CUTTING EDGE
COPCs Research Advances

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LEADERSHIP 301

Adults Living with IC/BPS May Qualify

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 April and June 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.

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About the Chronic Pain Research Alliance

FEATURE

[Effect of human genetic variability on gene expression in dorsal root ganglia and association with pain phenotypes.](#)
Parisien M, Khoury S, Chabot-Doré AJ, Sotocinal SG, Slade GD, Smith SB, Fillingim RB, Ohrbach R, Greenspan JD, Maixner W, Mogil JS, Belfer I, Diatchenko L.
Cell Rep. 2017 May 30;19(9):1940-1952. doi: 10.1016/j.celrep.2017.05.018.

Dorsal root ganglia (DRG) relay sensory information to the brain, giving rise to the perception

of pain, disorders of which are prevalent and burdensome. Here, we mapped expression quantitative trait loci (eQTLs) in a collection of human DRGs. DRG eQTLs were enriched within untranslated regions of coding genes of low abundance, with some overlapping with other brain regions and blood cell cis-eQTLs. We confirm functionality of identified eQTLs through their significant enrichment within open chromatin and highly deleterious SNPs, particularly at the exon level, suggesting substantial contribution of eQTLs to alternative splicing regulation. We illustrate pain-related genetic association results explained by DRG eQTLs, with the strongest evidence for contribution of the human leukocyte antigen (HLA) locus, confirmed using a mouse inflammatory pain model. Finally, we show that DRG eQTLs are found among hits in numerous genome-wide association studies, suggesting that this dataset will help address pain components of non-pain disorders.

NATIONAL MULTICENTER STUDIES

[Clinical and psychosocial predictors of urologic chronic pelvic pain symptom change over one year: A prospective study from the MAPP Research Network.](#)
Naliboff BD, Stephens AJ, Lai HH, Griffith JW, Clemens JQ, Lutgendorf S, Rodriguez LV, Newcomb C, Sutcliffe S, Guo W, Kusek JW, Landis JR; MAPP Research Network.
J Urol. 2017 May 18. pii: S0022-5347(17)71368-7. doi: 10.1016/j.juro.2017.05.065. [Epub ahead of print]

OBJECTIVE: To examine baseline clinical and psychosocial characteristics that predict 12-month symptom change in men and women with urologic chronic pelvic pain syndromes (UCPPS). METHODS: 221 female and 176 male UCPPS patients were recruited from 6 academic medical centers in the United States and evaluated at baseline with a comprehensive battery of symptom, psychosocial, and illness-impact measures. Based on biweekly symptom reports, a functional clustering procedure classified participant's outcome as worse, stable, or improved on pain and urinary symptom severity. Cumulative logistic modeling was used to examine individual predictors associated with symptom change as well as multiple predictor combinations and interactions. RESULTS: About 60% of participants had stable symptoms with smaller numbers (13% to 22%) showing clear symptom worsening or improvement. For both pain and urinary outcomes the extent of widespread pain, amount of non-urological symptoms and poorer overall health were predictive of worsening outcomes. Anxiety, depression and general mental health were not significant predictors of outcomes, but pain catastrophizing and self-reported stress were associated with pain outcome. Prediction models did not differ between men and women and for the most part were independent of symptom duration and age. CONCLUSION: These results demonstrate for the first time in a large multisite prospective study that presence of widespread pain, non-urological symptoms and poorer general health are risk factors for poorer pain and urinary outcomes in both men and women. The results point to the importance of broad based assessment in UCPPS and future studies of mechanisms that underlie these findings.

[Resting-state functional connectivity predicts longitudinal pain symptom change in urologic chronic pelvic pain syndrome: a MAPP network study.](#)
Kutch JJ, Labus JS, Harris RE, Martucci KT, Farmer MA, Fenske S, Fling C, Ichesco E, Peltier S, Petre B, Guo W, Hou X, Stephens AJ, Mullins C, Clauw DJ, Mackey SC, Apkarian AV, Landis JR, Mayer EA; MAPP Research Network.
Pain. 2017 Jun;158(6):1069-1082. doi: 10.1097/j.pain.0000000000000886.

Chronic pain symptoms often change over time, even in individuals who have had symptoms for years. Studying biological factors that predict trends in symptom change in chronic pain may uncover novel pathophysiological mechanisms and potential therapeutic targets. In this study, we investigated whether brain functional connectivity measures obtained from resting-state functional magnetic resonance imaging at baseline can predict longitudinal symptom change (3, 6, and 12 months after scan) in urologic chronic pelvic pain syndrome.

