndrome.
Altman D, Iliadou AN, Lundholm C, Milsom I, Pedersen NL
J Urol. 2016 Feb 18. pii: S0022-5347(16)00353-0. doi: 10.1016/j.juro.2016.02.076.

PURPOSE: To explore the influence of co-occurring somatic illnesses on prevalent overactive bladder in women of premenopausal age. METHODS: Data for the present study was derived from a nationwide survey on complex diseases among all twins in the Swedish Twin Registry born 1959-1985. The present study was limited to female twins participating in the survey (n = 12,850). Generalized estimating equations (GEE) were used to estimate odds ratios (ORs) with 95% confidence intervals (CIs). Environmental and genetic influences were assessed in co-twin control analysis. RESULTS: GEE analysis showed a significant association between overactive bladder and migraine (OR 1.34, 95% CI 1.15-1.57), fibromyalgia (1.83, 1.54-2.18), chronic fatigue (1.81, 1.49-2.19) and eating disorders (1.56, 1.24-1.96). There was also a significant association with allergic disorders including asthma (1.24, 1.01-1.52) and eczema (1.22, 1.04-1.43). Among reproductive disorders, urinary tract infections (1.60, 1.40-1.84), dysmenorrhea (1.53, 1.33-1.76) and pelvic pain (1.60, 1.31-1.94) showed the strongest association with overactive bladder. Results from co-twin control analysis indicated that the significant associations observed in GEE-analysis were influenced by both environmental and genetic factors without a common pathway model. CONCLUSIONS: Our results suggest a multifactorial and complex pathogenesis of overactive bladder where associations between various somatic illnesses and overactive bladder may be affected by both

environmental and genetic factors.

Self-Reported Migraine and Chronic Fatigue Syndrome are More Prevalent in People with Myofascial vs Nonmyofascial Temporomandibular Disorders.

Dahan H, Shir Y, Nicolau B, Keith D, Allison P
J Oral Facial Pain Headache. 2016 Winter;30(1):7-13. doi: 10.11607/ofph.1550.

AIMS:To compare the number of comorbidities and the prevalence of five specific comorbidities in people who have temporomandibular disorders (TMD) with or without myofascial pain. METHODS:This cross-sectional study included 180 patients seeking TMD treatment in Boston and Montreal hospitals. A self-administered questionnaire was used to collect information on sociodemographic and behavioral factors, as well as the presence of the following five comorbidities: migraine, chronic fatigue syndrome, irritable bowel syndrome, interstitial cystitis, and restless leg syndrome. TMD was diagnosed using the Research Diagnostic Criteria for TMD. Chi-square and Student t tests were used for categorical and continuous variables, respectively, to test for differences between myofascial (n = 121) and nonmyofascial (n = 59) TMD groups. Multiple logistic regression analysis was used to compare the type and number of self-reported comorbidities in both groups, controlling for confounding variables. RESULTS:The following were found to be significantly higher in the myofascial TMD group than in the nonmyofascial TMD group: self-reported migraine (55% vs 28%, P = .001), chronic fatigue syndrome (19% vs 5%, P = .01), and the mean total number of comorbidities (1.30 vs 0.83, P = .01). CONCLUSION:Individuals with myofascial TMD had a higher prevalence of self-reported migraine and chronic fatigue syndrome than those with nonmyofascial TMD.

Remission, Relapse, and Persistence of Vulvodynia: A Longitudinal Population-Based Study.

Reed BD, Harlow SD, Plegue MA, Sen A
J Womens Health (Larchmt). 2016 Jan 11.

