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CUTTING EDGE

a publication of  CHRONIC PAIN
Research Alliance

COPCs Research Advances

Issue 3 - July 2016

Developed to keep the medical-scientific community abreast of research advances, this electronic publication of the Chronic Pain Research Alliance features abstracts of studies published between March and July 2016 on the pathophysiology, epidemiology and clinical management of Chronic Overlapping Pain Conditions (COPCs). Past issues are available on our website, <http://www.cpralliance.org>.

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PATHOPHYSIOLOGY STUDIES

[Relationship between nongenital tender point tenderness and intravaginal muscle pain intensity: ratings in women with provoked vestibulodynia and implications for treatment.](#)

Phillips N, Brown C, Bachmann G, Wan J, Wood R, Ulrich D, Bachour C, Foster D.

Am J Obstet Gynecol. 2016 Jul 1. pii: S0002-9378(16)30392-1. doi:

10.1016/j.ajog.2016.06.047. Epub ahead of print

BACKGROUND: Vulvodynia is a chronic vulvar pain disorder and fibromyalgia is a chronic widespread musculoskeletal pain disorder, both of unknown etiology. Association of these conditions is well documented. Intravaginal algometer measurement of tenderness to pressure applied to the pelvic floor muscles helps define vulvodynia associated with musculoskeletal factors. Women with both vulvodynia and fibromyalgia might have increased pelvic muscle pain compared to women with vulvodynia alone, defining the possible link of these 2 conditions. **OBJECTIVE:** We sought to: (1) correlate pain intensity during the nongenital tender point tenderness examination to pain intensity with the vaginal algometer in women with provoked vestibulodynia, and (2) determine whether subjects with provoked vestibulodynia and fibromyalgia had higher pain intensity scores with the vaginal algometer than those without fibromyalgia. **STUDY DESIGN:** In all, 92 subjects referred for vulvar pain were confirmed to have provoked vestibulodynia using the cotton swab test. A diagnosis of fibromyalgia was made if pain was present (numeric rating scale >1) in at least 11 sites of the 18-point nongenital tender point tenderness exam. Vaginal pain sensitivity was measured using an intravaginal pressure algometer, where 0.1, 0.3, and 0.5 kg/cm² forces were applied digitally in random assignment by force and location to the right and left iliococcygeus muscle regions and the posterior vaginal wall. Both tender point tenderness and algometer pain intensity were reported on a 0 (no pain) to 10 (worst pain) numeric rating scale. Correlations were computed between the composite pain intensity (total of rating scale from each pressure threshold at specified site) of nongenital and those of iliococcygeus regions and the posterior vaginal wall. Independent t tests were used to determine differences in iliococcygeus regions and the posterior vaginal algometer pain ratings and presence or absence of fibromyalgia. The significance level was at $P < .05$. The data were expressed as mean \pm SD. **RESULTS:** A significant correlation was found between numeric rating scale pain scores on the nongenital tender point tenderness exam and algometer testing on the iliococcygeus region ($r = 0.44$, $P < .0001$) and the posterior vaginal wall ($r = 0.45$, $P < .0001$). Subjects with fibromyalgia by tender point tenderness had significantly higher iliococcygeal pain (6.14 ± 2.07 vs 3.74 ± 2.22 , $P = .0001$) and posterior vaginal wall pain (5.67 ± 2.10 vs 3.07 ± 2.16 , $P < .0001$) than women without fibromyalgia by tender point tenderness. **CONCLUSION:** Women with provoked vestibulodynia who experience more severe pain with nongenital tender point palpation also experience more deep vaginal pain on pelvic exam. Those who fulfill the diagnosis of fibromyalgia show significantly more intense deep vaginal pain to palpation of iliococcygeus muscles and posterior vaginal wall. Further research using a more precise definition of fibromyalgia is necessary to confirm this relationship, but findings suggest that women with provoked vestibulodynia coexisting with fibromyalgia have greater risk of superimposed vaginal muscle pain and may be candidates for early adjunctive pelvic floor physical therapy. These findings need to be explored in women with generalized, nonprovoked vulvodynia.