We studied 52 individuals with urologic chronic pelvic pain syndrome (34 women, 18 men) who had baseline neuroimaging followed by symptom tracking every 2 weeks for 1 year as part of the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network study. We found that brain functional connectivity can make a significant prediction of short-term (3 month) pain reduction with 73.1% accuracy (69.2% sensitivity and 75.0% precision). In addition, we found that the brain regions with greatest contribution to the classification were preferentially aligned with the left frontoparietal network. Resting-state functional magnetic resonance imaging measures seemed to be less informative about 6- or 12-month symptom change. Our study provides the first evidence that future trends in symptom change in patients in a state of chronic pain may be linked to functional connectivity within specific brain networks.

PATHOPHYSIOLOGY STUDIES

[Fecal metagenomic profiles in subgroups of patients with myalgic encephalomyelitis/chronic fatigue syndrome.](#)
Nagy-Szakal D, Williams BL, Mishra N, Che X, Lee B, Bateman L, Klimas NG, Komaroff AL, Levine S, Montoya JG, Peterson DL, Ramanan D, Jain K, Eddy ML, Hornig M, Lipkin WI. Microbiome. 2017 Apr 26;5(1):44. doi: 10.1186/s40168-017-0261-y.

BACKGROUND: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is characterized by unexplained persistent fatigue, commonly accompanied by cognitive dysfunction, sleeping disturbances, orthostatic intolerance, fever, lymphadenopathy, and irritable bowel syndrome (IBS). The extent to which the gastrointestinal microbiome and peripheral inflammation are associated with ME/CFS remains unclear. We pursued rigorous clinical characterization, fecal bacterial metagenomics, and plasma immune molecule analyses in 50 ME/CFS patients and 50 healthy controls frequency-matched for age, sex, race/ethnicity, geographic site, and season of sampling. RESULTS: Topological analysis revealed associations between IBS co-morbidity, body mass index, fecal bacterial composition, and bacterial metabolic pathways but not plasma immune molecules. IBS co-morbidity was the strongest driving factor in the separation of topological networks based on bacterial profiles and metabolic pathways. Predictive selection models based on bacterial profiles supported findings from topological analyses indicating that ME/CFS subgroups, defined by IBS status, could be distinguished from control subjects with high predictive accuracy. Bacterial taxa predictive of ME/CFS patients with IBS were distinct from taxa associated with ME/CFS patients without IBS. Increased abundance of unclassified Alistipes and decreased Faecalibacterium emerged as the top biomarkers of ME/CFS with IBS; while increased unclassified Bacteroides abundance and decreased Bacteroides vulgatus were the top biomarkers of ME/CFS without IBS. Despite findings of differences in bacterial taxa and metabolic pathways defining ME/CFS subgroups, decreased metabolic pathways associated with unsaturated fatty acid biosynthesis and increased atrazine degradation pathways were independent of IBS co-morbidity. Increased vitamin B6 biosynthesis/salvage and pyrimidine ribonucleoside degradation were the top metabolic pathways in ME/CFS without IBS as well as in the total ME/CFS cohort. In ME/CFS subgroups, symptom severity measures including pain, fatigue, and reduced motivation were correlated with the abundance of distinct bacterial taxa and metabolic pathways. CONCLUSIONS: Independent of IBS, ME/CFS is associated with dysbiosis and distinct bacterial metabolic disturbances that may influence disease severity. However, our findings indicate that dysbiotic features that are uniquely ME/CFS-associated may be masked by disturbances arising from the high prevalence of IBS co-morbidity in ME/CFS. These insights may enable more accurate diagnosis and lead to insights that inform the development of specific therapeutic strategies in ME/CFS subgroups.

