CUTTING EDGE

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LEADERSHIP 301

Adults Living with IC/BPS May Qualify

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Published by the Chronic Pain Research Alliance and developed to keep the medical-scientific community abreast of research advances, this e-newsletter contains abstracts of studies on the epidemiology, pathophysiology and clinical management of Chronic Overlapping Pain Conditions (COPCs) published between January and April 2017. Past issues are available on our website, http://www.cpralliance.org. To read the CPRA's White Paper, click here. Please direct any questions or comments to the CPRA's Director, Christin Veasley - cveasley@cpralliance.org.

In this Issue...

About the Chronic Pain Research Alliance

FEATURED EDITORIAL

The burden of neurological disease in the United States: A summary report and call to action.
Gooch CL, Pracht E, Borenstein AR.
Ann Neurol. 2017 Feb 15. doi: 10.1002/ana.24897.

The United States carries a substantial fiscal burden resulting from the nearly 100 million Americans with neurological disease. The combined annual costs of Alzheimer's and other dementias, low back pain, stroke, traumatic brain injury, migraine, epilepsy, multiple sclerosis, spinal cord injury and Parkinson's disease totals nearly 800 billion dollars and is

rapidly rising due to the aging of the U.S. POPULATION: We provide a summary overview of the substantial current and future economic impact of neurological disease, and provide an action plan for reducing this burden through neurological research and enhanced clinical management of neurological disorders in the United States.

PATHOPHYSIOLOGY STUDIES

Heterogeneity in chronic fatigue syndrome - empirically defined subgroups from the PACE trial.
Williams TE, Chalder T, Sharpe M, White PD.
Psychol Med. 2017 Jan 23:1-12. doi: 10.1017/S0033291716003615.

BACKGROUND: Chronic fatigue syndrome is likely to be a heterogeneous condition. Previous studies have empirically defined subgroups using combinations of clinical and biological variables. We aimed to explore the heterogeneity of chronic fatigue syndrome. METHOD: We used baseline data from the PACE trial, which included 640 participants with chronic fatigue syndrome. Variable reduction, using a combination of clinical knowledge and principal component analyses, produced a final dataset of 26 variables for 541 patients. Latent class analysis was then used to empirically define subgroups. RESULTS: The most statistically significant and clinically recognizable model comprised five subgroups. The largest, 'core' subgroup (33% of participants), had relatively low scores across all domains and good self-efficacy. A further three subgroups were defined by: the presence of mood disorders (21%); the presence of features of other functional somatic syndromes (such as fibromyalgia or irritable bowel syndrome) (21%); or by many symptoms - a group which combined features of both of the above (14%). The smallest 'avoidant-inactive' subgroup was characterized by physical inactivity, belief that symptoms were entirely physical in nature, and fear that they indicated harm (11%). Differences in the severity of fatigue and disability provided some discriminative validation of the subgroups. CONCLUSIONS: In addition to providing further evidence for the heterogeneity of chronic fatigue syndrome, the subgroups identified may aid future research into the important aetiological factors of specific subtypes of chronic fatigue syndrome and the development of more personalized treatment approaches.

Prefrontal structure varies as a function of pain symptoms in chronic fatigue syndrome.
van der Schaaf ME, De Lange FP, Schmits IC, Geurts DE, Roelofs K, van der Meer JW, Toni I, Knoop H.
Biol Psychiatry. 2017 Feb 15;81(4):358-365. doi: 10.1016/j.biopsych.2016.07.016.

BACKGROUND: Chronic fatigue syndrome (CFS) is characterized by severe fatigue persisting for ≥6 months and leading to considerable impairment in daily functioning. Neuroimaging studies of patients with CFS have revealed alterations in prefrontal brain morphology. However, it remains to be determined whether these alterations are specific for fatigue or whether they relate to other common CFS symptoms (e.g., chronic pain, lower psychomotor speed, and reduced physical activity). METHODS: We used magnetic resonance imaging to quantify gray matter volume (GMV) and the N-acetylaspartate and N-acetylaspartylglutamate/creatine ratio (NAA/Cr) in a group of 89 women with CFS. Building on previous reports, we tested whether GMV and NAA/Cr in the dorsolateral prefrontal cortex are associated with fatigue severity, pain, psychomotor speed, and physical activity, while controlling for depressive symptoms. We also considered GMV and NAA/Cr differences between patients with CFS and 26 sex-, age-, and education-matched healthy controls. RESULTS: The presence of pain symptoms was the main predictor of both GMV and NAA/Cr in the left dorsolateral prefrontal cortex of patients with CFS. More pain was associated with reduced GMVs and NAA/Cr, over and above the effects of fatigue, depressive symptoms, physical activity, and psychomotor speed. In contrast to

previous reports and despite a large representative sample, global GMV did not differ between the CFS and healthy control groups. CONCLUSIONS: CFS, as diagnosed by Centers for Disease Control and Prevention criteria, is not a clinical entity reliably associated with reduced GMV. Individual variation in the presence of pain, rather than fatigue, is associated with neuronal alterations in the dorsolateral prefrontal cortex of patients with CFS.

The neuroinflammatory etiopathology of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).
Glassford JAG.
Front. Physiol. 17 Feb 2017.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a debilitating multi-systemic chronic illness of unknown etiology, classified as a neurological disorder by the World Health Organization (WHO). The symptomatology of the condition appears to emanate from a variety of sources of chronic neurological disturbance and associated distortions, and chronicity, in noxious sensory signaling and neuroimmune activation. This article incorporates a summary review and discussion of biomedical research considered relevant to this essential conception perspective. It is intended to provide stakeholders with a concise, integrated outline disease model in order to help demystify this major public health problem. The primary etiopathological factors presented are: (A) Postural/biomechanical pain signaling, affecting adverse neuroexcitation, in the context of compression, constriction, strain, or damage of vertebral-regional bone and neuromuscular tissues; (B) Immune mediated inflammatory sequelae, in the context of prolonged immunotropic neurotrophic infection-with lymphotropic/gliotropic/glio-toxic varieties implicated in particular; (C) A combination of factors A and B. Sustained glial activation under such conditions is associated with oxidative and nitrosative stress, neuroinflammation, and neural sensitivity. These processes collectively enhance the potential for multi-systemic disarray involving endocrine pathway aberration, immune and mitochondrial dysfunction, and neurodegeneration, and tend toward still more intractable synergistic neuro-glial dysfunction (gliopathy), autoimmunity, and central neuronal sensitization.

