CUTTING EDGE

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COPCs Research Advances

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

In this Issue...

PATHOPHYSIOLOGY STUDIES

Cortical thickness alterations in chronic pain disorder: An exploratory MRI study.
Magon S, Sprenger T, Otti A, Papdopoulou A, Gundel H, Noll-Hussong M.
Psychosom Med. 2018 Sep;80(7):592-598. doi: 10.1097/PSY.0000000000000605.

OBJECTIVE: Chronic pain disorder (CPD) has been associated with brain changes, especially in limbic circuits. However, in most patients with chronic pain, depression or anxiety is a common comorbidity. In this exploratory and naturalistic study, we investigated brain cortical thickness (CTh) differences between patients with CPD and healthy controls, with consideration of concurrent psychiatric symptoms. METHODS: Twenty-three patients with CPD and 23 age- and sex-matched healthy volunteers were included in this study. CTh was estimated using Freesurfer on high-resolution three-dimensional T1-weighted images acquired with a 3T scanner. Group differences were investigated using an analysis of covariance model that included age, sex, and Beck Depression Inventory I and Trait Anxiety Inventory scores as covariates. The relationship between CTh and Toronto Alexithymia Scale (TAS-20) scores was also investigated in patients. Data were corrected for multiplicity using the False Discovery Rate approach ($q < .05$). RESULTS: The comparison between groups using demographics and Beck Depression Inventory I scores as covariates showed thinner cortex in patients compared with controls, after correction for multiplicity in the left precentral ($F(1,42) = 21.9$, $p < .05$) and postcentral gyri ($F(1,42) = 26.9$, $p < .05$) and in the left inferior temporal sulcus ($F(1,42) = 19.6$, $p < .05$). Moreover, using the Trait Anxiety Inventory as

covariate, a trend toward significance ($p < .001$ uncorrected) was seen for the left precentral gyrus ($F(1,42) = 13.8$), right middle frontal ($F(1,42) = 14.3$) and inferior parietal gyri ($F(1,42) = 13.4$), and right anterior temporal pole ($F(1,42) = 15.9$). CONCLUSIONS: The results indicate that brain morphological differences between patients with chronic pain disorder and healthy controls are localized to regions that correspond to sensory as well as affective dimensions of pain processing.

Genome-wide meta-analysis of 158,000 individuals of European ancestry identifies three loci associated with chronic back pain.
Suri P, Palmer MR, Tsepilov YA, Freidin MB, Boer CG, Yau MS, Evans DS, Gelemanovic A, Bartz TM, Nethander M, Arbeeva L, Karssen L, Neogi T, Campbell A, Mellstrom D, Ohlsoon C, Marshall LM, Orwoll E, Uitterlinden A, Rotter JI, Lauc G, Psaty BM, Karlsson MK, Lane NE, Jarvik GP, Polasek O, Hochberg M, Jordan JM, Van Meurs JBJ, Jackson R, Nielson CM, Mitchell BD, Smith BH, Hayward C, Smith NL, Aulchenko YS, Williams FMK.
PLoS Genet. 2018 Sep 27;14(9):e1007601. doi: 10.1371/journal.pgen.1007601.

Back pain is the #1 cause of years lived with disability worldwide, yet surprisingly little is known regarding the biology underlying this symptom. We conducted a genome-wide association study (GWAS) meta-analysis of chronic back pain (CBP). Adults of European ancestry were included from 15 cohorts in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium, and from the UK Biobank interim data release. CBP cases were defined as those reporting back pain present for ≥3-6 months; non-cases were included as comparisons ("controls"). Each cohort conducted genotyping using commercially available arrays followed by imputation. GWAS used logistic regression models with additive genetic effects, adjusting for age, sex, study-specific covariates, and population substructure. The threshold for genome-wide significance in the fixed-effect inverse-variance weighted meta-analysis was $p<5\times10\text{-}8$. Suggestive ($p<5\times10\text{-}7$) and genome-wide significant ($p<5\times10\text{-}8$) variants were carried forward for replication or further investigation in the remaining UK Biobank participants not included in the discovery sample. The discovery sample comprised 158,025 individuals, including 29,531 CBP cases. A genome-wide significant association was found for the intronic variant rs12310519 in SOX5 (OR 1.08, $p = 7.2\times10\text{-}10$). This was subsequently replicated in 283,752 UK Biobank participants not included in the discovery sample, including 50,915 cases (OR 1.06, $p = 5.3\times10\text{-}11$), and exceeded genome-wide significance in joint meta-analysis (OR 1.07, $p = 4.5\times10\text{-}19$). We found suggestive associations at three other loci in the discovery sample, two of which exceeded genome-wide significance in joint meta-analysis: an intergenic variant, rs7833174, located between CCDC26 and GSDMC (OR 1.05, $p = 4.4\times10\text{-}13$), and an intronic variant, rs4384683, in DCC (OR 0.97, $p = 2.4\times10\text{-}10$). In this first reported meta-analysis of GWAS for CBP, we identified and replicated a genetic locus associated with CBP (SOX5). We also identified 2 other loci that reached genome-wide significance in a 2-stage joint meta-analysis (CCDC26/GSDMC and DCC).

Somatosensory function and pain in extremely preterm young adults from the UK EPICure cohort: Sex-dependent differences and impact of neonatal surgery.
Walker SM, Melbourne A, O'Reilly H, Beckman J, Eaton-Rosen Z, Ourselin S, Marlow N.
Br J Anaesth. 2018 Sep;121(3):623-635. doi: 10.1016/j.bja.2018.03.035.

