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CUTTING EDGE

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COPCs Research Advances

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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-publication contains abstracts of studies on the epidemiology, pathophysiology and clinical management of Chronic Overlapping Pain Conditions (COPCs) published between July and October 2016. 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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FEATURED EDITORIAL

[The ACTION-American Pain Society Pain Taxonomy \(AAPT\) Multidimensional Framework for the Classification and Diagnosis of Chronic Pain.](#)

Edited by Dworkin RH, Bruehl S, Fillingim RB, Loeser JD, Terman GW, Turk DC,

Geisser ME.

J Pain. September 2016, Volume 17, Issue 9, Supplement

A variety of approaches have been used to develop diagnostic criteria for chronic pain. The published evidence of the reliability and validity of existing diagnostic criteria is limited, and these criteria have typically not been used in clinical practice. The availability of a widely accepted, consistently applied, and evidence-based taxonomy of diagnostic criteria would improve the quality of clinical research on chronic pain and would be of great value in clinical practice. To address the need for evidence-based diagnostic criteria for the major chronic pain conditions, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) public-private partnership with the US Food and Drug Administration and the American Pain Society (APS) have collaborated on the development of the ACTTION-APS Pain Taxonomy (AAPT). AAPT provides a multidimensional framework that is applied systematically in the development of diagnostic criteria. This article (1) describes the background and rationale for AAPT; (2) presents the AAPT taxonomy and the specific conditions for which diagnostic criteria have been developed (to be published separately); (3) briefly reviews the 5 dimensions that constitute the AAPT multi-dimensional framework and describes the 7 accompanying articles that discuss these dimensions and other important issues involving AAPT; and (4) provides an overview of next steps, specifically, the general processes by which the initial set of diagnostic criteria (for which the evidence base has been drawn from the literature, systematic reviews, and secondary analyses of existing databases) will undergo additional assessments of reliability and validity.

[Assessment of chronic pain: Domains, methods and mechanisms.](#)

Fillingim RB, Loeser, JD, Baron R, Edwards RR.

[Assessment of psychological and functional impact of chronic pain.](#)

Turk DC, Fillingim RB, Ohrbach R, Patel KV.

[Toward a mechanism-based approach to pain diagnosis.](#)

Vardeh D, Mannion RJ, Woolf CJ.

[The role of psychosocial processes in the development and maintenance of chronic pain.](#)

Edwards RR, Dworkin RH, Sullivan MD, Turk DC, Wasan AD.

[Overlapping chronic pain conditions: Implications for diagnosis and classification.](#)

Maixner W, Fillingim RB, Williams DA, Smith SB, Slade GD.

[Applying a lifespan developmental perspective to chronic pain: Pediatrics to geriatrics.](#)

Walco GA, Krane EJ, Schmader K, Weiner DK.

[Approaches to demonstrating the reliability and validity of core diagnostic criteria for chronic pain.](#)

Bruehl S, Ohrbach R, Sharma S, Widerstrom-Noga E, Dworkin RH, Fillingim RB,

NATIONAL MULTICENTER STUDIES

[Temporal change in headache and its contribution to risk of developing first-onset TMD in the OPPERA study.](#)

Tchivileva IE, Ohrbach R, Fillingim RB, Greenspan JD, Maixner W, Slade GD.
Pain. 2016 Sep 29. [Epub ahead of print]

While cross-sectional studies have demonstrated an association between headache and temporomandibular disorder (TMD), whether headache can predict the onset of TMD is unknown. The aims of this study were to evaluate contribution of headache to the risk of developing TMD and describe patterns of change in headache types over time. An initially TMD-free cohort of 2,410 persons with low frequency of headache completed quarterly questionnaires assessing TMD and headache symptoms over a median 3.0-year follow-up period. First-onset TMD was confirmed by clinical examination in 199 participants. Baseline reports of migraine (HR=1.67, 95% CI: 1.06-2.62) or mixed headache (HR=4.11, 95% CI: 1.47-11.46) types, or headache frequency (HR=2.13, 95% CI: 1.31-3.48) predicted increased risk of developing TMD. Additionally, headache dynamics across the follow-up period prior to the TMD onset were evaluated in a nested case-control study where 248 incident TMD cases were matched to 191 TMD-free controls. Both headache prevalence and frequency increased across the observation period among those who developed TMD but not among controls. TMD cases were more likely to experience worsening in headache type compared to controls, e.g., prevalence of definite migraine among TMD cases increased ten-fold. Among all headache types experienced by TMD cases prior to the TMD onset, migraine had the highest odds of progression relative to remission (OR=2.8, 95% CI: 1.6-4.8), while for controls this ratio was significant only for tension-type headache (OR=2.1, 95% CI: 1.2-3.9). The important clinical implication of these findings is that adequate treatment of migraine may reduce the risk for developing TMD.