The gut peptide neuropeptide Y and post-traumatic stress disorder.
Rasmusson AM.
Curr Opin Endocrinol Diabetes Obes. 2017 Feb;24(1):3-8. doi: 10.1097/MED.0000000000000301.

PURPOSE OF REVIEW: This article reviews the role of neuropeptide Y (NPY) in the pathophysiology of post-traumatic stress disorder (PTSD) and gastrointestinal disorders such as irritable bowel syndrome (IBS) with which PTSD is highly comorbid. NPY is low in the cerebrospinal fluid and plasma of male combat veterans with PTSD and correlates negatively with sympathetic nervous system (SNS) hyperreactivity, PTSD symptoms and time to recovery. NPY regulation has not yet been evaluated in women with PTSD. RECENT FINDINGS: NPY levels in bowel tissue are low in IBS with diarrhea (IBS-D) versus IBS with constipation. The density of ghrelin containing cells of the gastric oxyntic mucosa is markedly increased in IBS-D. PTSD-related SNS hyperreactivity may interact with this substrate to increase ghrelin release, which activates receptors in the lumbosacral spinal cord and basolateral amygdala to increase colonic motility and amygdala hyperreactivity, respectively. Loss of function gene polymorphisms in adrenergic α2-autoreceptors and increased corticotropin-releasing hormone, as observed in PTSD, are also thought to contribute to IBS-D. SUMMARY: Knowledge of shared underlying NPY system-related neurobiological factors that contribute to the comorbidity of PTSD and gastrointestinal disorders may help guide research, development and prescription of targeted and more effective individualized therapeutic interventions.

Are the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) and the

[undifferentiated connective tissue disease (UCTD) related to each other? A case-control study of environmental exposures.]
Scanzi F, Andreoli L, Martinelli M, Taraborelli M, Cavazzana I, Carabellese N, Ottaviani R, Allegri F, Franceschini F, Agmon-Levin N, Shoenfeld Y, Tincani A.
Immunol Res. 2017 Mar 22. doi: 10.1007/s12026-017-8912-4.

The autoimmune/inflammatory syndrome induced by adjuvants (ASIA) is an entity that includes different autoimmune conditions observed after exposure to an adjuvant. Patients with undifferentiated connective tissue disease (UCTD) present many signs and symptoms of ASIA, alluding to the idea that an exposure to adjuvants can be a trigger also for UCTD. The aim of this case-control study was to investigate exposure to adjuvants prior to disease onset in patients affected by UCTD. Ninety-two UCTD patients and 92 age- and sex-matched controls with no malignancy, chronic infections, autoimmune disease nor family history of autoimmune diseases were investigated for exposure to adjuvants. An ad hoc-created questionnaire exploring the exposure to vaccinations, foreign materials and environmental and occupational exposures was administered to both cases and controls. Autoantibodies were also analyzed (anti-nuclear, anti-extractable nuclear antigens, anti-double-stranded DNA, anti-cardiolipin, anti-β2 glycoprotein I). UCTD patients displayed a greater exposure to HBV ($p = 0.018$) and tetanus toxoid ($p < 0.001$) vaccinations, metal implants ($p < 0.001$), cigarette smoking ($p = 0.006$) and pollution due to metallurgic factories and foundries ($p = 0.048$) as compared to controls. UCTD patients exposed to major ASIA triggers (vaccinations, silicone implants) ($n = 49$) presented more frequently with chronic fatigue ($p < 0.001$), general weakness ($p = 0.011$), irritable bowel syndrome ($p=0.033$) and a family history for autoimmunity ($p = 0.018$) in comparison to non-exposed UCTDs. ASIA and UCTD can be considered as related entities in the "mosaic of autoimmunity": the genetic predisposition and the environmental exposure to adjuvants elicit a common clinical phenotype characterized by signs and symptoms of systemic autoimmunity.

[Generalized hyperalgesia in children and adults diagnosed with hypermobility syndrome and ehlers-danlos syndrome hypermobility type: A discriminative analysis.]
Scheper MC, Pacey V, Rombaut L, Adams RD, Tofts L, Calders P, Nicholson LL, Engelbert RH.
Arthritis Care Res (Hoboken). 2017 Mar;69(3):421-429. doi: 10.1002/acr.22998.

OBJECTIVE: Lowered pressure-pain thresholds have been demonstrated in adults with Ehlers-Danlos syndrome hypermobility type (EDS-HT), but whether these findings are also present in children is unclear. Therefore, the objectives of the study were to determine whether generalized hyperalgesia is present in children with hypermobility syndrome (HMS)/EDS-HT, explore potential differences in pressure-pain thresholds between children and adults with HMS/EDS-HT, and determine the discriminative value of generalized hyperalgesia. METHODS: Patients were classified in 1 of 3 groups: HMS/EDS-HT, hypermobile (Beighton score ≥4 of 9), and healthy controls. Descriptive data of age, sex, body mass index, Beighton score, skin laxity, and medication usage were collected. Generalized hyperalgesia was quantified by the average pressure-pain thresholds collected from 12 locations. Confounders collected were pain locations/intensity, fatigue, and psychological distress. Comparisons between children with HMS/EDS-HT and normative values, between children and adults with HMS/EDS-HT, and corrected confounders were analyzed with multivariate analysis of covariance. The discriminative value of generalized hyperalgesia employed to differentiate between HMS/EDS-HT, hypermobility, and controls was quantified with logistic regression. RESULTS: Significantly lower pressure-pain thresholds were found in children with HMS/EDS-HT compared to normative values. When applying a threshold of 30.8 N/cm^2 for males and 29.0 N/cm^2 for females, the presence of generalized hyperalgesia discriminated between individuals with HMS/EDS-HT, hypermobility, and healthy controls (odds ratio 6.0). CONCLUSION: Children and adults with HMS/EDS-HT are characterized by hypermobility, chronic pain, and generalized hyperalgesia. The presence of generalized hyperalgesia may indicate involvement of the central nervous system in the development of chronic pain.

Clear differences in cerebrospinal fluid proteome between women with chronic widespread pain and healthy women - a multivariate explorative cross-sectional study.
Olausson P, Ghafouri B, Bäckryd E, Gerdle B.
J Pain Res. 2017 Mar 13;10:575-590. doi: 10.2147/JPR.S125667. eCollection 2017.