[Reduced thermal threshold in patients with temporomandibular disorders.](#)

Carvalho GF, Chaves TC, Florencio LL, Dach F, Bigal ME, Bevilacqua-Grossi D. J Oral Rehabil. 2016 Jun;43(6):401-8. doi: 10.1111/joor.12386.

BACKGROUND: Many studies have demonstrated the presence of somatosensory

modulation changes at different sites in patients with temporomandibular disorders (TMDs) using different modalities. However, the neck area, a well-known condition related to TMD, remains unexplored. **OBJECTIVE:** To assess the thermal pain threshold in patients with TMD and controls at cephalic and extra-cephalic areas, including the neck. **METHODS:** Twenty female patients with TMDs diagnosed by the Research Diagnostic Criteria for TMD (RDC/TMD) and twenty age-matched controls underwent a first interview about neck pain and disability (NDI questionnaire). A blinded evaluator assessed the thermal pain threshold for cold (CPT) and heat (HPT) stimuli in accordance with an ascending method of limits of the Quantitative Sensory Testing at the following sites: periorbital, masseter, cervical posterior and ventral forearm. The groups were compared using a t-test with $\alpha = 5\%$. **RESULTS:** Patients with TMDs reported pain at higher temperature for cold stimuli in all sites ($P < 0.05$) and at lower temperature for heat stimuli in the right periorbital site ($P < 0.05$) than controls. Pain and disability due to this symptom were reported more often in the TMD group ($P < 0.05$). **CONCLUSION:** Patients with TMD have pain modulation changes in the neck area as well, especially for cold stimuli, associated with higher disability and a higher report of neck pain than controls. These findings reinforce the evidence regarding the relationship between TMDs and neck pain.

[Liposome based intravesical therapy targeting nerve growth factor 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 Jun;195(6):1920-6. 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-trinitrobenzene 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.

[Fibromyalgia syndrome pathology and environmental influences on afflictions with medically unexplained symptoms.](#)

Albrecht PJ, Rice FL.

Rev Environ Health. 2016 Apr 22. pii: /j/reveh.ahead-of-print/reveh-2015-0040/reveh-2015-0040.xml. doi: 10.1515/reveh-2015-0040. Epub ahead of print

Fibromyalgia syndrome (FMS) is a clinical disorder predominant in females with unknown etiology and medically unexplained symptoms (MUS), similar to other afflictions, including irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS), post-traumatic stress disorder (PTSD), Gulf War illness (GFI), and others. External environmental stimuli drive behavior and impact physiologic homeostasis (internal environment) via autonomic functioning. These environments directly impact the individual affective state (mind), which feeds back to regulate physiology (body). FMS has emerged as a complex disorder with pathologies identified among neurotransmitter and enzyme levels, immune/cytokine functionality, cortical volumes, cutaneous innervation, as well as an increased frequency among people with a history of traumatic and/or emotionally negative events, and specific personality trait profiles. Yet, quantitative physical evidence of pathology or disease etiology among FMS has been limited (as with other afflictions with MUS). Previously, our group published findings of increased peptidergic sensory innervation associated with the arterio-venous shunts (AVS) in the glabrous hand skin of FMS patients, which provides a plausible mechanism for the wide-spread FMS symptomology. This review focuses on FMS as a model affliction with MUS to discuss the implications of the recently discovered peripheral innervation alterations, explore the role of peripheral innervation to central sensitization syndromes (CSS), and examine possible estrogen-related mechanisms through which external and internal environmental factors may contribute to FMS etiology and possibly other afflictions with MUS.

[Melatonin in chronic pain syndromes.](#)

Danilov A, Kurganova J.

Pain Ther. 2016 Jun;5(1):1-17. doi: 10.1007/s40122-016-0049-y.

Melatonin is a neurohormone secreted by epiphysis and extrapineal structures. It performs several functions including chronobiotic, antioxidant, oncostatic, immune modulating, normothermic, 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.