BACKGROUND: Vulvodynia has been considered to be a chronic disorder. We sought to estimate the probability of and risk factors for remission, relapse, and persistence among women screening positive for vulvodynia. METHODS:Survey-based assessment in a longitudinal population-based study of women (the Woman to Woman Health Study) who screened positive for vulvodynia and completed at least four follow-up surveys. Outcome measures included remission without relapse, relapse (after remission), and persistence of a positive vulvodynia screen. Multinomial regression was used to assess factors associated with outcomes. RESULT: Of 441 women screening for vulvodynia during the study, 239 completed 4 additional surveys. Of these, 23 (9.6%) had consistently positive vulvodynia screens, 121 (50.6%) remitted without relapse, and 95 (39.7%) relapsed following remission. Overall, factors associated with both relapse and persistence (compared with remission alone) included increased severity of pain ever ($p<0.001$) or after intercourse ($p=0.03$), longer duration of symptoms ($p\leq0.001$), and screening positive for fibromyalgia ($p<0.001$). Factors associated with persistence (but

not relapse) included more severe symptoms with intercourse (p=0.001) and pain with oral sex (p=0.003) or partner touch (p=0.04). Factors associated with relapse (but not persistence) included having provoked pain (p=0.001) or screening positive for interstitial cystitis (p=0.05) at first positive vulvodynia screen. Demographic characteristics, age at pain onset, and whether vulvodynia was primary or secondary did not predict outcome. CONCLUSION:Remission of vulvodynia symptoms is common with approximately half of remitters experiencing a relapse within 6-30 months. Persistence without remission is the exception rather than the rule. Pain history and comorbid conditions were associated with the more severe outcomes of relapse and/or persistence compared with those who remitted only. These findings provide further support that vulvodynia is heterogeneous and often occurs in an episodic pattern.

Comorbidities Among Women with Vulvovaginal Complaints in Family Practice.

Leusink P, Kaptheijns A, Laan E, van Boven K, Lagro-Janssen A
J Sex Med. 2016 Jan 9. pii: S1743-6095(15)00026-0. doi: 10.1016/j.jsxm.2015.12.010.

BACKGROUND:The lifetime prevalence of women suffering from provoked vestibulodynia (PVD) is estimated to be approximately 15%. The etiology of PVD is not yet clear. Recent studies approach PVD as a chronic multifactorial sexual pain disorder. PVD is associated with pain syndromes, genital infections, and mental disorders, which are common diseases in family practice. PVD, however, is not included in the International Classification of Primary Care. Hence, the vulvovaginal symptoms, which could be suggestive of PVD, are likely to be missed. AIM:To explore the relationship between specific vulvovaginal symptoms that could be suggestive of PVD (genital pain, painful intercourse, other symptoms/complaints related to the vagina/vulva), and related diseases such as pain syndromes, psychological symptom diagnoses, and genital infections in family practice. METHODS:A retrospective analysis of all episodes from 1995 to 2008 in 784 women between 15 and 49 years were used to determine the posterior probability of a selected diagnosis in the presence of specific vulvovaginal symptoms suggestive of PVD expressed in an odds ratio. Selected comorbidities were pain syndromes (muscle pain, general weakness, irritable bowel syndrome [IBS]), psychological symptom diagnoses (anxiety, depression, insomnia), vulvovaginal candidiasis, and sexual and physical abuse. RESULTS:Women with symptoms suggestive of PVD were 4 to 7 times more likely to be diagnosed with vulvovaginal candidiasis and 2 to 4 times more likely to be diagnosed with IBS. Some symptoms suggestive of PVD were 1 to 3 times more likely to be diagnosed with complaints of muscle pain, general weakness, insomnia, depressive disorder, and feeling anxious. CONCLUSION:Data from daily family practice showed a clear relationship between symptoms suggestive of PVD and the diagnoses of vulvovaginal candidiasis and IBS in premenopausal women. Possibly, family doctors make a diagnosis of vulvovaginal candidiasis or IBS based only on clinical manifestations in many women in whom a diagnosis of PVD would be more appropriate.

Predictors of Fibromyalgia: A Population-Based Twin Cohort Study.

Markkula RA, Kalso EA, Kaprio JA

BMC Musculoskelet Disord. 2016 Jan 15;17(1):29. doi: 10.1186/s12891-016-0873-6.