BACKGROUND: Surgery or multiple procedural interventions in extremely preterm neonates influence neurodevelopmental outcome and may be associated with long-term changes in somatosensory function or pain response. METHODS: This observational study recruited extremely preterm (EP, <26 weeks' gestation; n=102, 60% female) and term-born controls (TC; n=48) aged 18-20 yr from the UK EPICure cohort. Thirty EP but no TC participants had neonatal surgery. Evaluation included: quantitative sensory testing (thenar eminence, chest wall); clinical pain history; questionnaires (intelligence quotient; pain catastrophising; anxiety); and structural brain imaging. RESULTS: Reduced thermal threshold sensitivity in EP vs TC participants persisted at age 18-20 yr. Sex-dependent effects varied with stimulus intensity and were enhanced by neonatal surgery, with reduced threshold sensitivity in EP

surgery males but increased sensitivity to prolonged noxious cold in EP surgery females ($P<0.01$). Sex-dependent differences in thermal sensitivity correlated with smaller amygdala volume ($P<0.05$) but not current intelligence quotient. While generalised decreased sensitivity encompassed mechanical and thermal modalities in EP surgery males, a mixed pattern of sensory loss and sensory gain persisted adjacent to neonatal scars in males and females. More EP participants reported moderate-severe recurrent pain (22/101 vs 4/48; $\chi^2=0.04$) and increased pain intensity correlated with higher anxiety and pain catastrophising. CONCLUSIONS: After preterm birth and neonatal surgery, different patterns of generalised and local scar-related alterations in somatosensory function persist into early adulthood. Sex-dependent changes in generalised sensitivity may reflect central modulation by affective circuits. Early life experience and sex/gender should be considered when evaluating somatosensory function, pain experience, or future chronic pain risk.

Spinal fluid evacuation may provide temporary relief for patients with unexplained widespread pain and fibromyalgia.
Hulens M, Rasschaert R, Dankaerts W, Stalmans I, Vansant G, Bruyninckx F.
Med Hypotheses. 2018 Sep;118:55-58. doi: 10.1016/j.mehy.2018.06.017.

Fibromyalgia (FM) exhibits characteristics of a neurological disorder, and similarities have been identified between FM and idiopathic intracranial hypertension (IICH). When intracranial pressure rises, the drainage of excess cerebrospinal fluid (CSF) through the subarachnoid space of the cranial and spinal nerves increases. Higher CSF pressure irritates nerve fibers inside nerve root sheaths and may consequently cause radicular pain, as was reported in patients with IICH. Moreover, the cut-off of 20-25 cm H_20 used to define IICH may be too high, as has been suggested in patients with chronic fatigue syndrome. We hypothesize that the neurological symptoms of FM are caused by the dysregulation of cerebrospinal pressure (CSP) and that spinal fluid drainage can relieve this pain. Exploring the processes underlying increased CSP may provide an alternative explanation for the generation of unexplained widespread pain (WSP) and FM as opposed to central sensitization. Additionally, when performing a lumbar puncture for diagnostic reasons, it is useful to measure opening pressure in patients with chronic WSP.

Intolerance to environmental chemicals and sounds in irritable bowel syndrome: Explained by central sensitization?
Stahlberg L, Palmquist E, Nordin S.
J Health Psychol. 2018 Sep;23(10):1367-1377. doi: 10.1177/1359105316656242.

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.

The comorbidity of fibromyalgia syndrome and attention deficit and hyperactivity disorder from a pathogenic perspective.
Bou Khalil R, Khoury E, Richa S.
Pain Med. 2018 Sep 1;19(9):1705-1709. doi: 10.1093/pm/pny142.

No abstract available.

Attention-deficit/hyperactivity disorder, joint hypermobility-related disorders and pain: expanding body-mind connections to the developmental age.
Baeza-Velasco C, Sinibaldi L, Castori M.

Atten Defic Hyperact Disord. 2018 Sep;10(3):163-175. doi: 10.1007/s12402-018-0252-2.

Attention-deficit/hyperactivity disorder (ADHD) and generalized joint hypermobility (JH) are two separated conditions, assessed, and managed by different specialists without overlapping interests. Recently, some researchers highlighted an unexpected association between these two clinical entities. This happens in a scenario of increasing awareness on the protean detrimental effects that congenital anomalies of the connective tissue may have on human health and development. To review pertinent literature to identify possible connections between ADHD and GJH, special emphasis was put on musculoskeletal pain and syndromic presentations of GJH, particularly the hypermobile Ehlers-Danlos syndrome. A comprehensive search of scientific databases and references lists was conducted, encompassing publications based on qualitative and quantitative research. Impaired coordination and proprioception, fatigue, chronic pain, and dysautonomia are identified as potential bridges between ADHD and JH. Based on these findings, a map of the pathophysiological and psychopathological pathways connecting both conditions is proposed. Although ADHD and JH are traditionally separated human attributes, their association may testify for the dyadic nature of mind-body connections during critical periods of post-natal development. Such a mixed picture has potentially important consequences in terms of disability and deserves more clinical and research attention.