PATHOPHYSIOLOGY STUDIES

[Why sickness hurts: A central mechanism for pain induced by peripheral inflammation.](#)

Karshikoff B, Jensen KB, Kosek E, Kalpouzos G, Soop A, Ingvar M, Olgart Höglund C, Lekander M, Axelsson J.
Brain Behav Immun. 2016 Oct;57:38-46. doi: 10.1016/j.bbi.2016.04.001.

Low-grade systemic inflammation has been implicated in chronic pain, as well as in comorbid diseases like depression and fatigue. We have previously shown that women's pain perception and regulation is more affected by systemic inflammation than that of men. Here we investigated the neural substrates underlying these effects using an fMRI paradigm previously employed in a clinical population. Fifty-one participants (29 women) were injected with 0.6ng/kg lipopolysaccharide (LPS) or saline to induce a peripheral inflammatory response. The subjects were then tested with a pressure pain

fMRI paradigm designed to capture descending pain inhibitory activity 2h after injection, and blood was sampled for cytokine analysis. The subjects injected with LPS became more pain sensitive compared to the placebo group, and the heightened pain sensitivity was paralleled by decreased activity in the ventrolateral prefrontal cortex and the rostral anterior cingulate cortex (rACC) compared to placebo; areas involved in descending pain regulation. The LPS group also had higher activity in the anterior insular cortex, an area underpinning affective and interoceptive pain processing. Women displayed overall less pain-evoked rACC activity compared to men, which may have rendered women less resilient to immune provocation, possibly explaining sex differences in LPS-induced pain sensitivity. Our findings elucidate the pain-related brain circuits affected by experimental peripheral inflammation, strengthening the theoretical link between systemic inflammation and weakened pain regulation in chronic pain disorders. The results further suggest a possible mechanism underlying the female predominance in many chronic pain disorders.

[Pain sensitivity and its relation to spreading on the body, intensity, frequency, and duration of pain: A cross-sectional population-based study \(SwePain\).](#)

Larsson B, Gerdle B, Björk J, Grimby-Ekman A.
Clin J Pain. 2016 Sep 17. [Epub ahead of print]

OBJECTIVES: Individuals with chronic pain often report increased pain sensitivity compared to pain free individuals, so it is crucial to determine if and how different pain characteristics influence or interact with pain sensitivity. An alternative to experimental pain sensitivity testing is the self-reported pain sensitivity questionnaire (PSQ), that captures pain sensitivity in various body areas. This study compares PSQ in individuals with and without pain and clarifies how pain sensitivity relates to spreading of pain on the body, and to intensity, frequency, duration of pain and to age and sex. **METHODS:** 5905 individuals with pain and 572 individuals without pain from the general population in southeastern Sweden completed and returned a postal questionnaire. **RESULTS:** Mean PSQ score was 3.9 (95% confidence interval: 3.88; 3.98) in individuals with pain, and in pain free subjects 3.5 (3.38; 3.64). Hence, PSQ was highest in individuals with pain, with a difference of 0.4 (0.30; 0.56). There was a considerable variation in the PSQ values (mean 3.5; standard deviation 1.54) among pain free individuals. Pain sensitivity was positively related to spreading, intensity, and frequency of pain; correlation coefficients 0.3. PSQ was higher in widespread pain; women 4.5 (4.27; 4.69) and men; 4.3 (3.94; 4.71) than in local pain; women 3.7 (3.61; 3.91) and men 3.8 (CI 3.66; 3.95). The score for women with regional pain was between local and widespread pain 4.0 (3.95; 4.11) and for men with regional 3.8 (3.69; 3.87) that is equal to local pain. **DISCUSSION:** The positive association between pain sensitivity and spreading of pain on the body provides some evidence that extent of spreading may be related to the degree of pain sensitivity. Prior to clinical use of PSQ psychometric development and further research are needed.

[Gastrointestinal disorders associated with migraine: A comprehensive review.](#)

Cámara-Lemarroy CR, Rodríguez-Gutierrez R, Monreal-Robles R, Marfil-Rivera A.
World J Gastroenterol. 2016 Sep 28;22(36):8149-60. doi: 10.3748/wjg.v22.i36.8149.