BACKGROUND: Fibromyalgia (FM) is a pain syndrome, the mechanisms and predictors of which are still unclear. We have earlier validated a set of FM-symptom questions for detecting possible FM in an epidemiological survey and thereby identified a cluster with "possible FM". This study explores prospectively predictors for membership of that FM-symptom cluster. METHODS:A population-based sample of 8343 subjects of the older Finnish Twin Cohort replied to health questionnaires in 1975, 1981, and 1990. Their answers to the set of FM-symptom questions in 1990 classified them in three latent classes (LC): LC1 with no or few symptoms, LC2 with some symptoms, and LC3 with many FM symptoms. We analysed putative predictors for these symptom classes using baseline (1975 and 1981) data on regional pain, headache, migraine, sleeping, body mass index (BMI), physical activity, smoking, and zygosity, adjusted for age, gender, and education. Those with a high likelihood of having fibromyalgia at baseline were excluded from the analysis. In the final multivariate regression model, regional pain, sleeping problems, and overweight were all predictors for membership in the class with many FM symptoms. RESULTS:The strongest non-genetic predictor was frequent headache (OR 8.6, CI 95 % 3.8-19.2), followed by persistent back pain (OR 4.7, CI 95 % 3.3-6.7) and persistent neck pain (OR 3.3, CI 95 % 1.8-6.0). CONCLUSIONS:Regional pain, frequent headache, and persistent back or neck pain, sleeping problems, and overweight are predictors for having a cluster of symptoms consistent with fibromyalgia.

Dry Eye Syndrome Risks in Patients with Fibromyalgia: A National Retrospective Cohort Study.

Chen CH, Yang TY, Lin CL, Chen CS, Lin WM, Kuo CN, Lin MC, Kao CH
Medicine (Baltimore). 2016 Jan;95(4):e2607. doi: 10.1097/MD.0000000000002607.

The coexistence of fibromyalgia (FM) and dry eye syndrome (DES) has been previously reported. However, there are few studies on how patients with FM may develop concomitant DES. Patients with chronic widespread pain, like FM, chronic fatigue syndrome, and irritable bowel syndrome (IBS), was concerned for the rheumatic or psychosomatic disorders which might adequately reflect the long-term risk of DES. We retrieved data on FM patients from the National Health Insurance Research Database of Taiwan covering the years 2000 to 2011. Our FM population consisted of 25,777 patients versus 103,108 patients in the non-FM group: the overall incidence of DES in these populations was 7.37/10,000 and 4.81/10,000, respectively. Male FM patients had a higher incidence of DES, with a 1.39-fold DES risk for males and a 1.45-fold for females after adjustment for confounding factor. Notably, FM patients aged ≤49 years had an elevated 80% risk of DES compared with the non-FM group. Without comorbidities, FM patients had an approximately 1.40-fold risk of DES than those without FM. The additive effects of FM and IBS or FM and sleep disturbance were pointed out that the risk for DES would be elevated when the FM patients with IBS or sleep disturbance. FM patients have a higher incidence of DES than that of non-FM patients. They carry long-term DES risks from a relatively young age, particularly those with psychiatric problems. Risk stratification for a timely psychiatric medication intervention and risk modifications are not intended.

Child Abuse and Physical Health in Adulthood.

Afifi TO, MacMillan HL, Boyle M, Cheung K, Taillieu T, Turner S, Sareen J
Health Rep. 2016 Mar 16;27(3):10-8.