EPIDEMIOLOGY STUDIES

Self-medication with over-the-counter analgesics: A survey of patient characteristics and concerns about pain medication.
Mehuys E, Crombez G, Paemeleire K, Adriaens E, Van Hees T, Demarche S, Christiaens T, Van Bortel L, Van Tongelen I, Remon JP, Boussery K.
J Pain. 2018 Sep 28. pii: S1526-5900(18)30641-2. doi: 10.1016/j.jpain.2018.09.003.

Pain is a common reason for self-medication with over-the-counter (OTC) analgesics. However, this self-treating population has remained largely uncharacterized. This cross-sectional observational study investigated individuals who self-medicate their pain with OTC analgesics to elucidate their pain characteristics and medication use. In addition, presence of and risk factors for concerns about pain medication were examined. The clinical profile of the participants (n=1889) was worse than expected with long-standing pain complaints (median pain duration of 9 years), pain located at multiple body sites (median of 4, and 13% with ≥10 painful body areas), about one third suffering from daily pain and about 40% experiencing substantial pain-related disability. Head (58.6% of sample), low back (43.6%) and neck (30.7%) were the most common pain locations. About 73% had a physician diagnosis, mainly migraine and osteoarthritis. Paracetamol (used by 68.6% of patients) and NSAID (46.8%) were the most frequently used pain medications. About 40% of our sample showed substantial concern about the perceived need for pain medication and the perceived potential for harmful effects (e.g. fear for addiction). These findings highlight the importance for health professionals to systematically probe pain patients about their self-medication practices and explore attitudes about pain medication. PERSPECTIVE: This study found that the clinical picture of people who self-medicate their pain with OTC analgesics looked worse than expected. We also identified substantial concerns about pain medication. Therefore, we recommend that health professionals systematically probe pain patients about their self-medication practices and explore concerns about pain medication.

The associated features of multiple somatic symptom complexes.
Creed F, Tomenson B, Chew-Graham C, Macfarlane G, McBeth J.
J Psychosom Res. 2018 Sep;112:1-8. doi: 10.1016/j.jpsychores.2018.06.007.

OBJECTIVE: To assess whether two or more functional somatic symptom complexes (SSCs) showed stronger association with psychosocial correlates than single or no SSC after

adjustment for depression/anxiety and general medical disorders. METHODS: In a population-based sample we identified, by standardised questionnaire, participants with chronic widespread pain, chronic fatigue and irritable bowel syndrome, excluding those with a medical cause for pain/fatigue. We compared psychosocial variables in three groups: multiple (>1), single or no FSS, adjusting for depression/anxiety and general medical disorders using ordinal logistic regression. We evaluated whether multiple SSCs predicted health status 1 year later using multiple regression to adjust for confounders. RESULTS: Of 1443 participants (58.0% response) medical records were examined in 990: 4.4% (n=44) had 2 or 3 symptom complexes, 16.2% a single symptom complex. Many psychosocial adversities were significantly associated with number of SSCs in the expected direction but, for many, statistical significance was lost after adjustment for depression/anxiety and medical illness. Somatic symptoms, health anxiety, impairment and number of prior doctor visits remained significantly associated. Impaired health status 1 year later was predicted by multiple somatic symptom complexes even after adjustment for depression, anxiety, medical disorders and number of symptoms. CONCLUSIONS: Depression, anxiety, medical illness and health anxiety, demonstrated an exposure-response relationship with number of somatic symptom complexes. These may be core features of all Functional Somatic Syndromes and may explain why number of somatic symptom complexes predicted subsequent health status. These features merit inclusion in prospective studies to ascertain causal relationships.

Health-related quality of life of people with multimorbidity at a community-based, interprofessional student-assisted clinic: Implications for assessment and intervention.
Tyack Z, Kuys, Cornwell P, Frakes KA, McPhail S.
Chronic Illn. 2018 Sep;14(3):169-181. doi: 10.1177/1742395317724849.

Objective This study examined the relationship between the number of comorbidities and health-related quality of life (HRQoL) and between select physical conditions and HRQoL. Differences in HRQoL in comparison to a normative sample were also examined. Method A cross-sectional study among people with multimorbidity (n = 401) attending a community-based, interdisciplinary health clinic was conducted. HRQoL was measured using the eight dimensions of the SF-36. Multiple linear regression and t-tests were used to analyse the data. Results A downward trend in HRQoL continued from 2 to 14 concurrent comorbidities. Patients with a higher number of comorbidities reported greater deficits in HRQoL, when age, gender, education and perceived social support were controlled for (beta = -0.11 to -0.31). The impact of the number of comorbidities was greatest for the bodily pain dimension of the SF-36 (beta = -0.31). Deficits were greatest for people with gastrointestinal conditions and back pain or sciatica. Moderate to large deficits in HRQoL compared to a normative population were found (Cohen's d = 0.54-1.16). Discussion Understanding associations between the number and type of physical comorbidities and HRQoL may assist clinical services to design broad but targeted interventions to optimize HRQoL in this group of people.