[Differences in gut microbial composition correlate with regional brain volumes in irritable bowel syndrome.](#)

BACKGROUND: Preclinical and clinical evidence supports the concept of bidirectional brain-gut microbiome interactions. We aimed to determine if subgroups of irritable bowel syndrome (IBS) subjects can be identified based on differences in gut microbial composition, and if there are correlations between gut microbial measures and structural brain signatures in IBS. METHODS: Behavioral measures, stool samples, and structural brain images were collected from 29 adult IBS and 23 healthy control subjects (HCs). 16S ribosomal RNA (rRNA) gene sequencing was used to profile stool microbial communities, and various multivariate analysis approaches were used to quantitate microbial composition, abundance, and diversity. The metagenomic content of samples was inferred from 16S rRNA gene sequence data using Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt). T1-weighted brain images were acquired on a Siemens Allegra 3T scanner, and morphological measures were computed for 165 brain regions. RESULTS: Using unweighted Unifrac distances with hierarchical clustering on microbial data, samples were clustered into two IBS subgroups within the IBS population [IBS1 (n13) and HC-like IBS (n16) and HCs (n23) AUROC 0.96, sensitivity 0.95, specificity 0.67). A Random Forest classifier provided further support for the differentiation of IBS1 and HC groups. Microbes belonging to the genera Faecalibacterium, Blautia, and Bacteroides contributed to this subclassification. Clinical features distinguishing the groups included a history of early life trauma and duration of symptoms (greater in IBS1), but not self-reported bowel habits, anxiety, depression, or medication use. Gut microbial composition correlated with structural measures of brain regions including sensory- and salience-related regions, and with a history of early life trauma. CONCLUSIONS: The results confirm previous reports of gut microbiome-based IBS subgroups and identify for the first time brain structural alterations associated with these subgroups. They provide preliminary evidence for the involvement of specific microbes and their predicted metabolites in these correlations.

[Differences in pain processing between patients with chronic low back pain, recurrent low back pain, and fibromyalgia.](#)

BACKGROUND: The impairment in musculoskeletal structures in patients with low back pain (LBP) is often disproportionate to their complaint. Therefore, the need arises for exploration of alternative mechanisms contributing to the origin and maintenance of non-specific LBP. The recent focus has been on central nervous system phenomena in LBP and the pathophysiological mechanisms underlying the various symptoms
and characteristics of chronic pain. Knowledge concerning changes in pain processing in LBP remains ambiguous, partly due to the diversity in the LBP population. OBJECTIVE: The purpose of this study is to compare quantitative sensory assessment in different groups of LBP patients with regard to chronicity. Recurrent low back pain (RLBP), mild chronic low back pain (CLBP), and severe CLBP are compared on the one hand with healthy controls (HC), and on the other hand with fibromyalgia (FM) patients, in which abnormal pain processing has previously been reported. STUDY DESIGN: Cross-sectional study. SETTING: Department of Rehabilitation Sciences, Ghent University, Belgium. METHODS: Twenty-three RLBP, 15 mild CLBP, 16 severe CLBP, 26 FM, and 21 HC participated in this study. Quantitative sensory testing was conducted by manual pressure algometry and computer-controlled cuff algometry. A manual algometer was used to evaluate hyperalgesia as well as temporal summation of pain and a cuff algometer was used to evaluate deep tissue hyperalgesia, the efficacy of the conditioned pain modulation and spatial summation of pain. RESULTS: Pressure pain thresholds by manual algometry were significantly lower in FM compared to HC, RLBP, and severe CLBP. Temporal summation of pain was significantly higher in FM compared to HC and RLBP. Pain tolerance thresholds assessed by cuff algometry were

significantly lower in FM compared to HC and RLBP and also in severe CLBP compared to RLBP. No significant differences between groups were found for spatial summation or conditioned pain modulation LIMITATIONS: No psychosocial issues were taken into account for this study. CONCLUSION: The present results suggest normal pain sensitivity in RLBP, but future research is needed. In mild and severe CLBP some findings of altered pain processing are evident, although to a lesser extent compared to FM patients. In conclusion, mild and severe CLBP presents within a spectrum, somewhere between completely healthy persons and FM patients, characterized by pain augmentation.

[Evidence of altered trigeminal nociception in an animal model of fibromyalgia.](#)
Nazeri M, Zarei MR, Pourzare AR, Ghahreh-Chahi HR, Abareghi F, Shabani M.
Pain Med. 2017 May 13. doi: 10.1093/pm/pnx114. [Epub ahead of print]