INTRODUCTION: Frequent chronic local pain can develop
into chronic widespread pain (CWP). The spread of pain is correlated with pain intensity, anxiety, and depression, conditions that ultimately lead to a poor quality of life. Knowledge is incomplete about CWP's etiology, although it has been suggested that both central hyperexcitability and/or a combination with peripheral factors may be involved. Cerebrospinal fluid (CSF) could act as a mirror for the central nervous system as proteins are signal substances that activate the formation of algesics and control nociceptive processes. To this end, this study investigates the CSF protein expression in women with CWP and in female healthy controls. MATERIALS AND METHODS: This study included 12 female patients with CWP diagnosed according to the American College of Rheumatology criteria with 13 healthy age- and sex-matched pain-free subjects. All subjects went through a clinical examination and answered a health questionnaire that registered sociodemographic and anthropometric data, pain characteristics, psychological status, and quality of life rating. CSF was collected by lumbar puncture from each subject. Two-dimensional gel electrophoresis in combination with mass spectrometry was used to analyze the CSF proteome. This study identifies proteins that significantly discriminate between the two groups using multivariate data analysis (MVDA) (i.e., orthogonal partial least squares discriminant analysis [OPLS-DA]). RESULTS: There were no clinically significant levels of psychological distress and catastrophization presented in subjects with CWP. MVDA revealed a highly significant OPLS-DA model where 48 proteins from CSF explained 91% (R^2) of the variation and with a prediction of 90% (Q^2). The highest discriminating proteins were metabolic, transport, stress, and inflammatory. CONCLUSION: The highest discriminating proteins (11 proteins), according to the literature, are involved in apoptotic regulations, anti-inflammatory and anti-oxidative processes, the immune system, and endogenous repair. The results of this explorative study may indicate the presence of neuro-inflammation in the central nervous system of CWP patients. Future studies should be larger and control for confounders and determine which alterations are unspecific/general and which are specific changes.

Neuroplasticity of supraspinal structures associated with pathological pain.
Boadas-Vaello P, Homs J, Reina F, Carrera A, Verdú E.
Anat Rec (Hoboken). 2017 Mar 6. doi: 10.1002/ar.23587.

Peripheral nerve and spinal cord injuries, along with other painful syndromes such as fibromyalgia, diabetic neuropathy, chemotherapeutic neuropathy, trigeminal neuralgia, complex regional pain syndrome, and/or irritable bowel syndrome, cause several neuroplasticity changes in the nervous system along its entire axis affecting the different neuronal nuclei. This paper reviews these changes, focusing on the supraspinal structures that are involved in the modulation and processing of pain, including the periaqueductal gray matter, red nucleus, locus coeruleus, rostral ventromedial medulla, thalamus, hypothalamus, basal ganglia, cerebellum, habenula, primary, and secondary somatosensory cortex, motor cortex, mammillary bodies, hippocampus, septum, amygdala, cingulated, and prefrontal cortex. Hyperexcitability caused by the modification of postsynaptic receptor expression, central sensitization, and potentiation of presynaptic delivery of neurotransmitters, as well as the reduction of inhibitory inputs, changes in dendritic spine, neural circuit remodeling, alteration of gray matter, and upregulation of proinflammatory mediators (e.g., cytokines) by reactivation of astrocytes and microglial cells are the main functional, structural, and molecular neuroplasticity changes observed in the above supraspinal structures, associated with pathological pain. Studying these changes in greater depth may lead to the implementation and improvement of new therapeutic strategies

against pathological pain.

Temporomandibular disorders and painful comorbidities: clinical association and underlying mechanisms.
Costa YM, Conti PC, de Faria FA, Bonjardim LR.
Oral Surg Oral Med Oral Pathol Oral Radiol. 2017 Mar;123(3):288-297. doi: 10.1016/j.oooo.2016.12.005.

The association between temporomandibular disorders (TMDs) and headaches, cervical spine dysfunction, and fibromyalgia is not artefactual. The aim of this review is to describe the comorbid relationship between TMD and these three major painful conditions and to discuss the clinical implications and the underlying pain mechanisms involved in these relationships. Common neuronal pathways and central sensitization processes are acknowledged as the main factors for the association between TMD and primary headaches, although the establishment of cause-effect mechanisms requires further clarification and characterization. The biomechanical aspects are not the main factors involved in the comorbid relationship between TMD and cervical spine dysfunction, which can be better explained by the neuronal convergence of the trigeminal and cervical spine sensory pathways as well as by central sensitization processes. The association between TMD and fibromyalgia also has supporting evidence in the literature, and the proposed main mechanism underlying this relationship is the impairment of the descending pain inhibitory system. In this particular scenario, a cause-effect relationship is more likely to occur in one direction, that is, fibromyalgia as a risk factor for TMD. Therefore, clinical awareness of the association between TMD and painful comorbidities and the support of multidisciplinary approaches are required to recognize these related conditions.

Fibromyalgia syndrome and temporomandibular disorders with muscular pain. A review.
Moreno-Fernández AM, Jiménez-Castellanos E, Iglesias-Linares A, Bueso-Madrid D, Fernández-Rodríguez A, de Miguel M.
Mod Rheumatol. 2017 Mar;27(2):210-216. doi: 10.1080/14397595.2016.1221788.

OBJECTIVES: Temporomandibular disorders (TMD) refer to a group of clinical picture affecting the masticatory muscles and temporomandibular joint that are characterized by muscular or joint pain, dysfunction (limited or altered functions) and joint noises, as well as other associated symptoms, such as tension headaches, otalgia, dizziness, tinnitus, and others. Fibromyalgia (FM) is a syndrome of unknown etiology involving generalized chronic pain accompanied, in a high percentage of cases, by other symptoms such as asthenia, anxiety, depression, sleep disturbances, and other less frequent symptoms, such as temporomandibular disorders (TMD). DATA: Data were compiled by two experienced examiners following a specific form. SOURCES: An electronic search was carried out in the Cochrane Central Register of Controlled Trials (CENTRAL), PUBMED, and SCOPUS electronic databases (up to April 2016, unrestricted by date or language). STUDY SELECTION: Comparative clinical studies with patients with both clinical pictures involving the study of pathogenic processes. CONCLUSIONS: Fibromyalgia and temporomandibular disorders with muscle pain both have profiles that affect the muscular system and therefore share many epidemiological, clinical, and physiopathological symptoms. Because of this, we are led to think that there is, if not a common etiology, at least a common pathogenesis. This article revises the physiopathological processes of both clinical pictures in an attempt to determine their similarities and likenesses. This would undoubtedly help in providing a better therapeutic approach.

Panic disorder comorbidity with medical conditions and treatment implications.
Meuret AE, Kroll J, Ritz T.
Annu Rev Clin Psychol. 2017 Mar 27. doi: 10.1146/annurev-clinpsy-021815-093044.