[Psychological stress in early life as a predisposing factor for the development of chronic pain: Clinical and preclinical evidence and neurobiological mechanisms.](#)

Burke NN, Finn DP, McGuire BE, Roche M.

J Neurosci Res. 2016 Jul 12. doi: 10.1002/jnr.23802. Epub ahead of print

A wealth of research over the past 2 decades has expanded our understanding of the impact of early-life adversity on physiological function and, consequently, health and well being in later life. Early-life adversity increases the risk of developing a number of disorders, such as chronic pain, fibromyalgia, and irritable bowel syndrome. Although much of the research has examined the impact of physical maltreatment, an increasing number of studies have been published over the past few years examining the effect of childhood psychological stress and trauma on the development of various types of chronic pain conditions. We review the clinical and preclinical data examining the link among early-life psychological stress, altered nociceptive behavior, and chronic pain in later life. Evidence supporting a role for certain key neurobiological substrates, including the hypothalamic-pituitary-adrenal axis; monoaminergic, opioidergic, endocannabinoid and immune systems; and epigenetic mechanisms in the association between early-life psychological stress and chronic pain, is provided. Greater understanding of the impact of early-life stress may inform the development of personalized treatments for chronic pain in later life and strategies to prevent its onset in susceptible individuals.

EPIDEMIOLOGY STUDIES

[A systematic review of the comorbidity between temporomandibular disorders and chronic fatigue syndrome.](#)

Robinson LJ, Durham J, Newton JL.

J Oral Rehabil. 2016 Apr;43(4):306-16. doi: 10.1111/joor.12367.

The most common cause of chronic oro-facial pain is a group of disorders collectively termed temporomandibular disorders (TMDs). Chronic painful TMD is thought to be a 'central sensitivity syndrome' related to hypersensitivity of the nervous system, but the cause is unknown. A similar understanding is proposed for other unexplained conditions, including chronic fatigue syndrome (CFS). Exploring the comorbidity of the two conditions is a valuable first step in identifying potential common aetiological mechanisms or treatment targets. **METHOD:** Systematic literature review. Studies were included if they recruited community or control samples and identified how many reported having both TMD and CFS, or if they recruited a sample of patients with either TMD or CFS and measured the presence of the other condition. **RESULTS:** Six papers met inclusion criteria. In studies of patients with CFS (n = 3), 21-32% reported having TMD. In a sample of people with CFS and fibromyalgia, 50% reported having TMD. Studies in people with TMD (n = 3) reported 0-43% having CFS. Studies in samples recruited from oro-facial pain clinics (n = 2) reported a lower comorbidity with CFS (0-10%) than a study that recruited individuals from a TMD self-help organisation (43%). **CONCLUSION:** The review highlights the limited standard of evidence addressing the comorbidity between oro-facial pain and CFS. There is a valuable signal that the

potential overlap in these two conditions could be high; however, studies employing more rigorous methodology including standardised clinical assessments rather than self-report of prior diagnosis are needed.

[Intolerance to environmental chemicals and sounds in irritable bowel syndrome: Explained by central sensitization?](#)

Ståhlberg L, Palmquist E, Nordin S.

J Health Psychol. 2016 Jul 7. pii: 1359105316656242. Epub ahead of print

This study tested the hypotheses of irritable bowel syndrome showing (1) comorbidity with chemical and sound intolerance, other types of functionally somatic syndromes, and psychiatric disorders and (2) stronger than normal affective reactions to and behavioral disruptions from odorous/pungent chemicals and sounds in daily life. These hypotheses were tested by means of data from a large-scale population-based questionnaire study. The results showed comorbidity in irritable bowel syndrome with chemical and sound intolerance, fibromyalgia, migraine, post-traumatic stress disorder, generalized anxiety disorder, panic syndrome, and depression as well as strong reactions/disruptions from odorous/pungent chemicals and sounds in irritable bowel syndrome.

[Statistically modeling the relationship between Type D personality and social support, health behaviors and symptom severity in chronic illness groups.](#)

Horwood S, Anglim J, Tooley G.