OBJECTIVE: Fibromyalgia (FM) is a debilitating chronic condition that significantly affects quality of life. A strong association has been demonstrated between FM and chronic pain in the trigeminal region in clinical studies. This study was performed to evaluate the response to acute and chronic noxious stimuli applied to the facial region. METHODS: Adult male Wistar rats (250 to 270g, n of 10 for each group) were used in the current study. A subchronic swim stress model was used as the animal model of FM. Anxiety-like behaviors and response to acute and chronic noxious stimuli were assayed using the elevated plus maze, eye wiping test, and orofacial formalin test, respectively. Balance and motor function were evaluated using rotarod and wire grip tests. RESULTS: An increased anxiety-like behavior was observed in swim stress rats in comparison with control and sham subjects. Response to acute and chronic noxious stimuli in the trigeminal region was increased in the stressed rats. Motor and balance function were not altered following stress. CONCLUSIONS: Results of the current study demonstrated a hyperalgesic state in the trigeminal region in a possible animal model of FM. This study provides a reliable animal model for further research on the possible mechanisms of orofacial pain in FM.

[Fragile X syndrome: an overview and update of the FMR1 gene.](#)
Mila M, Alvarez-Mora MI, Madrigal I, Rodriguez-Revenga L.
Clin Genet. 2017 Jun 15. doi: 10.1111/cge.13075. [Epub ahead of print]

Fragile X syndrome (FXS) is the most common cause of inherited intellectual disability and the leading form of the monogenic cause of autism. FMR1 premutation is the first single-gene cause of primary ovarian failure (FXPOI) and one of the most common causes of ataxia (FXTAS), multiple additional phenotypes such as fibromyalgia, hypothyroidism, migraine headaches, sleep disturbances, sleep apnea, restless legs syndrome, central pain syndrome, neuropathy and neuropsychiatric alterations has been described. Clinical involvement in men and women carrying the FMR1 premutation currently constitutes a real health problem in the society that should be taken into account. It is important to highlight that while in FXS there is a loss of function of the FMR1 gene, in premutation associated disorders there is a gain of FMR1 mRNA function. To date, the tremendous progress achieved in the understanding of the pathophysiology of FXS, has led to the development of several targeted therapies aimed at preventing or improving the neurological manifestations of the disease. This review is an update of the diseases associated with the FMR1 gene.

EPIDEMIOLOGY STUDIES

[The influence of multisite pain and psychological comorbidity on prognosis of chronic low back pain: longitudinal data from the Norwegian HUNT Study.](#)
Nordstoga AL, Nilsen TIL, Vasseljen O, Unsgaard-Tøndel M, Mork PJ.

OBJECTIVES: This study aimed to investigate the prospective influence of multisite pain, depression, anxiety, self-rated health and pain-related disability on recovery from chronic low back pain (LBP). SETTING: The data is derived from the second (1995-1997) and third (2006-2008) wave of the Nord-Trøndelag Health Study (HUNT) in Norway. PARTICIPANTS: The study population comprises 4484 women and 3039 men in the Norwegian HUNT Study who reported chronic LBP at baseline in 1995-1997. PRIMARY OUTCOME MEASURES: The primary outcome was recovery from chronic LBP at the 11-year follow-up. Persons not reporting pain and/or stiffness for at least three consecutive months during the last year were defined as recovered. A Poisson regression model was used to estimate adjusted risk ratios (RRs) with 95% CIs. RESULTS: At follow-up, 1822 (40.6%) women and 1578 (51.9%) men reported recovery from chronic LBP. The probability of recovery was inversely associated with number of pain sites (P-trend<0.001). Compared with reporting 2-3 pain sites, persons with only LBP had a slightly higher probability of recovery, whereas people reporting 6-9 pain sites had substantially lower probability of recovery. Poor/not so good self-rated general health, symptoms of anxiety and depression, and pain-related disability in work and leisure were all associated with reduced probability of recovery, but there was no statistical interaction between multisite pain and these comorbidities. CONCLUSIONS: Increasing number of pain sites was inversely associated with recovery from chronic LBP. In addition, factors such as poor self-rated health, psychological symptoms and pain-related disability may further reduce the probability of recovery from chronic LBP.

Predictors of persistent disability and back pain in older adults with a new episode of care for back pain.

Rundell SD, Sherman KJ, Heagerty PJ, Mock CN, Dettori NJ, Comstock BA, Avins AL, Nedeljkovic SS, Nerenz DR, Jarvik JG.