Panic disorder (PD) is unique among the anxiety disorders in that panic symptoms are primarily of a physical nature. Consequently, comorbidity with medical illness is significant. This review examines the association between PD and medical illness. We identify shared pathophysiological and psychological correlates and illustrate how physiological activation in panic sufferers underlies their symptom experience in the context of the fight-or-flight response and beyond a situation-specific response pattern. We then review evidence for bodily symptom perception accuracy in PD. Prevalence of comorbidity for PD and medical illness is presented, with a focus on respiratory and cardiovascular illness, irritable bowel syndrome, and diabetes, followed by an outline for potential pathways of a bidirectional association. We conclude by illustrating commonalities in mediating mechanistic pathways and moderating risk factors across medical illnesses, and we discuss implications for diagnosis and treatment of both types of conditions.

Does exercise increase or decrease pain? Central mechanisms underlying these two phenomena.
Lima LV, Abner TS, Sluka A.
J Physiol. 2017 Mar 29. doi: 10.1113/JP273355.

Exercise is an integral part of the rehabilitation of patients suffering a variety of chronic musculoskeletal conditions, such as fibromyalgia, chronic low back pain and myofascial pain. Regular physical activity is recommended for treatment of chronic pain and its effectiveness has been established in clinical trials for people with a variety of pain conditions. However, exercise can also increase pain making participation in rehabilitation challenging for the person with pain. Animal models of exercise-induced pain have been developed and point to central mechanisms underlying this phenomena, such as increased activation of NMDA receptors in pain-modulating areas. Meanwhile, a variety of basic science studies testing different exercise protocols, show exercise-induced analgesia involves activation of central inhibitory pathways. Opioid, serotonin and NMDA mechanisms acting in rostral ventromedial medulla (RVM) promote analgesia associated with exercise. This review explores and discusses current evidence on central mechanisms underlying exercised-induced pain and analgesia.

Undifferentiated connective tissue disease, fibromyalgia and the environmental factors.
Andreoli L, Tincani A.
Curr Opin Rheumatol. 2017 Mar 31. doi: 10.1097/BOR.0000000000000392.

PURPOSE OF REVIEW: The aim of this study was to discuss the role of environmental factors in the induction and perpetuation of autoimmunity, with particular focus on undifferentiated connective tissue disease (UCTD) and fibromyalgia. These two entities may share undefined clinical and laboratory features and recognize environmental exposures as triggering factors. From this particular point of view, both UCTD and fibromyalgia may resemble the picture of the 'Autoimmune/Inflammatory Syndrome Induced by Adjuvants' (ASIA). RECENT FINDINGS: A case-control study on environmental exposures showed that patients with UCTD were significantly more exposed to several adjuvants (vaccines, metal implants, proximity to metal factories and foundries) than age and sex-matched healthy controls. UCTD exposed to major ASIA triggers (vaccines, silicone) displayed typical features of ASIA (general weakness, chronic fatigue, irritable bowel syndrome) in the context of a predisposing genetic background (familiarity for autoimmunity). SUMMARY: The induction and perpetuation of autoimmunity is a complex process that requires the interaction between the individual genetic background and the environment. Environmental factors are gaining increasing attention since the description of ASIA, a syndrome that includes symptoms typically seen in patients with fibromyalgia and UCTD. A recent case-control study focusing on environmental exposures suggested that nearly half of patients with UCTD may fall within the ASIA spectrum.

EPIDEMIOLOGY STUDIES

Gender differences in demographic and clinical correlates among veterans with musculoskeletal disorders.

Higgins DM, Fenton BT, Driscoll MA, Heapy AA, Kerns RD, Bair MJ, Carroll C, Brennan PL, Burgess DJ, Piette JD, Haskell SG, Brandt CA, Goulet JL.
Womens Health Issues. 2017 Mar 18. pii: S1049-3867(16)30130-X. doi: 10.1016/j.whi.2017.01.008.

BACKGROUND: Studies suggest that women may be at greater risk for developing chronic pain and pain-related disability. METHODS: Because musculoskeletal disorders (MSD) are the most frequently endorsed painful conditions among veterans, we sought to characterize gender differences in sociodemographic and clinical correlates among veterans upon entry into Veterans Health Administration's Musculoskeletal Disorders Cohort (n = 4,128,008).
RESULTS: Women were more likely to be younger, Black, unmarried, and veterans of recent conflicts. In analyses adjusted for gender differences in sociodemographics, women were more likely to have diagnoses of fibromyalgia, temporomandibular disorders, and neck pain. Almost one in five women (19.4%) had more than one MSD diagnosis, compared with 15.7% of men; this higher risk of MSD multimorbidity remained in adjusted analyses. Adjusting for sociodemographics, women with MSD were more likely to have migraine headache and depressive, anxiety, and bipolar disorders. Women had lower odds of cardiovascular diseases, substance use disorders, and several MSDs, including back pain conditions. Men were more likely to report "no pain" on the pain intensity Numeric Rating Scale, whereas more women (41%) than men (34%) reported moderate to severe pain (Numeric Rating Scale 4+).
CONCLUSIONS: Because women veterans are more likely to have conditions such as fibromyalgia and mental health conditions, along with greater pain intensity in the setting of MSD, women-specific pain services may be needed.

Concussion/mild traumatic brain injury-related chronic pain in males and females: A diagnostic modelling study.

Mollayeva T, Cassidy JD, Shapiro CM, Mollayeva S, Colantonio A.
Medicine (Baltimore). 2017 Feb;96(7):e5917. doi: 10.1097/MD.0000000000005917.

Pain is an unpleasant, complex, and perceived experience that places a significant burden on patients and clinicians. Its severity may be mediated by emotion, attitude, and environmental influences, and pain may be expressed differently in males and females. Traumatic brain injury (TBI) is frequently associated with chronic pain. This diagnostic modeling study examined sex differences in the construct of chronic pain in patients with delayed recovery from concussion/mild traumatic brain injury (mTBI). Data were collected from standardized questionnaires, neuroimaging records, and comprehensive clinical assessments. Bivariate associations were calculated using the Spearman correlation coefficient or analysis of variance. We established sex-specific stepwise multivariate linear regression models of factors associated with pain. Of the 94 participants diagnosed with mTBI (the mean age was 45.2 +/- 9.9 years; 61.2% were males; the median time since injury was 197 days [interquartile range 139-416]), head/neck, and bodily pain were reported by 93% and 64%, respectively. No sex differences were identified in pain frequencies or severity. Pain was significantly associated with certain socio-demographic, injury-related, behavioral, and clinical variables. In the multivariable regression analysis, several determinants explained 60% of the pain variance in males and 46% in females. Pain is common in patients with delayed recovery from mTBI and is significantly associated with potentially modifiable clinical and nonclinical variables. Examining the multidimensional construct of pain in concussion/mTBI through a sex lens garners new directions for future

longitudinal research on the pain mechanisms involved in postconcussion syndrome.