BACKGROUND: A large literature exists on the association between child abuse and mental health, but less is known about associations with physical health. The study objective was to determine if several types of child abuse were related to an increased likelihood of negative physical health outcomes in a nationally representative sample of Canadian adults. DATA AND METHODS: Data are from the 2012 Canadian Community Health Survey-Mental Health (n = 23,395). The study sample was representative of the Canadian population aged 18 or older. Child physical abuse, sexual abuse, and exposure to intimate partner violence were assessed in relation to self-perceived general health and 13 self-reported, physician-diagnosed physical conditions. RESULTS: All child abuse types were associated with having a physical condition (odds ratios = 1.4 to 2.0) and increased odds of obesity (odds ratios = 1.2 to 1.4). Abuse in childhood was associated with arthritis, back problems, high blood pressure, migraine headaches, chronic bronchitis/emphysema/COPD, cancer, stroke, bowel disease, and chronic fatigue syndrome in adulthood, even when sociodemographic characteristics, smoking, and obesity were taken into account (odds ratios = 1.1 to 2.6). Child abuse remained significantly associated with back problems, migraine headaches, and bowel disease when further adjusting for mental conditions and other physical conditions (odds ratios = 1.2 to 1.5). Sex was a significant moderator between child abuse and back problems, chronic bronchitis/emphysema/COPD, cancer, and chronic fatigue syndrome, with slightly stronger effects for women than men. INTERPRETATION: Abuse in childhood was associated with increased odds of having 9 of the 13 physical conditions assessed in this study and reduced self-perceived general health in adulthood. Awareness of associations between child abuse and physical conditions is important in the provision of health care.

Analgesic Opioid Use in a Health-Insured Epilepsy Population During 2012.

Wilner AN, Sharma BK, Thompson AR, Krueger A
Epilepsy Behav. 2016 Mar 2;57(Pt A):126-132. doi: 10.1016/j.yebeh.2016.01.033.

RATIONALE: Analgesic opioid use has increased dramatically in the general population. Although opioid analgesics are not indicated for the treatment of epilepsy, frequent opioid use has been reported in the epilepsy population. It is not clear whether comorbid disorders and/or epilepsy-associated injuries due to seizures foster opioid use. Our primary objective was to compare the prevalence of analgesic opioid use in an insured patient population with epilepsy to a matched control population without epilepsy. After observing increased frequency of opioid use in people with epilepsy compared with matched controls, we assessed the contribution of age, gender, pain diagnosis, and psychiatric illness as possible drivers regarding the use of opioids. METHODS: Health insurance claims and membership data from nine United States (U.S.) health plans for the year 2012 were analyzed. Individuals with epilepsy (n=10,271) were match-paired at

a 1:2 ratio to individuals without epilepsy (n=20,542) within each health plan using propensity scores derived from age group, gender, and insurance type. Matched comparison groups had 53% females and 47% males with an average age of 34years for the group with epilepsy and 33years for controls. Each matched comparison group included 66% of individuals with commercial insurance, 30% with Medicaid insurance, and 4% with Medicare coverage. Based on prescriptions filled at least once during 2012, prevalence of analgesic opioid use was determined. The percentages of individuals with diagnosis for specific pain conditions and those with psychiatric diagnoses were also determined for the two comparison groups. RESULTS: Analgesic opioids were used by 26% of individuals in the group with epilepsy vs. 18% of matched controls (p<0.001). Compared with matched controls, the group with epilepsy had a significantly higher percentage of individuals with all 16 pain conditions examined: joint pain or stiffness (16% vs. 11%), abdominal pain (14% vs. 9%), headache (14% vs. 5%), pain in limb (12% vs. 7%), chest pain (11% vs. 6%), sprain of different parts (9% vs. 7%), sinusitis (9% vs. 7%), migraine (8% vs. 2%), lumbago (8% vs. 6%), backache (6% vs. 4%), cervicalgia (6% vs. 3%), fracture (5% vs. 3%), fibromyalgia (4% vs. 3%), chronic pain (3% vs. 1%), sciatica (1.4% vs. 1%), and jaw pain (0.4% vs. 0.1%) (all p<0.001). The prevalence of pain diagnosis was 51% in the group with epilepsy and 39% in the matched control group (p<0.0001). The prevalence of 'psychiatric diagnoses' was 27% in the group with epilepsy and 12% in the matched control group (p<0.0001). CONCLUSION: The prevalences of analgesic opioid use, psychiatric diagnoses, and 16 pain conditions were significantly higher in the patient population with epilepsy than in the control population without epilepsy. Our study also showed how opioid use rate varied by gender, age category, and depression. The reasons for the greater prevalence of opioid use in people with epilepsy are unclear. It seems that increased pain prevalence is an important driver for the higher frequency of opioid use in people with epilepsy. Psychiatric illness and other factors also appear to contribute. Further analysis including more detailed clinical information that cannot be obtained through claims data alone will be required to provide more insight into opioid use in people with epilepsy. If opioid use is higher in people with epilepsy as our results suggest, physicians managing patients with epilepsy need to pay special attention to safe opioid prescribing habits in order to prevent adverse outcomes such as abuse, addiction, diversion, misuse, and overdose.