OBJECTIVE: To identify predictors of persistent disability and back pain in older adults. DESIGN: Prospective cohort study. SETTING: Back pain outcomes using longitudinal data registry. SUBJECTS: 5,220 adults age 65 and older with a new primary care visit for back pain. METHODS: Baseline measurements included: demographics, health,and back pain characteristics. We abstracted imaging findings from 348 radiology reports. The primary outcomes were the Roland Morris Disability Questionnaire (RMDQ) and back pain intensity. We defined persistent disability as RMDQ of 4/24 or higher at both six and 12 months and persistent back pain as 3/10 or higher at both six and 12 months. RESULTS: There were 2,498 of 4,143 (60.3%) participants with persistent disability, and 2,099 of 4,144 (50.7%) had persistent back pain. Adjusted analyses showed the following characteristics most strongly predictive of persistent disability and persistent back pain: sex, race, worse baseline clinical characteristics of back pain, leg pain, back-related disability and duration of symptoms, smoking, anxiety symptoms, depressive symptoms, a history of falls, greater number of comorbidities, knee osteoarthritis, widespread pain syndromes, and an index diagnosis of lumbar spinal stenosis. Within the imaging data subset, central spinal stenosis was not associated with disability or pain. CONCLUSION: We found that many predictors in older adults were similar to those for younger populations.

Age and preoperative pain are major confounders for sex differences in postoperative pain outcome: A prospective database analysis.

Zheng H, Schnabel A, Yahiaoui-Doktor M, Meissner W, Van Aken H, Zahn P, Pogatzki-Zahn E.

OBJECTIVES: Current literature is in disagreement regarding female sex as a risk factor for pain after surgery. We hypothesized, that sex differences exist but that they are influenced by certain factors. Here, we investigated the influence of sex for different clinically relevant

postoperative pain (POP) outcome parameters and evaluated the role of assumed confounders for sex differences. METHODS: From 1372 screened patients undergoing orthopedic surgery at the university hospital of Muenster between March 2010 and June 2011, 890 patients were included. The validated International Pain Outcomes questionnaire was used to assess the role of sex for several aspects of POP including pain severity, physical and emotional functional interference as well as the patient's perceptions of the care they received on the first day after surgery. Assessed confounders were age, preoperative chronic pain, anesthetic technique employed and surgical procedure. All statistical analyses were performed with SPSS Statistics Software 22. RESULTS: Linear regression analysis demonstrated that sex was a statistically significant risk factor for "worst pain since surgery". Additionally, significant sex differences in "time spent in severe pain", "feeling anxious due to pain", "feeling helpless due to pain" and "opioid consumption since surgery" could be identified. An univariate general linear model showed that "age" and "preoperative pain" were significant confounders for sex differences. Further descriptive subgroup analysis revealed consistent sex differences for several POP outcome variables especially in patients older than 50 years or patients with preoperative chronic pain. However, sex differences disappeared in younger patients and in patients without preoperative pain. DISCUSSION: Our data confirmed that sex differences exist in pain intensity and frequency, pain interference with feelings and opioid consumption during the first 24 hours postoperatively. However, sex differences were significantly influenced by the factors "age" and "preoperative pain". These findings may in part explain why clinical studies get different results related to sex differences and renders specific awareness in older women and female patients with preoperative chronic pain.

Comorbidity in chronic fatigue syndrome/myalgic encephalomyelitis: A nationwide population-based cohort study.
Castro-Marrero J, Faro M, Aliste L, Sáez-Francàs N, Calvo N, Martínez-Martínez A, de Sevilla TF, Alegre J.
Psychosomatics. 2017 Apr 21. pii: S0033-3182(17)30118-4. doi: 10.1016/j.psym.2017.04.010. [Epub ahead of print]

BACKGROUND: Previous studies have shown evidence of comorbid conditions in chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). OBJECTIVE: To estimate the prevalence of comorbidities and assess their associations using a nationwide population-based database of a Spanish CFS/ME cohort. METHOD: A nationally representative, retrospective, cross-sectional cohort study (2008-2015) assessed 1757 Spanish subjects who met both the 1994 Centers for Disease Control and Prevention/Fukuda definition and 2003 Canadian Criteria for CFS/ME. Sociodemographic and clinical data, comorbidities, and patient-reported outcome measures at baseline were recorded. A cluster analysis based on baseline clinical variables was performed to classify patients with CFS/ME into 5 categories according to comorbidities. A multivariate logistic regression analysis was conducted adjusting for potential confounding effects such as age and sex; response and categorical predictor variables were also assessed. RESULTS: A total of 1757 CFS/ME patients completed surveys were collected. We identified 5 CFS/ME clusters: group 1-fibromyalgia, myofascial pain, multiple chemical hypersensitivity, sicca syndrome, epicondylitis, and thyroiditis; group 2-alterations of ligaments and subcutaneous tissue, hypovitaminosis D, psychopathology, ligamentous hyperlaxity, and endometriosis. These 2 subgroups comprised mainly older women, with low educational level, unemployment, high levels of fatigue, and poor quality of life; group 3-with hardly any comorbidities, comprising mainly younger women, university students or those already employed, with lower levels of fatigue, and better quality of life; group 4-poorly defined comorbidities; and group 5-hypercholesterolemia. CONCLUSION: Over 80% of a large population-based cohort of Spanish patients with CFS/ME presented comorbidities. Among the 5 subgroups created, the most interesting were groups 1-3. Future research should consider multidisciplinary approaches for the management and treatment of CFS/ME with comorbid conditions.