Psychol Health. 2016 Apr 6:1-17. Epub ahead of print

OBJECTIVE:The study aimed to develop a predictive model of how Type D personality influences health behaviours, social support and symptom severity and assess its generalisability to a range of chronic illnesses.**DESIGN:**Participants were classified as either healthy (n = 182) or having a chronic illness (n = 207). Participants completed an online survey measuring Type D and a range of health-related variables. Chronic illness participants were classified as having either a functional somatic syndrome (i.e. chronic fatigue syndrome or fibromyalgia), where the underlying pathological processes were unclear, or illnesses such as type 2 diabetes, osteoarthritis or rheumatoid arthritis, where the causes are well understood. **MAIN OUTCOME MEASURES:** Outcome measures were health behaviours, social support and both physical and psychological symptoms. **RESULTS:**The rate of Type D was higher in chronic illness participants (53%) than in healthy controls (39%). Negative affectivity (NA) and social inhibition (SI) both correlated with outcome measures, although NA was generally the stronger predictor. Using NA and SI as independent subscales led to superior prediction of health outcomes than using categorical or continuous representations. **CONCLUSION:**Findings suggest that the relationship between Type D and health outcomes may generalise across different chronic illnesses.

FUNCTIONAL STATUS/QUALITY OF LIFE STUDIES

[Neurocognitive complaints and functional status among patients with chronic fatigue syndrome and fibromyalgia.](#)

Schamaling KB, Betterton KL.

Qual Life Res. 2016 May;25(5):1257-63. doi: 10.1007/s11136-015-1160-y.

PURPOSE: The purpose of this study was to conduct a longitudinal examination of cognitive complaints and functional status in patients with chronic fatigue syndrome (CFS) alone and those who also had fibromyalgia (CFS/FM). **METHODS:** A total of 93 patients from a tertiary care fatigue clinic were evaluated on four occasions, each 6 months apart. Each evaluation included a tender point assessment, and self-reported functional status and cognitive complaints. **RESULTS:** Patients with CFS/FM reported significantly worse physical functioning, more bodily pain, and more cognitive difficulties (visuo-perceptual ability and verbal memory) than patients with CFS alone. Over time, bodily pain decreased only for participants with CFS alone. Verbal memory problems were associated with more bodily pain for both patient groups, whereas visuo-perceptual problems were associated with worse functional status for patients with CFS alone. **CONCLUSIONS:** This study adds to the literature on functional status, longitudinal course, and cognitive difficulties among patients with CFS and those with CFS and FM. The results suggest that patients with CFS/FM are more disabled, have more cognitive complaints, and improve more slowly over time than patients with CFS alone. Specific cognitive difficulties are related to worse functional status, which supports the addition of cognitive difficulties to the FM case criteria.

[Activity pacing is associated with better and worse symptoms for patients with long-term conditions.](#)

Antcliff D, Campbell M, Woby S, Keeley P.

Clin J Pain. 2016 Jun 17. Epub ahead of print

BACKGROUND: Activity pacing has been associated with both improved and worsened symptoms, and its role in reducing disability among patients with long-term conditions has been questioned. However, existing studies have measured pacing according to uni-dimensional subscales, and therefore the empirical evidence for pacing as a multifaceted construct remains unclear. We have developed a 26-item Activity Pacing Questionnaire (APQ-26) for chronic pain/fatigue containing five themes of pacing: activity adjustment, activity consistency, activity progression, activity planning and activity acceptance. **OBJECTIVE:** To assess the associations between the five APQ-26 pacing themes and symptoms of pain, physical fatigue, depression, avoidance and physical function. **METHODS:** Cross-sectional questionnaire design study. Data analysed using multiple regression. **PARTICIPANTS:** 257 adult patients with diagnoses of chronic low back pain, chronic widespread pain, fibromyalgia and chronic fatigue syndrome/myalgic encephalomyelitis. **RESULTS:** Hierarchical multiple regression showed that activity adjustment was significantly associated with increased physical fatigue, depression and avoidance, but decreased physical function (all $P \leq 0.030$). Activity consistency was associated with decreased pain, physical fatigue, depression and avoidance but increased physical function (all $P \leq 0.003$). Activity planning was associated with reduced physical fatigue ($P = 0.025$) and activity acceptance was associated with increased avoidance ($P = 0.036$). **CONCLUSION:** Some APQ-26 pacing themes were associated with worse symptoms and others with symptom improvement. Specifically, pacing themes involving adjusting/reducing activities were