CLINICAL STUDIES

Multimodal Assessment of Body Pain in Orofacial Pain Patients.
Hawkins JM, Schmidt JE, Hargitai IA, Johnson JF, Howard RS, Bertrand PM
Pain Med. 2016 Feb 10. pii: pnv093.

OBJECTIVE: Patients with complaints of orofacial pain (OFP) often have other body pain, yet many do not report these to their providers. Uncontrolled pain at any location may impact the successful management of an OFP complaint. The objective of this study was to determine the number of pain regions throughout the body, and the underreporting of pain, in patients who presented to a tertiary military OFP clinic. DESIGN: A retrospective chart review was conducted on 423 consecutive new patients.

Patients were given three assessment opportunities to report their pain on a whole-body pain map: 1) prior to evaluation (Pt1), 2) following an explanatory statement by their provider on the relationship between pain and prognosis (Pt2), and 3) during directed pain inquiry of specific body regions (Pro). The pain map was divided into nine anatomical regions that were assessed for the presence of pain after Pt1, Pt2, and Pro. RESULTS:Initially, 60.5% of patients did not report all pain locations (Pt1). Following the explanatory statement (Pt2), 30.5% still did not report all pain. Following the completion of all assessment methods, the most commonly reported number of pain regions was five (17.0%), and 91.5% of patients reported multiple pain regions. CONCLUSIONS: Most patients had multiple pain complaints outside the chief complaint, yet the majority did not report these until multiple forms of assessment were utilized. These data encourage the use of a pain map, a verbal pain explanation, and directed pain questioning to more accurately capture pain location and facilitate multidisciplinary care.

Chronic Pelvic Pain in Women.

Speer LM, Mushkbar S, Erbele T
Am Fam Physician. 2016 Mar 1;93(5):380-7.

Chronic pelvic pain in women is defined as persistent, noncyclic pain perceived to be in structures related to the pelvis and lasting more than six months. Often no specific etiology can be identified, and it can be conceptualized as a chronic regional pain syndrome or functional somatic pain syndrome. It is typically associated with other functional somatic pain syndromes (e.g., irritable bowel syndrome, nonspecific chronic fatigue syndrome) and mental health disorders (e.g., posttraumatic stress disorder, depression). Diagnosis is based on findings from the history and physical examination. Pelvic ultrasonography is indicated to rule out anatomic abnormalities. Referral for diagnostic evaluation of endometriosis by laparoscopy is usually indicated in severe cases. Curative treatment is elusive, and evidence-based therapies are limited. Patient engagement in a biopsychosocial approach is recommended, with treatment of any identifiable disease process such as endometriosis, interstitial cystitis/painful bladder syndrome, and comorbid depression. Potentially beneficial medications include depot medroxyprogesterone, gabapentin, nonsteroidal anti-inflammatory drugs, and gonadotropin-releasing hormone agonists with add-back hormone therapy. Pelvic floor physical therapy may be helpful. Behavioral therapy is an integral part of treatment. In select cases, neuromodulation of sacral nerves may be appropriate. Hysterectomy may be considered as a last resort if pain seems to be of uterine origin, although significant improvement occurs in only about one-half of cases. Chronic pelvic pain should be managed with a collaborative, patient-centered approach.