BACKGROUND: Central sensitization is an important epiphenomenon of the adult migraine, clinically expressed by allodynia, pericranial tenderness and comorbidity for fibromyalgia in a relevant number of patients. This study aimed to evaluate the frequency and the clinical characteristics of allodynia, pericranial tenderness, and comorbidity for Juvenile Fibromyalgia (JFM) in a cohort of migraine children selected in a tertiary headache center. METHODS: This was an observational cross-sectional study on 8-15 years old migraine patients. Allodynia was assessed by a questionnaire. Pericranial tenderness and comorbidity for JFM as well as their possible association with poor quality of life and migraine related disability, and with other clinical symptoms as anxiety, depression, sleep disorders and pain catastrophizing, were also evaluated. RESULTS: One hundred and fifty one patients were selected, including chronic migraine (n°47), migraine without aura (n° 92) and migraine with aura (n° 12) sufferers. Allodynia was reported in the 96,6% and pericranial tenderness was observed in the 68.8% of patients. Pericranial tenderness was more severe in patients with more frequent migraine and shorter sleep duration. Allodynia seemed associated with anxiety, pain catastrophizing and high disability scores. Comorbidity for JFM was present in the 0.03% of patients. These children presented with a severe depression and a significant reduction of quality of life as compared to the other patients. CONCLUSIONS: This study outlined a relevant presence of symptoms of central sensitization among children with migraine. Severe allodynia and comorbidity for JFM seemed to cause a general decline of quality of life, which would suggest the opportunity of a routine assessment of these clinical features.

BACKGROUND: Severe pain and chronic pain have a high impact on individuals and society. Body location of pain is important with regard to perception, articulation, and underlying biological, mental or social causes of pain. METHODS: A cross-sectional survey was performed in the general Austrian population with 15,474 personally interviewed subjects aged 15 years and older. RESULTS: The 1-year period prevalence of severe pain in any body site was 38.6% and of chronic pain 24.9%. In all, 8.1% had pain in at least three body sites. Subjects aged 65 years and older (52.2%), those with low education (43.4%), unemployed subjects (50.4%), retired subjects (52.4%), those with anxiety/depression (67.7%), and subjects with lack of social support (49.6%) were sub-populations with high pain prevalence. In multivariate analyses, depression/anxiety was associated with prevalence and chronicity of severe pain in all body sites (range of ORs 1.89-5.01), while such associations were found for lack of social support (range of ORs 1.33-1.65), female sex (range of ORs 1.38-2.34), higher age (range of ORs 1.09-1.18 for 5 year intervals), as well as low educational (range of ORs 1.47-2.06 primary vs. tertiary education) and unemployment status (range of ORs 1.50-2.62) in most body sites. Being born in non-EU or EFTA states was associated with pain in many body sites (range of ORs 1.38-2.10). CONCLUSIONS: Psychosocial factors are associated with pain presence in similar ways irrespective of location. Regarding socio-demographic factors, differences towards the magnitude and the direction in the association with pain frequency and chronicity in different body sites emerged.