Headache attributed to TMD Is associated with the presence of comorbid bodily pain: A case-control study.
Vivaldi D, Di Giosia M, Tchivileva IE, Jay GW, Slade GD, Lim PF.
Headache. 2018 Sep 4. doi: 10.1111/head.13404. [Epub ahead of print]

Headache attributed to temporomandibular disorders (TMDH) is defined as a secondary headache by the International Classification of Headache Disorders 3rd edition (ICHD-3). OBJECTIVE: The objective of this case-control study is to investigate the phenotypic characteristics of of chronic TMD with and without TMDH. We hypothesize that chronic TMD with TMDH is associated with increased number of bodily pain conditions, more painful sites in the head and neck region, and greater TMD pain intensity. METHODS: This is a retrospective cross-sectional review of the medical records of consecutive patients who sought treatment at the University of North Carolina Orofacial Pain Clinic between 2013 and 2014. The inclusion criterion was a diagnosis of myalgia or arthralgia according to the

Research Diagnostic Criteria for Temporomandibular Disorders. In addition, cases had a diagnosis of TMDH according to the ICHD-3 criteria. Data on the presence and the number of self-reported bodily pain conditions (such as fibromyalgia and low back pain), pain intensity, number of painful sites in the head and neck upon palpation, and TMD pain onset were analyzed. RESULTS: A total of 295 records were reviewed. Thirty-four (29.3%) patients fulfilled inclusion criteria for cases (TMD+TMDH) and 82 (70.7%) for controls (TMD-TMDH). Cases reported greater number of bodily pain conditions than controls, with a mean of 1.97 ± 1.50 and 1.26 ± 1.28 of bodily pain conditions, respectively (P = .012, OR = 1.43 [95% CI 1.07-1.92]). In fact, 55.9% of cases reported at least 2 comorbid pain conditions compared to 37.8% controls (P = .044). Compared to controls (8.65 ± 5.32), cases (13.05 ± 4.46) exhibited greater number of painful sites upon palpation in the head and neck region (P < .0001, OR = 1.18 [95% CI 1.09-1.30]), and greater TMD pain intensity, with a mean of 6.00 ± 2.17 for cases and 5.09 ± 2.14 for controls (P = .041, OR = 1.22 [95% CI 1.01-1.47]). CONCLUSION: In a population of patients with chronic TMD seeking pain management, TMDH was significantly associated with an increased number of self-reported bodily pain conditions, a greater number of painful sites in the head and neck regions, and higher TMD pain intensity.

Deployment-related traumatic brain injury and risk of new episodes of care for back pain in veterans.
Suri P, Stolzmann K, Williams R, Pogoda TK.
J Pain. 2018 Aug 30. pii: S1526-5900(18)30490-5. doi: 10.1016/j.jpain.2018.08.002.

Traumatic brain injury (TBI) may be a predisposing factor to pain syndromes other than headache. We conducted a longitudinal cohort study among Veterans evaluated for TBI in the Department of Veterans Affairs (VA). Among 36,880 Veterans at baseline, 55% reported back pain. TBI history was classified by trained clinicians according to VA-Department of Defense criteria. 14,223 Veterans without back pain were followed for up to 6 years for new (incident) episodes of VA care for back pain. We estimated adjusted odds ratios (aORs), adjusted hazard ratios (aHRs) and 95% confidence intervals (CI), accounting for covariates. Deployment-related mild TBI was significantly associated with self-reported back pain in cross-sectional analyses (aOR 1.27, 95% CI 1.21-1.35), but not with incident episodes of VA care for back pain in longitudinal analysis (aHR 1.07, 95% CI 0.99-1.17). Deployment-related moderate/severe TBI was significantly associated with self-reported back pain in cross-sectional (aOR 1.74, 95% CI 1.58-1.91), and longitudinal analyses (aHR 1.20, 95% CI 1.05-1.38; p=.01). These findings indicate that deployment-related moderate/severe TBI confers increased back pain risk, but do not support a causal effect of deployment-related mild TBI on back pain. PERSPECTIVE: Findings from this longitudinal study of Veterans indicate that deployment-related moderate/severe TBI confers increased back pain risk, but do not support a causal effect of deployment-related mild TBI on back pain.

Painful temporomandibular disorders (TMD) and comorbidities in primary care: Associations with pain-related disability.
Kotiranta U, Forssell H, Kauppila T.
Acta Odontol Scand. 2018 Sep 28:1-6. doi: 10.1080/00016357.2018.1493219.

OBJECTIVE: We studied whether primary care temporomandibular disorder (TMD) patients reporting different levels of pain-related disability differ in terms of comorbid pains, general health conditions and quality of life. MATERIAL AND METHODS: Consecutive TMD pain patients (n=399) seeking treatment in primary care completed a questionnaire on comorbid pains and their interference and the Finnish version of the RAND-36-item quality of life questionnaire. Medical diagnoses confirmed by doctors were recorded. The patients were classified according to the Graded Chronic Pain Scale (GCPS) of the Research Diagnostic Criteria for TMD (RDC/TMD). The patients were classified: no disability group (0 disability points), low disability group (1-2 disability points) and high disability group (3-6 disability points). RESULTS: Compared to patients in the no-disability group, patients in the high- and low-disability groups reported more comorbid pain conditions (p<0.001), and experienced these as more intense and interfering more with daily life (p<0.05). Patients in

the high-disability group reported more general health-related medical diagnoses than patients in the no-disability group ($p<0.05$). Furthermore, patients with low or high pain-related disability indicated poorer quality of life in all RAND-36 subscales than those with no disability ($p<0.05$). CONCLUSIONS: The findings suggest that GCPS-related disability scoring can be used as a simple screening instrument to identify TMD patients with different degrees of health burdens.