Characterizing health care utilization, direct costs, and comorbidities associated with interstitial cystitis: A retrospective claims analysis.
Tung A, Hepp Z, Bansal A, Devine EB.
J Manag Care Spec Pharm. 2017 Apr;23(4):474-482. doi: 10.18553/jmcp.2017.23.4.474.

BACKGROUND: Interstitial cystitis (IC) is a debilitating condition that affects up to 5% of the U.S. POPULATION: This condition is characterized by bladder pain, urinary urgency and frequency, nocturia, and, in some patients, bladder lesions called Hunner's lesions (HL). IC patients who have HL experience a clinical course that is distinct from those without HL and, as a result, respond differently to existing treatments. Without effective and lasting therapeutic options, IC patients are expected to experience a reduced quality of life and be a significant economic burden. Previous research describing the burden of IC is not only outdated but lacks stratification by HL. OBJECTIVES: To (a) characterize health care utilization, direct costs, and comorbidities associated with IC and (b) elucidate differences between patients with and without HL. METHODS: A retrospective analysis was conducted using health care claims from the Truven Health MarketScan Research Databases. Adults with an incident IC diagnosis between 2009 and 2014 were identified and matched 1:4 to non-IC patients on age, gender, and geographic region. Health care utilization, direct costs, and comorbidities during the first 12 months after diagnosis were compared between the 2 groups, as well as between IC subgroups with and without HL. Associations were evaluated after adjustment for potential confounders using regression models. RESULTS: A total of 24,836 IC patients were identified and matched to 99,344 non-IC patients. Patients were predominantly female (92%), with a mean age of 49.0 (SD = 15.3) years. IC patients used significantly more health care resources across all categories compared with non-IC patients. On average, having IC was associated with $7,223 higher total health care costs than not having IC (95% CI = $6,650-$7,796), with outpatient costs contributing to 71% of the difference, after adjusting for baseline age, gender, region, insurance type, plan type, and Charlson Comorbidity Index (CCI) score. The odds of developing select comorbidities were 2.61 times greater in IC patients compared with non-IC patients (95% CI = 2.52-2.70), adjusting for baseline age, sex, region, and CCI score. Among IC patients, the HL subgroup (n = 292) used more health care resources, and having HL was associated with $6,895 higher total health care costs compared with not having HL (95% CI = $3,770-$10,020) after adjusting for baseline age, gender, region, insurance type, and plan type. CONCLUSIONS: Findings suggest that patients with IC have significantly higher health care utilization, costs, and comorbidities compared with non-IC patients. This economic burden is further amplified in those with HL.

Influence of culture on pain comorbidity in women with and without temporomandibular disorder-pain.
Al-Harthy M, Michelotti A, List T, Ohrbach R.
J Oral Rehabil. 2017 Feb 28. doi: 10.1111/joor.12499.

Evidence on cultural differences in prevalence and impact of common chronic pain conditions, comparing individuals with temporomandibular disorders (TMD) versus individuals without TMD, is limited. The aim was to assess cross-cultural comorbid pain conditions in women with chronic TMD pain. Consecutive women patients (n = 122) with the index condition of chronic TMD pain diagnosed per the research diagnostic criteria for TMD and TMD-free controls (n = 121) matched for age were recruited in Saudi Arabia, Italy and Sweden. Self-report questionnaires assessed back, chest, stomach and head pain for prevalence, pain intensity and interference with daily activities. Logistic regression was used for binary variables, and ancova was used for parametric data analysis, adjusting for age and education. Back pain was the only comorbid condition with a different prevalence across cultures; Swedes reported a lower prevalence compared to Saudis (P < 0·01). Saudis reported higher prevalence of work reduced >50% due to back pain compared to

Italians or Swedes (P < 0·01). Headache was the most common comorbid condition in all three cultures. The total number of comorbid conditions did not differ cross-culturally but were reported more by TMD-pain cases than TMD-free controls (P < 0·01). For both back and head pain, higher average pain intensities (P < 0·01) and interference with daily activities (P < 0·01) were reported by TMD-pain cases, compared to TMD-free controls. Among TMD-pain cases, Italians reported the highest pain-related disability (P < 0·01). Culture influences the associated comorbidity of common pain conditions. The cultural influence on pain expression is reflected in different patterns of physical representation.

Common pediatric pain disorders and their clinical associations.
Donnelly T, Bott A, Bui M, Goh S, Jaaniste T, Chapman C, Crawford M, Hopper JL, Champion.
Clin J Pain. 2017 Mar 7. doi: 10.1097/AJP.0000000000000496.

BACKGROUND: Common childhood pain conditions (non-migraine headache, migraine, recurrent abdominal pain, growing pains, low back pain) and persistent pains are often associated with each other and have significant implications in later life. Emerging evidence suggests additional associations between these pain conditions and restless legs syndrome, iron deficiency, anxiety and depression. The aim of this cross-sectional study in pediatric twin individuals and their siblings was to investigate these associations. METHODS: Surveys were sent to Australian twin families via the Australian Twin Registry, yielding responses from 2530 pediatric individuals. The lifetime prevalence of the common pain disorders of childhood and of other persistent pains, restless legs syndrome and iron deficiency, and anxious/depressed score were determined by questionnaires. Random-effects logistic regression modelling was used to investigate univariate and multivariate associations between conditions. RESULTS: Univariate associations were found between each of the pain conditions and persistent pain, and between the pain conditions with restless legs syndrome, iron deficiency and anxious/depressed score. Derivative multivariate analyses retained statistically significant associations between each of the pain disorders included in the respective models (odds ratios (OR) 1.69-7.04) with the exception of growing pains with persistent pain. Of the non-pain conditions included in the multivariate analyses, restless legs syndrome remained associated with growing pains (OR 8.50) and persistent pain (OR 2.01). Iron deficiency remained significantly associated with migraine (OR 2.38), persistent pain (OR 3.70) and restless legs syndrome (OR 5.10). CONCLUSIONS: In light of their extensive associations, the common pain conditions, persistent pain, restless legs syndrome, iron deficiency, anxiety and depression, are likely to involve common etiological mechanisms that warrant further investigation.