OBJECTIVE: The aim of this study was to investigate the magnitude of association of the severity of temporomandibular disorders (TMDs) in women with episodic and chronic migraine. METHODS: Thirty-one women with episodic migraine (mean age: 33 years), 21 with chronic migraine (mean age: 35 years) and 32 healthy controls (mean age: 31 years) were included. The Fonseca Anamnestic Index was applied to assess severity of TMDs. TMD severity was considered as follows: no TMD (0-19 points), mild TMD (20-49 points), moderate TMD (50-69 points), and severe TMD (70-100 points). To compare the proportion of TMD severity among groups, a χ^2 test was performed. Prevalence ratio (PR) was calculated to determine the association of TMD severity and both migraine groups using the control group as the reference. RESULTS: Women with chronic and episodic migraine were more likely to exhibit TMD signs and symptoms of any severity than healthy controls (χ^2 = 30.26; P < .001). TMD prevalence was 54% for healthy controls, 78% for episodic migraine, and 100% for chronic migraine. Women with chronic migraine exhibited greater risk of more severe manifestations of TMD than healthy controls (PR: 3.31; P = .008). This association was not identified for episodic migraine (PR: 2.18; P = .101). CONCLUSION: The presence of TMD signs and symptoms was associated with migraine independently of the frequency; however, the magnitude of the association of more severe TMD was significantly greater in chronic, but not episodic, migraine.

OBJECTIVES: To investigate the occurrence of postinfectious IBS in routine outpatient care, comparing different types of GI infection and its interaction with psychosomatic comorbidity. DESIGN: Retrospective cohort study using routinely collected claims data covering statutorily insured patients in Bavaria, Germany. Cases were defined as patients without prior record of functional intestinal disorder with a first-time diagnosis of GI infection between January 2005 and December 2013 and classed according to the type of infection. Each case was matched by age, sex and district of residence to a patient without history of GI infection. Prior psychological disorder (depression, anxiety or stress reaction disorder) was assessed in the 2 years prior to inclusion. Proportional hazards regression models were used to estimate the HRs for GI infection and psychological disorder. Chronic fatigue syndrome (CFS) was assessed as a comparator outcome. RESULTS: A total of 508,278 patients with first diagnosis of GI infection were identified, resulting in a matched cohort of 1 016 556 patients. All infection types were associated with an increased risk of IBS (HR: 2.19-4.25) and CFS (HR 1.35-1.82). Prior psychological disorder was a distinct risk factor for IBS (HR: 1.73) and CFS (HR: 2.08). Female sex was a further risk factor for both conditions. CONCLUSION: Psychological disorder and GI infections are distinct risk factors for IBS. The high incidence of non-specific GI infection suggests that postinfectious IBS is a common clinical occurrence in primary care. Chronic fatigue is a further significant sequela of GI infection.

This study aims to estimate the reliable prevalence of fibromyalgia using meta-analysis

method. Available databanks were searched using appropriate keywords. According to the heterogeneity between the results (indicated by Cochrane and I square indices), random- or fixed-effects model was applied to combine the point prevalences. Meta-regression models were used to assess the suspected factors in the heterogeneity. In 65 selected papers, 81 evidences regarding prevalence of fibromyalgia among 3,609,810 subjects from general population and specific groups were investigated. The total prevalences (95% confidence intervals) of fibromyalgia among general population, women, men, patients referring to rheumatology and internal departments, patients with Irritable bowel syndrome (IBS), hemodialysis patients and those with type 2 diabetes mellitus were estimated as of 1.78% (1.65, 1.92), 3.98% (2.80, 5.20), 0.01% (-0.04, 0.06), 15.2% (13.6, 16.90), 12.9% (12.70, 13.10), 6.30% (4.60, 7.90) and 14.80% (11.10, 18.40), respectively. In addition, prevalence of fibromyalgia in specified groups varied from 3.90% in hemodialysis patients to 80% in patients suffering from Behcet syndrome. This meta-analysis showed that prevalence of fibromyalgia in general population was significantly lower than that in populations with some diseases.

CLINICAL STUDIES

Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews.
Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA, Smith BH.
Cochrane Database Syst Rev. 2017 Apr 24;4:CD011279. doi: 10.1002/14651858.CD011279.pub3.