Relationships between temporomandibular disorders, MSD conditions, and mental health comorbidities: Findings from the Veterans Musculoskeletal Disorders Cohort.
Fenton BT, Goulet JL, Bair MJ, Cowley T, Kerns RD.
Pain Med. 2018 Sep 1;19(suppl_1):S61-S68. doi: 10.1093/pm/pny145.

OBJECTIVE: Temporomandibular disorders (TMDs) have been associated with other chronic painful conditions (e.g., fibromyalgia, headache) and suicide and mood disorders. Here we examined musculoskeletal, painful, and mental health comorbidities in men vs women veterans with TMD (compared with non-TMD musculoskeletal disorders [MSDs] cases), as well as comorbidity patterns within TMD cases. DESIGN: Observational cohort. SETTING: National Veterans Health Administration. SUBJECTS: A cohort of 4.1 million veterans having 1 or more MSDs, entering the cohort between 2001 and 2011. METHODS: Chi-square tests, t tests, and logistic regression were utilized for cross-sectional analysis. RESULTS: Among veterans with any MSD, those with TMD were younger and more likely to be women. The association of TMD with race/ethnicity differed by sex. Odds of TMD were higher in men of Hispanic ethnicity (OR=1.38, 95% CI = 1.27-1.48) and and nonwhite race/ethnicity other than black or Hispanic (OR=1.29, 95% CI = 1/16-1.45) compared with white men. Odds of TMD were significantly lower for black (OR=0.54, 95% CI = 1/49-0.60) and Hispanic women (OR=0.84, 95% CI = 0.73-0.995) relative to white women. Non-MSD comorbidities (e.g., irritable bowel syndrome, mental health, headaches) were significantly associated with TMD in male veterans; their pattern was similar in women. Veterans with back pain, nontraumatic joint disorder, or osteoarthritis had more MSD multimorbidity than those with TMD. CONCLUSIONS: Complex patterns of comorbidity in TMD cases may indicate different underlying mechanisms of association in subgroups or phenotypes, thereby suggesting multiple targets to improve TMD. Longitudinal comprehensive studies powered to look at sex and racial/ethnic groupings are needed to identify targets to personalize care.

Fibromyalgia in patients with chronic CCD and CMD - A retrospective study of 555 patients.
Losert-Bruggener B, Hulse M, Hulse R.
Cranio. 2018 Sep;36(5):318-326. doi: 10.1080/08869634.2017.1334376.

OBJECTIVE: Craniomandibular dysfunction (CMD) and craniocervical dysfunction (CCD) are clearly defined musculoskeletal pain syndromes. Relationships with fibromyalgia syndrome (FMS) have not yet been investigated. The aim of the present study is to establish possible relationships between FMS and CMD/ CCD. METHODS: In a retrospective study, 555 patients with CCD and CMD were investigated with respect to the diagnostic criteria of FMS. In addition to otolaryngologic and dental examination, an instrumental functional analysis for the diagnosis of CMD/CCD was performed. RESULTS: Three hundred fifty-one (63%) of the 555 patients evaluated met the diagnostic criteria for FMS. Seventy-two percent of the patients had a widespread pain index of at least 7 and a severity scale score of at least 5. Twenty-nine percent had a widespread pain index of 3-6 and a severity scale score of at least 9. Using myocentric bite splint therapy and therapy with oral orthesis in combination with neuromuscular relaxation measures, a good to very good improvement of physical symptoms was seen in 84% of CMD-FMS patients, and an improvement of the symptoms in the jaw was achieved in 77% of cases. DISCUSSION: The substantial proportion of CMD and CCD patients who meet the criteria for FMS emphasizes the complexity of the two diseases. It must be assumed that FMS is a crucial factor for the formation of CMD and CCD. Conversely, CMD/ CCD could also be responsible for diverse clinical pictures of the FMS. FMS patients with synchronous CCD/CMD benefit from an interdisciplinary CMD/CCD treatment.

Fatigue and its associated factors in microscopic colitis.
Kane JS, Irvine AJ, Derwa Y, Ford AC.
Therap Adv Gastronenterol. 2018 Sep 13;11:1756284818799599. doi: 10.1177/1756284818799599. eCollection 2018.

BACKGROUND: Fatigue is a well-recognized symptom in patients with inflammatory bowel disease and irritable bowel syndrome (IBS), and has been associated with psychological comorbidity and impaired quality of life in both. However, features associated with fatigue in patients with microscopic colitis (MC) are less clear. MATERIALS AND METHODS: We conducted a cross-sectional survey of patients with a new diagnosis of MC including levels of anxiety, depression, somatization, quality of life, and IBS-type symptoms. Levels and impact of fatigue were assessed using the Inflammatory Bowel Disease Fatigue self-assessment scale. Mean scores were compared against various patient characteristics, and were also correlated with anxiety, depression, somatization, and quality-of-life scores. RESULTS: In total, 129 patients with MC diagnosed between 2010 and 2015 returned completed postal questionnaires. Common histological subtypes were collagenous colitis (53.5%, $n = 69$) and lymphocytic colitis (38.8%, $n = 50$). Higher mean fatigue severity and impact scores were associated with the presence of irritable-bowel-syndrome-type symptoms, abnormal levels of anxiety and depression, and high levels of somatization ($p < 0.0001$ for all), but those reporting ongoing symptoms attributable to MC did not report significantly higher scores. There were significant positive correlations between total anxiety, depression, or somatization scores and fatigue severity and impact scores, and significant negative correlations with quality-of-life measures ($p < 0.001$ for all). CONCLUSIONS: Fatigue in MC appears to be associated with reporting IBS-type symptoms, psychological comorbidity and impaired quality of life. It may therefore represent an important target for treatment.