Migraine is a recurrent and commonly disabling primary headache disorder that affects over 17% of women and 5%-8% of men. Migraine susceptibility is multifactorial with genetic, hormonal and environmental factors all playing an important role. The physiopathology of migraine is complex and still not fully understood. Many different neuropeptides, neurotransmitters and brain pathways have been implicated. In connection with the myriad mechanisms and pathways implicated in migraine, a variety of multi systemic comorbidities (e.g., cardiovascular, psychiatric and other neurological conditions) have been found to be closely associated with migraine. Recent reports demonstrate an increased frequency of gastrointestinal (GI) disorders in patients with migraine compared with the general population. *Helicobacter pylori* infection, irritable bowel syndrome, gastroparesis, hepatobiliary disorders, celiac disease and alterations in the microbiota have been linked to the occurrence of migraine. Several mechanisms involving the gut-brain axis, such as a chronic inflammatory response with inflammatory and vasoactive mediators passing to the circulatory system, intestinal microbiota modulation of the enteric immunological milieu and dysfunction of the autonomic and enteric nervous system, have been postulated to explain these associations. However, the precise mechanisms and pathways related to the gut-brain axis in migraine need to be fully elucidated. In this review, we survey the available literature linking migraine with GI disorders. We discuss the possible physiopathological mechanisms, and clinical implications as well as several future areas of interest for research.

[Concomitant migraine and temporomandibular disorders are associated with higher heat pain hyperalgesia and cephalic cutaneous allodynia.](#)

Chaves TC, Dach F, Florencio LL, Carvalho GF, Gonçalves MC, Bigal ME, Speciali JG, Bevilacqua-Grossi D.

Clin J Pain. 2016 Oct;32(10):882-8. doi: 10.1097/AJP.0000000000000369.

OBJECTIVES: The aim of this study was to assess differences in the levels of hyperalgesia and cutaneous allodynia (CA) among women with migraine, temporomandibular disorders (TMD), or both. **MATERIALS AND METHODS:** Eighty women participated in the study. Mean ages for the control group, TMD group, migraine group, and migraine+TMD group were 26.15 (95% confidence interval [CI], 23.57 to 28.73), 31.65 (95% CI, 25.48 to 37.82), 35.05 (95% CI, 29.73 to 40.37), and 34.20 (95% CI, 30.41 to 37.99) years, respectively. The 12-item Allodynia Symptom Checklist was administered to assess CA. All participants underwent the Quantitative Sensory Test to determine the cold-pain and heat-pain thresholds. Mechanical pain thresholds were assessed using Semmes-Weinstein monofilaments. One-way analysis of variance and χ tests were used for statistical analysis. Alpha was set at 0.05 level for statistical significance. **RESULTS:** For all sites evaluated, the mean cold-pain threshold values were significantly lower in the TMD, migraine, and TMD+migraine groups compared with the control group. However, the mean heat-pain threshold values in the extracephalic region were significantly smaller only for the TMD+migraine group compared with the control group (41.94°C; 95% CI, 40.54 to 43.34 vs. 44.79°C; 95% CI, 43.45 to 46.12; P=0.03). Mechanical hyperalgesia in orofacial and neck sites was significantly lower in the TMD and TMD+migraine groups compared with the control group. Mean total 12-item Allodynia Symptom Checklist score in the TMD+migraine group was significantly

higher than in the migraine group (9.53; 95% CI, 7.45 to 11.60 vs. 6.95; 95% CI, 5.35 to 8.55; $P=0.02$). CONCLUSIONS: More pronounced levels of hyperalgesia and CA were found in patients with both TMD and migraine. Thus, it is suggested that the concomitant presence of TMD and migraine may be related to intensification of central sensitization.

[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). 2016 Aug 2. doi: 10.1002/acr.22998. [Epub ahead of print]

INTRODUCTION: Lowered pressure pain thresholds have been demonstrated in adults with Ehlers-Danlos Hypermobility type (EDS-HT), however it remains unclear if these findings are also present in children. Therefore, the objectives of the study were to: (1) determine if generalized hyperalgesia is present in Hypermobility syndrome (HMS)/EDS-HT children, (2) explore potential differences in pressure pain thresholds between HMS/EDS-HT children and adults, and (3) determine the discriminative value of generalized hyperalgesia. METHODS: Patients classified in one of three groups: HMS/EDS-HT, hypermobile (Beighton score $\geq 4/9$) and healthy controls. Descriptive data of age, gender, body mass index, Beighton score, skin laxity and medication usage were collected. Generalized hyperalgesia was quantified by the averaged pressure pain thresholds collected from 12 locations. The following confounders were collected: pain location/intensity, fatigue, psychological distress. Comparisons between HMS/EDS-HT children and normative values, between children and adults with HMS/EDS-HT, corrected confounders, were analysed with MANCOVA. The discriminative value of generalized hyperalgesia employed in order to differentiate between HMS/EDS-HT, hypermobile 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 (range: -22.0% to -59.0%, $p < .05$). When applying a threshold of 30.8 N/cm² for males and 29.0 N/cm² for females, the presence of generalized hyperalgesia discriminated between individuals with HMS/EDS-HT, hypermobile and healthy controls (odds ratio=6.0). CONCLUSION: Children and adults with HMS/EDS-HT are characterized by hypermobility, chronic pain, as well as generalized hyperalgesia. The presence of generalized hyperalgesia may indicate involvement of the central nervous system in the development of chronic pain.