Sex-specific impact of early-life adversity on chronic pain: a large population-based study in Japan.
Yamada K, Matsudaira K, Tanaka E, Oka H, Katsuhira J, Iso H.
J Pain Res. 2017 Feb 16;10:427-433. doi: 10.2147/JPR.S125556. eCollection 2017.

BACKGROUND: Responses to early-life adversity may differ by sex. We investigated the sex-specific impact of early-life adversity on chronic pain, chronic multisite pain, and somatizing tendency with chronic pain. METHODS: We examined 4229 respondents aged 20-79 years who participated in the Pain Associated Cross-Sectional Epidemiological Survey in Japan. Outcomes were: 1) chronic pain prevalence, 2) multisite pain (≥3 sites) prevalence, and 3) multiple somatic symptoms (≥3 symptoms) among respondents with chronic pain related to the presence or absence of early-life adversity. Multivariable-adjusted odds ratios (ORs) were calculated with 95% confidence intervals using a logistic regression model including age, smoking status, exercise routine, sleep time, body mass index, household expenditure, and the full distribution of scores on the Mental Health Inventory-5. We further adjusted for pain intensity when we analyzed the data for respondents with chronic pain. RESULTS: The prevalence of chronic pain was higher among respondents reporting the presence of early-life adversity compared with those reporting its absence, with multivariable ORs of

1.62 (1.22-2.15, $p<0.01$) in men and 1.47 (1.13-1.90, $p<0.01$) in women. Among women with chronic pain, early-life adversity was associated with multisite pain and multiple somatic symptoms; multivariable ORs were 1.78 (1.22-2.60, $p<0.01$) for multisite pain and 1.89 (1.27-2.83, $p<0.01$) for ≥3 somatic symptoms. No associations were observed between early-life adversity and chronic multisite pain or multiple somatic symptoms among men with chronic pain. CONCLUSION: Early-life adversity may be linked to a higher prevalence of chronic pain among both sexes and to multisite pain and somatizing tendency among women with chronic pain.

Medically unexplained physical symptoms (MUPS) among adults in Canada: Comorbidity, health care use and employment.
Park J, Gilmour H.
Health Rep. 2017 Mar 15;28(3):3-8.

Based on data from the 2014 Canadian Community Health Survey and the 2012 Canadian Community Health Survey-Mental Health, this study provides estimates of the prevalence of medically unexplained physical symptoms (MUPS) in the household population aged 25 or older. MUPS are examined in relation to sociodemographic characteristics, physical and mental comorbidity, health care use and unmet needs, labour force participation and productivity. In 2014, 5.5% of Canadian adults-an estimated 1.3 million - reported having chronic fatigue syndrome (1.6%), fibromyalgia (2.0%) and/or multiple chemical sensitivity (2.7%). Half (51%) of people with MUPS reported other chronic physical conditions, compared with 8% of those without MUPS. Similarly, mental comorbidities were more prevalent among those with MUPS. Higher health care use was observed among people with MUPS, but 25% of them reported unmet health care needs, compared with 11% of those without MUPS. People with MUPS were more likely than those without MUPS to be permanently unable to work or to not have a job; fewer than half (45%) were employed. Among those who were employed, 18% had missed work because of a chronic condition, compared with 5% of workers without MUPS.

Association between chronic tension-type headache coexistent with chronic temporomandibular disorder pain and limitations in physical and emotional functioning: A case-control study.
Emshoff R, Bertram F, Schnabl D, Emshoff I.
J Oral Facial Pain Headache. 2017 Winter;31(1):55-60. doi: 10.11607/ofph.1654.

AIMS: To assess the association between chronic tension-type headache coexistent with chronic temporomandibular disorder (TMD) pain and severe limitations in physical and emotional functioning. METHODS: Sample size estimation was used to determine that this case-control study should include 126 subjects. Subjects suffering from chronic TMD who were aged between 18 and 68 were recruited in routine clinical practice. Of the 126 included subjects, 63 had TMD pain associated with chronic tension-type headache (cases) and 63 had TMD pain without a history of tension-type headache (controls). Clinical diagnosis of TMD was made according to the Research Diagnostic Criteria for TMD (RDC/TMD) Axis I criteria, and clinical diagnosis of headache was made according to the International Classification of Headache (ICHD-II). RDC/TMD Axis II criteria were applied to record the scores from the Graded Chronic Pain Scale (GCPS) and the Symptoms Checklist-90-Revised Depression (SCL-DEP) and Somatization (SCL-SOM) scales. A logistic regression analysis was used to assess the relationship between TMD pain with chronic tension-type headache and high levels of depression and somatization severity as scored on the SCLDEP and SCL-SOM scales, respectively, and high pain-related disability (GCPS grade III or IV). Data were adjusted to take into account age, gender, time since TMD pain onset, chronic TMD pain intensity, and characteristic pain intensity. RESULTS: The presence of chronic tension-type headache was significantly associated with severe SCL-DEP (odds ratio [OR] = 7.2; $P < .001$), severe SCLSOM (OR = 13.8; $P < .001$), and high pain-related disability (OR = 9.7; $P < .001$). CONCLUSION: This

study provides evidence of associations between the clinical diagnosis of chronic tension-type headache coexistent with chronic TMD pain and key aspects of physical and emotional functioning reflected in severe depression, severe somatization, and high pain-related disability.

Cohort description: The Danish study of functional disorders.
Dantoft TM, Ebstrup JF, Linneberg A, Skovbjerg S, Madsen AL, Mehlsen J, Brinth L, Eplov LF, Carstensen TW, Schroder A, Fink PK, Mortensen EL, Hansen T, Pedersen O, Jørgensen T.
Clin Epidemiol. 2017 Feb 23;9:127-139. doi: 10.2147/CLEP.S129335. eCollection 2017.