Insomnia and impaired quality of Life in the United States.
Oflson M, Wall M, Liu SM, Morin CM, Blanco C.
J Clin Psychiatry. 2018 Sep 11;79(5). pii: 17m12020. doi: 10.4088/JCP.17m12020.

OBJECTIVE: This analysis characterizes the individual-level and population-level burden of insomnia in relation to other medical conditions and describes the comorbidity of insomnia with other medical conditions, including the dependence of these comorbidities on pain, life events, and mental disorders. METHODS: Information from 34,712 adults in the National Epidemiologic Survey on Alcohol and Related Conditions-III (2012-2013) was analyzed. Quality-adjusted life-years (QALYs) were measured with the SF-6D, a 6-dimensional health state classification derived from the Short-Form-12, version 2. RESULTS: In the last 12 months, 27.3% of adults reported insomnia. The US annual loss of QALYs associated with insomnia (5.6 million; 95% CI, 5.33-5.86 million) was significantly larger than that associated with any of the other 18 medical conditions assessed, including arthritis (4.94 million; 95% CI, 4.62-5.26 million), depression (4.02 million; 95% CI, 3.87-4.17 million), and hypertension (3.63 million; 95% CI, 3.32-3.93 million). After control for demographic factors, all conditions examined from obesity (adjusted odds ratio [aOR] = 1.25) to mania (aOR = 5.04) were associated with an increased risk of insomnia. Further controlling for pain, stressful life events, and mental disorders decreased the odds of the co-occurrence of insomnia with these conditions. The decrease in insomnia comorbidity associated with pain was greatest for fibromyalgia (31.8%) and arthritis (20.1%); the decrease in insomnia comorbidity associated with life events was greatest for mania (13.4%) and drug use disorders (11.2%); and the decrease in insomnia comorbidity associated with mental disorders was greatest for peptic ulcer disease (11.2%) and liver diseases (11.1%). CONCLUSIONS: Insomnia is prevalent and associated with substantial population-level burden in self-assessed health. The co-occurrence of insomnia with common medical conditions is differentially related to pain and to a lesser extent to stressful life events and mental disorders.

Screening for adult ADHD in patients with fibromyalgia syndrome.
Van Rensburg R, Meyer HP, Hitchcock SA, Schuler CE.

Pain Med. 2018 Sep 1;19(9):1825-1831. doi: 10.1093/pm/pnx275.

OBJECTIVE: Fibromyalgia syndrome (FMS) is a common chronic pain disorder associated with altered activity of neurotransmitters involved in pain sensitivity such as dopamine, serotonin, and noradrenaline. FMS may significantly impact an individual's functioning due to the presence of chronic pain, fatigue, and cognitive impairment. Dyscognition may be more disabling than the chronic pain but is mostly under-recognized. This study aimed to assess the potential co-occurrence of FMS and adult attention deficit hyperactivity disorder (ADHD), a chronic neurodevelopmental disorder also associated with impaired cognition and dopaminergic function. METHODS: In a cross-sectional observational study, 123 previously confirmed FMS patients were screened for adult ADHD using the World Health Organization Adult ADHD Self Report scale v1.1. The Revised Fibromyalgia Impact Questionnaire (FIQ-R) was used to assess the impact of FMS. Cognitive assessment was based on self-report in accordance with the 2011 modified American College of Rheumatology criteria and the FIQ-R, respectively. RESULTS: Of the 123 participants, 44.72% (n=55) screened positive for adult ADHD. Participants with both FMS and a positive adult ADHD screening test scored higher on the FIQ-R score (64.74, SD=17.66, vs 54.10, SD=17.10). Self-reported cognitive impairment was rated higher in the combined group (OR=10.61, 95% CI; 3.77-29.86, p<0.01). CONCLUSIONS: These results indicate that the co-occurrence of adult ADHD in FMS may be highly prevalent and may also significantly impact the morbidity of FMS. Patients with FMS should be assessed for the presence of adult ADHD.

Prevalence of pain in COPD patients and associated factors: Report from a population-based study.
De Miguel-Diez J, Lopez-de-Andres A, Hernandez-Barrera V, Jimenez-Trujillo I, Del Barrio JL, Puente-Maestu L, Martinez-Huedo MA, Jimenez-Garcia R.
Clin J Pain. 2018 Sep;34(9):787-794. doi: 10.1097/AJP.0000000000000598.