associated with worse symptoms, whereas pacing themes involving undertaking consistent activities were associated with improved symptoms. Future study will explore the causality of these associations to add clarification regarding the effects of pacing on patients' symptoms.

CLINICAL STUDIES

[Development of the Sensory Hypersensitivity Scale \(SHS\): a self-report tool for assessing sensitivity to sensory stimuli.](#)

Dixon EA, Benham G, Sturgeon JA, Mackey S, Johnson KA, Younger J.
J Behav Med. 2016 Jun;39(3):537-50. doi: 10.1007/s10865-016-9720-3.

Sensory hypersensitivity is one manifestation of the central sensitization that may underlie conditions such as fibromyalgia and chronic fatigue syndrome. We conducted five studies designed to develop and validate the Sensory Hypersensitive Scale (SHS); a 25-item self-report measure of sensory hypersensitivity. The SHS assesses both general sensitivity and modality-specific sensitivity (e.g. touch, taste, and hearing). 1202 participants (157 individuals with chronic pain) completed the SHS, which demonstrated an adequate overall internal reliability (Cronbach's alpha) of 0.81, suggesting the tool can be used as a cross-modality assessment of sensitivity. SHS scores demonstrated only modest correlations (Pearson's r) with depressive symptoms (0.19) and anxiety (0.28), suggesting a low level of overlap with psychiatric complaints. Overall SHS scores showed significant but relatively modest correlations (Pearson's r) with three measures of sensory testing: cold pain tolerance (-0.34); heat pain tolerance (-0.285); heat pain threshold (-0.271). Women reported significantly higher scores on the SHS than did men, although gender-based differences were small. In a chronic pain sample, individuals with fibromyalgia syndrome demonstrated significantly higher SHS scores than did individuals with osteoarthritis or back pain. The SHS appears suitable as a screening measure for sensory hypersensitivity, though additional research is warranted to determine its suitability as a proxy for central sensitization.

[Headaches and myofascial temporomandibular disorders: overlapping entities, separate managements?](#)

Conti PC, Costa YM, Goncalves DA, Svensson P.
J Oral Rehabil. 2016 May 18. doi: 10.1111/joor.12410. Epub ahead of print

There are relevant clinical overlaps between some of the painful temporomandibular disorders (TMD) and headache conditions that may hamper the diagnostic process and treatment. A non-systematic search for studies on the relationship between TMD and headaches was carried out in the following databases: PubMed, Cochrane Library and Embase. Important pain mechanisms contributing to the close association and complex relationship between TMD and headache disorders are as follows: processes of peripheral and central sensitisation which take place in similar anatomical areas, the possible impairment of the descending modulatory pain pathways and the processes of referred pain. In addition, the clinical examination does not always provide distinguishing information to differentiate between headaches and TMD. So, considering the

pathophysiology and the clinical presentation of some types of headache and myofascial TMD, such overlap can be considered not only a matter of comorbid relationship, but rather a question of disorders where the distinction lines are sometimes hard to identify. These concerns are certainly reflected in the current classification systems of both TMD and headache where the clinical consequences of diagnosis such as headache attributed to or associated with TMD are uncertain. There are several similarities in terms of therapeutic strategies used to manage myofascial TMD and headaches. Considering all these possible levels of interaction, we reinforce the recommendation for multi-disciplinary approaches, by a team of oro-facial pain specialists and a neurologist (headache specialist), to attain the most precise differential diagnosis and initiate the best and most efficient treatment.

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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