The Danish study of Functional Disorders (DanFunD) cohort was initiated to outline the epidemiology of functional somatic syndromes (FSS) and is the first larger coordinated epidemiological study focusing exclusively on FSS. FSS are prevalent in all medical settings and can be defined as syndromes that, after appropriate medical assessment, cannot be explained in terms of a conventional medical or surgical disease. FSS are frequent and the clinical importance varies from vague symptoms to extreme disability. No well-described medical explanations exist for FSS, and how to delimit FSS remains a controversial topic. The specific aims with the cohort were to test delimitations of FSS, estimate prevalence and incidence rates, identify risk factors, delimitate the pathogenic pathways, and explore the consequences of FSS. The study population comprises a random sample of 9,656 men and women aged 18-76 years from the general population examined from 2011 to 2015. The survey comprises screening questionnaires for five types of FSS, ie, fibromyalgia, whiplash-associated disorder, multiple chemical sensitivity, irritable bowel syndrome, and chronic fatigue syndrome, and for the unifying diagnostic category of bodily distress syndrome. Additional data included a telephone-based diagnostic interview assessment for FSS, questionnaires on physical and mental health, personality traits, lifestyle, use of health care services and social factors, and a physical examination with measures of cardiorespiratory and morphological fitness, metabolic fitness, neck mobility, heart rate variability, and pain sensitivity. A biobank including serum, plasma, urine, DNA, and microbiome has been established, and central registry data from both responders and nonresponders are similarly available on morbidity, mortality, reimbursement of medicine, heath care use, and social factors. A complete 5-year follow-up is scheduled to take place from year 2017 to 2020, and further reexaminations will be planned. Several projects using the DanFunD data are ongoing, and findings will be published in the coming years.

When emotional pain becomes physical: Adverse childhood experiences, pain and the role of mood and anxiety disorders.
Sachs-Ericsson NJ, Sheffler JL, Stanley IH, Piazza JR, Preacher KJ.
J Clin Psychol. 2017 Mar 22. doi: 10.1002/jclp.22444.

OBJECTIVE: We examined the association between retrospective reports of adverse childhood experiences (ACEs) and painful medical conditions. We also examined the mediating and moderating roles of mood and anxiety disorders in the ACEs-painful medical conditions relationship. METHOD: Ten-year longitudinal data were obtained from the National Comorbidity Surveys (NCS-1, NCS-2; N = 5001). The NCS-1 obtained reports of ACEs, current health conditions, current pain severity, and mood and anxiety disorders. The NCS-2 assessed for painful medical conditions (e.g., arthritis/rheumatism, chronic back/neck problems, severe headaches, other chronic pain). RESULTS: Specific ACEs (e.g., verbal and sexual abuse, parental psychopathology, and early parental loss) were associated with the painful medical conditions. Baseline measures of depression, bipolar disorder, and posttraumatic stress disorder were also associated with the number of painful medical conditions. Anxiety and mood disorders were found to partially mediate the ACEs-painful medical conditions relationship. We determined through mediation analyses that ACEs were linked to an increase in anxiety and mood disorders, which, in turn, were associated with an increase in the number of painful medical conditions. We determined through moderation

analyses that ACEs had an effect on increasing the painful medical conditions at both high and low levels of anxiety and mood disorders; though, surprisingly, the effect was greater among participants at lower levels of mood and anxiety disorders. CONCLUSION: There are pernicious effects of ACEs across mental and physical domains. Dysregulation of the hypothalamic-pituitary-adrenal stress response and the theory of reserve capacity are reviewed to integrate our findings of the complex relationships.

CLINICAL STUDIES

Predictors of opioid efficacy in patients with chronic pain: A prospective multicenter observational cohort study.
Grosen K, Olesen AE, Gram M, Jonsson T, Kamp-Jensen M, Andresen T, Nielsen C, Pozlep G, Pfeiffer-Jensen M, Morlion B, Drewes AM.
PLoS One. 2017 Feb 3;12(2):e0171723. doi: 10.1371/journal.pone.0171723. eCollection 2017.

Opioids are increasingly used for treatment of chronic pain. However, they are only effective in a subset of patients and have multiple side effects. Thus, studies using biomarkers for response are highly warranted. The current study prospectively examined 63 opioid-naïve patients initiating opioid use for diverse types of chronic pain at five European centers. Quantitative sensory testing, electroencephalography (EEG) recordings, and assessment of pain catastrophizing were performed prior to treatment. The co-primary outcomes were change from baseline in ratings of chronic pain and quality of life after 14 days of opioid treatment. Secondary outcomes included patient's global impression of clinical change and side effects. Logistic regression models adjusted for age and sex were used to identify biomarkers predictive for successful treatment, defined as at least a 30% reduction in average pain intensity or an improvement in quality of life of at least 10 scale points. Fifty-nine patients (94%) completed the study. The mean age was 55 ± 16 years and 69% were females. Pain reduction was predicted by cold pain intensity (OR: 0.69; P = 0.01), pain catastrophizing (OR: 0.82; P = 0.03), relative delta (OR: 0.76; P = 0.03) and beta EEG activity (OR: 1.18; P = 0.04) induced by experimental cold pain. None of the study variables were related to improvement in quality of life. For the first time, individual pain processing characteristics have been linked to opioid response in a mixed chronic pain population. This has the potential to personalize treatment of chronic pain and restrict opioid use to patients with high likelihood for response.

Identifying fibromyalgia subgroups using cluster analysis: Relationships with clinical variables.
Yim YR, Lee KE, Park DJ, Kim SH, Nah SS, Lee JH, Kim SK, Lee YA, Hong SJ, Kim HS, Lee HS, Kim HA, Joung CI, Kim SH, Lee SS.
Eur J Pain. 2017 Feb;21(2):374-384. doi: 10.1002/ejp.935.

BACKGROUND: Patients with fibromyalgia (FM) exhibit significant clinical heterogeneity, in terms of physical, social and psychological functions, as well as therapeutic responses. Here, we examined FM patients in terms of pain, physical, social and psychological variables to identify clinical subgroups that may be predictive of treatment patterns. METHODS: A total of 313 FM patients were interviewed using a structured questionnaire that included sociodemographic data, current or past FM symptoms and current use of relevant medications. A K-means cluster analysis was conducted using variables reflecting tender points, the Fibromyalgia Impact Questionnaire, Beck Depression Inventory, State-Trait Anxiety Inventor and Social Support Scale. RESULTS: Four distinct clusters were identified in these patients. Group 1 was characterized by high pain levels, severe physical and mental impairment and low social support. Group 2 had moderate pain and physical impairment, mild mental impairment and moderate social support. Group 3 had

moderate pain, low physical and moderate mental impairment and low social support. Group 4 had low pain levels, nearly normal physical and mental function and high social support. Group 1 was more often a current or past smoker, more likely to have a variety of symptoms, including swelling, cognitive dysfunction, dizziness, syncope, oesophageal dysmotility, dyspepsia, irritable bladder, vulvodynia and restless leg syndrome. CONCLUSIONS: We identified four subgroups of FM patients based on pain, physical, social and psychological function. These subgroups had different clinical symptoms and medication profiles, suggesting that FM may be better managed using a more comprehensive assessment of an individual patient's symptoms. SIGNIFICANCE: FM patients can be clustered into four distinct subgroups based on clinically measurable variables - pain, physical involvement, psychological function and social support. These subgroups had different clinical symptoms and medication profiles.