OBJECTIVES: To assess the prevalence of chronic neck pain (CNP), chronic low back pain (CLBP), and migraine among Spanish adults with chronic obstructive pulmonary disease (COPD) compared with non-COPD patients matched by age and sex; and to identify predictors for each of these types of pains among COPD sufferers. MATERIALS AND METHODS: A cross-sectional study conducted with data collected from the European Health Interview Surveys for Spain (EHSS) conducted in years 2009/2010 (n=22,188) and 2014 (n=22,842). Data were analyzed using multivariable logistic models. RESULTS: The prevalence of COPD among patients aged 35 years or above were 7.6% (n=1328) for the EHSS 2009 and 5.4% (n=1008) for the EHSS 2014. We matched 2251 COPD patients with age and sex controls. The prevalence of all types of pain were significantly higher among those suffering COPD than those without COPD. For CNP the figures were 40.5% versus 26.1%, for CLBP 44.8% versus 28.4%, and for migraine 22.5% versus 13.2%. Multivariable analysis showed that COPD was associated to a 1.21 (95% confidence interval [CI], 1.02-1.45) higher risk of CNP, 1.38 (95% CI, 1.16-1.64) of CLBP, and 1.36 (95% CI, 1.12-1.65) of migraine. Associated factors with the presence of these types of pain among COPD patients included younger age (not for CLBP), female sex (not for CLBP), "fair/poor/very poor" self-rated health (not for migraine), high blood pressure (not for CNP), mental disorders, obesity (not for migraine), and use of pain medication. DISCUSSION: The prevalence of CNP, CLBP, and migraine was significantly higher among COPD patients in comparison with controls. Associated factors to suffering these types of pain in patients with COPD included age, sex, self-rated health, certain comorbidities including mental disorders, obesity, and using pain medication.

CLINICAL STUDIES

Gabapentin for off-label use: Evidence-based or cause for concern?
Peckham AM, Evoy KE, Ochs L, Covvey JR.
Subst Abuse. 2018 Sep 23;12:1178221818801311. doi: 10.1177/1178221818801311. eCollection 2018.

Gabapentin is widely used in the United States for a number of off-label indications, often as an alternative to opioid therapy. Increasing evidence has emerged suggesting that gabapentin may not be as benign as once thought and may be associated with substance abuse in concert with opioids. With concerns for safety mounting, it is prudent to examine the efficacy of gabapentin across its many uses to understand the risk-benefit balance. Reviews on off-label indications such as migraine, fibromyalgia, mental illness, and substance dependence have found modest to no effect on relevant clinical outcomes. This high-quality evidence has often been overshadowed by uncontrolled studies and limited case reports. Furthermore, the involvement of gabapentin in questionable marketing schemes further calls its use into question. Overall, clinicians should exercise rigorous appraisal of the available evidence for a given indication, and researchers should conduct larger, higher-quality studies to better assess the efficacy of gabapentin for many of its off-label uses.

Gender and the language of pain in chronic and terminal illness: A corpus-based discourse analysis of patients' narratives.
Jaworska S, Ryan K.
Soc Sci Med. 2018 Oct;215:107-114. doi: 10.1016/j.socscimed.2018.09.002.

Drawing on the notion of gender as a socially constructed category performed inter alia through language, this study examines the ways in which women and man use language to do person-in-pain in real-life interactions about chronic and terminal illness. It is based on a secondary analysis of a large corpus of health and illness narratives collected by the Health Experiences Research Group at the University of Oxford and published by the DIPEx charity. Sixteen chronic and terminal conditions were identified in which men and women talked about physical pain and their narratives examined using the linguistic approach of a corpus-assisted discourse analysis. Our study shows that there are significant quantitative and qualitative differences in the ways in which women and men report pain pointing to the existence of distinctive feminine and masculine lexical repertoires of pain talk. While these repertoires conform to some of the dominant societal stereotypes surrounding masculinity and femininity, they also transgress those. Women refer to pain more frequently and have a wider lexical repertoire for pain reporting. They use more specific and factual references as well as cognitive and psychological words in their pain talk. In contrast, men tend to use fewer descriptors in general, most of which are highly emotive suggesting that they report pain when it becomes unbearable enduring it until this point. There is also a conspicuous absence of references to psychological processes in the male narratives and the focus is on pain killers. Understanding this nuanced role of gender in communicating pain can help health professionals respond effectively to people's talk about pain and develop more holistic practices in pain consultation, assessment and treatment leading potentially to the reduction of gender biases and inequalities in healthcare.

Unraveling the molecular determinants of manual therapy: An approach to integrative therapeutics for the treatment of fibromyalgia and chronic fatigue syndrome/myalgic encephalomyelitis.
Espejo JA, Garcia-Escudero M, Oltra E.
Int J Mol Sci. 2018 Sep 9;19(9). pii: E2673. doi: 10.3390/ijms19092673.

Application of protocols without parameter standardization and appropriate controls has led manual therapy (MT) and other physiotherapy-based approaches to controversial outcomes. Thus, there is an urgency to carefully define standard protocols that elevate physiotherapy treatments to rigorous scientific demands. One way in which this can be achieved is by studying gene expression and physiological changes that associate to particular, parameter-controlled, treatments in animal models, and translating this knowledge to properly designed, objective, quantitatively-monitored clinical trials (CTs). Here, we propose a molecular physiotherapy approach (MPTA) requiring multidisciplinary teams, to uncover the scientific reasons behind the numerous reports that historically attribute health benefits to

MT-treatments. The review focuses on the identification of MT-induced physiological and molecular responses that could be used for the treatment of fibromyalgia (FM) and chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). The systemic effects associated to mechanical-load responses are considered of particular relevance, as they suggest that defined, low-pain anatomic areas can be selected for MT treatment and yet yield overall benefits, an aspect that might result in it being essential to treat FM. Additionally, MT can provide muscle conditioning to sedentary patients without demanding strenuous physical effort, which is particularly detrimental for CFS/ME patients, placing MT as a real option for integrative medicine programs to improve FM and CFS/ME.