Arthralgias, Fatigue, Paresthesias and Visceral Pain: Can Joint Hypermobility Solve the Puzzle? A Case Report.

Folci M, Capsoni F
BMC Musculoskelet Disord. 2016 Feb 4;17(1):58. doi: 10.1186/s12891-016-0905-2.

BACKGROUND: Joint hypermobility syndrome describes a disorder in which musculoskeletal pain occurs in a generalized joint hypermobility substrate. The clinical

picture comprises variable manifestations which involve mainly but not exclusively the musculoskeletal system, and evolve over the person's lifetime. CASE PRESENTATION: Describing the case of a 20-year-old female with generalized arthro-myalgias, persistent fatigue and troublesome visceral pain, we illustrate how a frequently ignored clinical sign such as joint hypermobility can be the keystone to clarify different simultaneous symptoms. All of the patient's physical complaints had been investigated separately during her previous medical examinations, and several tests repeatedly gave negative results. The patient received different diagnoses that describe only part of her problems, such as irritable bowel syndrome for visceral pain, fibromyalgia for arthralgias or depression for fatigue. These approaches gave rise to pharmacological or physical treatments which did not improve her quality of life in any way and in some instances worsened the situation. Pronounced joint hypermobility which led the patient to flex her joints excessively, causing subluxations in several districts, was the only sign overlooked. CONCLUSION: Exploring the patient's articular features in her clinical context led us to diagnose joint hypermobility syndrome, a complex and often ignored condition. The case highlights the utility of a multidisciplinary approach and coordinated interventions to define and manage this clinical entity.

Melatonin in Chronic Pain Syndromes.

Danilov A, Kurganova J
Pain Ther. 2016 Mar 16.

Melatonin is a neurohormone secreted by epiphysis and extrapineal structures. It performs several functions including chronobiotic, antioxidant, oncostatic, immune modulating, normothermal, and anxiolytic functions. Melatonin affects the cardiovascular system and gastrointestinal tract, participates in reproduction and metabolism, and body mass regulation. Moreover, recent studies have demonstrated melatonin efficacy in relation to pain syndromes. The present paper reviews the studies on melatonin use in fibromyalgia, headaches, irritable bowel syndrome, chronic back pain, and rheumatoid arthritis. The paper discusses the possible mechanisms of melatonin analgesic properties. On one hand, circadian rhythms normalization results in sleep improvement, which is inevitably disordered in chronic pain syndromes, and activation of melatonin adaptive capabilities. On the other hand, there is evidence of melatonin-independent analgesic effect involving melatonin receptors and several neurotransmitter systems.

Fecal Microbiota Transplantation: Current Applications, Effectiveness, and Future Perspectives.

Choi HH, Cho YS
Clin Endosc. 2016 Mar 9. doi: 10.5946/ce.2015.117.

Fecal microbiota transplantation (FMT) is the infusion of liquid filtrate feces from a healthy donor into the gut of a recipient to cure a specific disease. A fecal suspension can be administered by nasogastric or nasoduodenal tube, colonoscope, enema, or capsule. The high success rate and safety in the short term reported for recurrent Clostridium difficile infection has elevated FMT as an emerging treatment for a wide range of disorders, including Parkinson's disease, fibromyalgia, chronic fatigue

syndrome, myoclonus dystopia, multiple sclerosis, obesity, insulin resistance, metabolic syndrome, and autism. There are many unanswered questions regarding FMT, including donor selection and screening, standardized protocols, long-term safety, and regulatory issues. This article reviews the efficacy and safety of FMT used in treating a variety of diseases, methodology, criteria for donor selection and screening, and various concerns regarding FMT.

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 consider a contribution 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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