Establishing clinically relevant severity levels for the central sensitization inventory.
Neblett R, Hartzell MM, Mayer TG, Cohen H, Gatchel RJ.
Pain Pract. 2017 Feb;17(2):166-175. 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 joint disorder, 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 ($P \leq 0.02$). 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.

Endometriosis in patients with irritable bowel syndrome: Specific symptomatic and demographic profile, and response to the low FODMAP diet.
Moore JS, Gibson PR, Perry RE, Burgell RE.
Aust N Z J Obstet Gynaecol. 2017 Mar 17. doi: 10.1111/ajo.12594.

BACKGROUND: Women with endometriosis are frequently misdiagnosed with irritable bowel syndrome (IBS) for some time before a correct diagnosis is made. Visceral hypersensitivity is a key feature in both conditions. AIMS: To determine if there are distinct symptom patterns in women with IBS and endometriosis, and to determine the response of these women to a low FODMAP diet in comparison to those with IBS alone. MATERIALS AND METHODS: A retrospective analysis of prospectively collected data from women attending a specialist IBS service in Christchurch New Zealand. Data from those who met Rome III criteria for IBS were sorted into two groups: concurrent endometriosis and those with IBS alone. Demographics and symptom patterns were identified from a prospective questionnaire.

A low FODMAP (fermentable oligosaccharides disaccharides, monosaccharides and polyols) diet was taught to all women as the primary therapeutic intervention. Responses to the diet were noted against their ultimate disposition. RESULTS: Of the 160 women who met Rome III criteria for IBS, 36% had concurrent endometriosis. The presence of dyspareunia (P > 0.0001), referred pain (p=0.005), bowel symptoms exacerbated by menstruation (P = 0.0004) and a family history of endometriosis (P = 0.0003) were associated with concurrent endometriosis. Seventy two percent of these women reported a >50% improvement in bowel symptoms after four weeks of a low FODMAP diet compared with 49% in those with no known endometriosis (P = 0.001, odds ratio 3.11, 95% CI, 1.5-6.2). CONCLUSIONS: Women with concurrent endometriosis and IBS report a unique symptom phenotype. The low FODMAP diet appears effective in women with gut symptoms and endometriosis.

Alpha lipoic acid plus omega-3 fatty acids for vestibulodynia associated with painful bladder syndrome.

Murina F, Graziottin A, Felice R, Gambini D.

J Obstet Gynaecol Can. 2017 Mar;39(3):131-137. doi: 10.1016/j.jogc.2016.12.035.

OBJECTIVE: This study assessed the effectiveness of alpha lipoic acid (ALA) plus omega-3 polyunsaturated fatty acids (n-3 PUFAs) in combination with amitriptyline therapy in patients with vestibulodynia/painful bladder syndrome (VBD/PBS). METHODS: Women with VBD/PBS were randomly assigned to receive amitriptyline or amitriptyline plus a commercially available preparation (ALAnerv Age; Alfa Wassermann, Bologna, Italy) containing, in 2 capsules, ALA 600 mg plus docosahexaenoic acid 250 mg and eicosapentaenoic acid 16.67 mg. Symptoms of burning and pain were assessed using a 10-cm visual analog scale and the short form of the McGill-Melzack Pain Questionnaire. RESULTS: Among 84 women who were randomized, the mean ± standard deviation dose of amitriptyline was 21.7 ± 6.6 mg/day, without statistical difference between the two groups. Pain, as assessed using both the pain rating index of the visual analog scale and the short-form McGill Pain Questionnaire, decreased significantly in both trial groups, with a greater effect seen with the addition of ALA and n-3 PUFAs. The addition of ALA/n-3 PUFAs to amitriptyline treatment was also associated with improvements in dyspareunia and pelvic floor muscle tone. The overall incidence of adverse events was low, and none led to treatment discontinuation. CONCLUSIONS: The addition of ALA/n-3 PUFAs to amitriptyline treatment in patients with VBD/PBS appears to improve outcomes and may allow for a lower dosage of amitriptyline, which may lead to fewer adverse effects.

Pain management in the Ehlers-Danlos syndromes.

Chopra P, Tinkle B, Hamonet C, Brock I, Gompel A, Bulbena A, Francomano C.

Am J Med Genet C Semin Med Genet. 2017 Mar;175(1):212-219. doi: 10.1002/ajmg.c.31554.

Chronic pain in the Ehlers-Danlos syndromes (EDS) is common and may be severe. According to one study, nearly 90% of patients report some form of chronic pain. Pain, which is often one of the first symptoms to occur, may be widespread or localized to one region such as an arm or a leg. Studies on treatment modalities are few and insufficient to guide management. The following is a discussion of the evidence regarding the underlying mechanisms of pain in EDS. The causes of pain in this condition are multifactorial and include joint subluxations and dislocations, previous surgery, muscle weakness, proprioceptive disorders, and vertebral instability. Affected persons may also present with generalized body pain, fatigue, headaches, gastrointestinal pain, temporomandibular joint pain, dysmenorrhea, and vulvodynia. Pain management strategies may be focused around treating the cause of the pain (e.g., dislocation of a joint, proprioceptive disorder) and minimizing the sensation of pain. Management strategies for chronic pain in EDS includes physical therapy, medications, as well as durable medical equipment such as cushions, compressive garments, and braces. The different modalities are discussed in this paper.

About the Chronic Pain Research Alliance

The Chronic Pain Research Alliance (CPRA) is the *only* research-led collaborative advocacy effort dedicated to improving the lives of those affected by multiple pain conditions, termed *Chronic Overlapping Pain Conditions* (COPCs). These include vulvodynia, temporomandibular disorders, fibromyalgia, irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, migraine and tension-type headache, endometriosis, myalgic encephalomyelitis/chronic fatigue syndrome and chronic low back pain.

The CPRA envisions and is working towards a future where individuals with COPCs will receive a timely diagnosis, followed by comprehensive medical care, which includes the use of safe and effective approved treatments, informed by the latest and most rigorous scientific evidence.

Your support is vital to the CPRA's existence. Please donate today! One-hundred percent of your tax-deductible gift will be used to further CPRA's mission and will specifically support initiatives to: i) promote a rigorous, standardized and collaborative scientific research effort on COPCs; ii) translate research findings into educational initiatives for clinicians and patients; and iii) advance industry efforts to research and develop safe and effective therapies for COPCs.