Computer-assisted cognitive-behavior therapy in medical care settings.
Wright JH, McCray LW, Eells TD, Gopalraj R, Bishop LB.
Curr Psychiatry Rep. 2018 Sep 7;20(10):92. doi: 10.1007/s11920-018-0947-2.

PURPOSE OF REVIEW: We reviewed research on computer-assisted cognitive-behavior therapy (CCBT) performed in medical settings with the goals of assessing the effectiveness of this newer method of treatment delivery, evaluating the need for clinician support of therapeutic computer programs, and making suggestions for future research and clinical implementation. RECENT FINDINGS: The overall results of randomized, controlled trials suggest that CCBT can be an effective treatment for depression in primary care patients and health care anxiety. Also, it can be a useful component of treatment for somatic conditions including irritable bowel syndrome, diabetes, fibromyalgia, and chronic pain. The amount and type of clinician support needed for maximizing effectiveness remains unclear. CCBT offers promise for overcoming barriers to delivering effective psychotherapy in medical settings. We recommend that next steps for researchers include more definitive studies of the influence of clinician support, investigations focused on implementation in clinical practices, cost-benefit analyses, and use of technological advances.

Influence of comorbidities on patients reported outcomes in degenerative lumbar spinal stenosis.
Emmanuelle F, Guillaume L, Benjamin B, Marc S, Mourad OS, Pierre G.
Orthop Traumatol Surg Res. 2018 Sep 1. pii: S1877-0568(18)30240-8. doi: 10.1016/j.otsr.2018.07.012.

INTRODUCTION: In degenerative lumbar spinal stenosis (DLSS) variability of symptoms according to the severity of stenosis is not well understood. Therefore, another factor that impacts functional outcomes of DLSS patients has been evoked: patient's comorbidities. The aim of this study was to investigate influence of comorbidities on clinical symptoms and functional outcomes in DLSS patients. METHODS: In this prospective study, patients treated for DLSS were included during 12 consecutive months. Both clinical and radiographic exams were required to confirm DLSS diagnosis. Epidemiologic, clinical and radiographic data were collected. Two questionnaires were used to assess functional outcomes: a specific score dedicated to lumbar stenosis consequences assessment (self-administered Beaujon questionnaire, SABQ) and a non-specific score (Short Form 36, SF-36).
Four comorbidity scores were calculated: Cumulative Illness Rating Scale, Charlson index, Functional Comorbidity Index and Index of Co-Existent Diseases. Correlations between functional and comorbidity scores were calculated. RESULTS: 250 patients were included (65.6 ±12 years). The four comorbidities scores were significantly correlated to total SABQ, as well as lumbar and radicular ischemia components. Best correlations were observed for cumulative illness rating scale and SABQ. Two factors were observed that significantly influenced the relationship between SABQ and cumulative illness rating scale: herniated disc and SF-36 general health perception. DISCUSSION: This study highlighted that preoperative function is influenced by comorbidities in DLSS patients. Relationships existed between comorbidities and symptoms related to low back pain and neurogenic claudication, contrary to radicular pain. Therefore, comorbidities might impact the variability of patients' outcomes. This finding should be part of the patient's preoperative information. Moreover, role of comorbidities on postoperative outcomes need to be investigated.

Reduced symptoms of post-traumatic stress disorder and irritable bowel syndrome following mindfulness-based stress reduction among veterans.

Harding K, Simpson T, Kearney DJ.

J Altern Complement Med. 2018 Aug 30. doi: 10.1089/acm.2018.0135.

OBJECTIVES: Post-traumatic stress disorder (PTSD) and irritable bowel syndrome (IBS) are highly comorbid conditions associated with reduced health-related quality of life. Comorbid prevalence is especially high among veterans, ranging from 23% to 51%, but there is limited research on integrative treatments. DESIGN: To improve treatment of comorbid PTSD and IBS, this study examined the impact of mindfulness-based stress reduction (MBSR) on symptom reduction and mindfulness skill building among veterans with this comorbidity. We hypothesized that veterans would report reduced trauma-related, gastrointestinal (GI) symptom-specific anxiety (GSA), and depression symptoms and greater mindfulness skills post-treatment. We also hypothesized that veterans who reported lower trauma-related GSA and depression symptoms, and reported greater mindfulness skills and MBSR session attendance would report lower irritable bowel symptoms post-treatment. SETTINGS/LOCATION: VA (Veterans Administration) Puget Sound Health Care System, Seattle, Washington. SUBJECTS: Participants were 55 veterans with PTSD and IBS. INTERVENTIONS: Veterans participated in an 8-week open trial of MBSR group. OUTCOME MEASURES: This study measured the impact of MBSR on PTSD, IBS, GSA, and depression symptoms as well as mindfulness skills. RESULTS: Veterans reported reduced trauma-related, irritable bowel, GSA, and depression symptoms and greater mindfulness skills immediately post-treatment. Trauma-related and depression symptom reduction were maintained 4 months post-treatment, but irritable bowel and GSA symptoms were nonsignificant. Lower baseline GSA predicted lower irritable bowel symptoms immediately post-treatment. At 4 months post-treatment, 77.50% met PTSD criteria and 40.38% met IBS criteria compared with 100% veteran comorbidity pretreatment. CONCLUSIONS: MBSR holds promise as a transdiagnostic intervention for individuals with comorbid trauma-related, depression, GSA, and irritable bowel symptoms, with maintenance of trauma-related and depression symptom improvement 4 months post-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 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.