BACKGROUND: Chronic pain is defined as pain lasting beyond normal tissue healing time, generally taken to be 12 weeks. It contributes to disability, anxiety, depression, sleep disturbances, poor quality of life, and healthcare costs. Chronic pain has a weighted mean prevalence in adults of 20%.For many years, the treatment choice for chronic pain included recommendations for rest and inactivity. However, exercise may have specific benefits in reducing the severity of chronic pain, as well as more general benefits associated with improved overall physical and mental health, and physical functioning.Physical activity and exercise programmes are increasingly being promoted and offered in various healthcare systems, and for a variety of chronic pain conditions. It is therefore important at this stage to establish the efficacy and safety of these programmes, and furthermore to address the critical factors that determine their success or failure. OBJECTIVES: To provide an overview of Cochrane Reviews of adults with chronic pain to determine (1) the effectiveness of different physical activity and exercise interventions in reducing pain severity and its impact on function, quality of life, and healthcare use; and (2) the evidence for any adverse effects or harm associated with physical activity and exercise interventions. METHODS: We searched theCochrane Database of Systematic Reviews (CDSR) on the Cochrane Library (CDSR 2016, Issue 1) for systematic reviews of randomised controlled trials (RCTs), after which we tracked any included reviews for updates, and tracked protocols in case of full review publication until an arbitrary cut-off date of 21 March 2016 (CDSR 2016, Issue 3). We assessed the methodological quality of the reviews using the AMSTAR tool, and also planned to analyse data for each painful condition based on quality of the evidence.We extracted data for (1) self-reported pain severity, (2) physical function (objectively or subjectively measured), (3) psychological function, (4) quality of life, (5) adherence to the prescribed intervention, (6) healthcare use/attendance, (7) adverse events, and (8) death. Due to the limited data available, we were unable to directly compare and analyse interventions, and have instead reported the evidence qualitatively. MAIN RESULTS: We included 21 reviews with 381 included studies and 37,143 participants. Of these, 264 studies (19,642 participants) examined exercise versus no exercise/minimal intervention in adults with chronic pain and were used in the qualitative analysis.Pain conditions included rheumatoid arthritis, osteoarthritis, fibromyalgia, low back pain, intermittent claudication, dysmenorrhoea, mechanical neck disorder, spinal cord injury, postpolio syndrome, and patellofemoral pain. None of the reviews assessed 'chronic pain' or 'chronic widespread pain' as a general term or specific condition. Interventions included aerobic, strength, flexibility, range of motion, and core or balance training programmes, as well as yoga, Pilates, and tai chi.Reviews were well

performed and reported (based on AMSTAR), and included studies had acceptable risk of bias (with inadequate reporting of attrition and reporting biases). However the quality of evidence was low due to participant numbers (most included studies had fewer than 50 participants in total), length of intervention and follow-up (rarely assessed beyond three to six months). We pooled the results from relevant reviews where appropriate, though results should be interpreted with caution due to the low quality evidence. Pain severity: several reviews noted favourable results from exercise: only three reviews that reported pain severity found no statistically significant changes in usual or mean pain from any intervention. However, results were inconsistent across interventions and follow-up, as exercise did not consistently bring about a change (positive or negative) in self-reported pain scores at any single point. Physical function: was the most commonly reported outcome measure. Physical function was significantly improved as a result of the intervention in 14 reviews, though even these statistically significant results had only small-to-moderate effect sizes (only one review reported large effect sizes). Psychological function and quality of life: had variable results: results were either favourable to exercise (generally small and moderate effect size, with two reviews reporting significant, large effect sizes for quality of life), or showed no difference between groups. There were no negative effects. Adherence to the prescribed intervention: could not be assessed in any review. However, risk of withdrawal/dropout was slightly higher in the exercising group (82.8/1000 participants versus 81/1000 participants), though the group difference was non-significant. Healthcare use/attendance: was not reported in any review. Adverse events, potential harm, and death: only 25% of included studies (across 18 reviews) actively reported adverse events. Based on the available evidence, most adverse events were increased soreness or muscle pain, which reportedly subsided after a few weeks of the intervention. Only one review reported death separately to other adverse events: the intervention was protective against death (based on the available evidence), though did not reach statistical significance.

AUTHORS' CONCLUSIONS: The quality of the evidence examining physical activity and exercise for chronic pain is low. This is largely due to small sample sizes and potentially underpowered studies. A number of studies had adequately long interventions, but planned follow-up was limited to less than one year in all but six reviews.There were some favourable effects in reduction in pain severity and improved physical function, though these were mostly of small-to-moderate effect, and were not consistent across the reviews. There were variable effects for psychological function and quality of life.The available evidence suggests physical activity and exercise is an intervention with few adverse events that may improve pain severity and physical function, and consequent quality of life. However, further research is required and should focus on increasing participant numbers, including participants with a broader spectrum of pain severity, and lengthening both the intervention itself, and the follow-up period.

About the Chronic Pain Research Alliance

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

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

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