[Thermal temporal summation and decay of after-sensations in temporomandibular myofascial pain patients with and without comorbid fibromyalgia.](#)

Janal MN, Raphael KG, Cook DB, Sirois DA, Nemelivsky L, Staud R.

J Pain Res. 2016 Sep 12;9:641-52. doi: 10.2147/JPR.S109038. eCollection 2016.

INTRODUCTION: Chronic myofascial temporomandibular disorders (TMD) may have multiple etiological and maintenance factors. One potential factor, central pain sensitization, was quantified here as the response to the temporal summation (TS) paradigm, and that response was compared between case and control groups. OBJECTIVES: As previous research has shown that fibromyalgia (FM) is diagnosed in

20% of TMD patients, Aim 1 determined whether central sensitization is found preferentially in myofascial TMD cases that have orofacial pain as a regional manifestation of FM. Aim 2 determined if the report of after-sensations (AS) following TS varied depending on whether repeated stimuli were rated as increasingly painful. METHODS: One hundred sixty-eight women, 43 controls, 100 myofascial TMD-only cases, and 25 myofascial TMD + FM cases, were compared on thermal warmth and pain thresholds, thermal TS, and decay of thermal AS. All cases met Research Diagnostic Criteria for TMD; comorbid cases also met the 1990 American College of Rheumatology criteria for FM. RESULTS: Pain thresholds and TS were similar in all groups. When TS was achieved (~60%), significantly higher levels of AS were reported in the first post stimulus interval, and AS decayed more slowly over time, in myofascial TMD cases than controls. By contrast, groups showed similar AS decay patterns following steady state or decreasing responses to repetitive stimulation. CONCLUSION: In this case-control study, all myofascial TMD cases were characterized by a similar delay in the decay of AS. Thus, this indicator of central sensitization failed to suggest different pain maintenance factors in myofascial TMD cases with and without FM.

[TauG-guidance of dynamic balance control during gait initiation in patients with chronic fatigue syndrome and fibromyalgia.](#)

Rasouli O, Stensdotter AK, Van der Meer AL.
Clin Biomech (Bristol, Avon). 2016 Aug;37:147-52.

BACKGROUND: Impaired postural control has been reported in static conditions in chronic fatigue syndrome and fibromyalgia, but postural control in dynamic tasks have not yet been investigated. Thus, we investigated measurements from a force plate to evaluate dynamic balance control during gait initiation in patients with chronic fatigue syndrome and fibromyalgia compared to matched healthy controls. METHODS: Thirty female participants (10 per group) performed five trials of gait initiation. Center of pressure (CoP) trajectory of the initial weight shift onto the supporting foot in the mediolateral direction (CoPX) was analyzed using General Tau Theory. We investigated the hypothesis that tau of the CoPX motion-gap (τ_{CoPx}) is coupled onto an intrinsic tauG-guide (τ_G) by keeping the relation $\tau_{CoPx} = K\tau_G$, where K is a scaling factor that determines the relevant kinematics of a movement. FINDINGS: Mean K values were 0.57, 0.55, and 0.50 in fibromyalgia, chronic fatigue syndrome, and healthy controls, respectively. Both patient groups showed K values significantly higher than 0.50 ($P < 0.05$), indicating that patients showed poorer dynamic balance control, CoPX colliding with the boundaries of the base of support ($K > 0.5$). INTERPRETATION: The findings revealed a lower level of dynamic postural control in both fibromyalgia and chronic fatigue syndrome compared to controls.

[Microglial role in the development of chronic pain.](#)

Suter MR.
Curr Opin Anaesthesiol. 2016 Oct;29(5):584-9. doi: 10.1097/ACO.0000000000000373.

PURPOSE OF REVIEW: The review aims to present the latest research into microglia and their role in pain. RECENT FINDINGS: Microglia affect sex and age-dependent

differences in pain. The various microglial phenotypes make their involvement in pain more complex but provide more potential as pain modulators. **SUMMARY:** Glial cells, composed of microglia, astrocytes, and oligodendrocytes, outnumber neurons in the central nervous system. The crosstalk between these cells and neurons is now established as participating in the development of chronic pain. There has been a great advance in the description of microglia reactivity from pro to anti-inflammatory phenotypes. The modulation of these phenotypes could be a potential target for pain therapy. Recently, different microglial reactivity between man and woman and between neonates and adults, in response to nerve injury were described, which could explain some of the sex differences in pain sensitivity and the absence of neuropathic pain development in neonates. Clinical trials using microglia as a target have been carried out in various neurological diseases and pain, with limited efficacy in the latter, but there are nonetheless, indications that with some improvement in study strategies microglia could be a future target for pain control.

[Microglia in health and pain: impact of noxious early life events.](#)

Burke NN, Fan CY, Trang T.

Exp Physiol. 2016 Aug 1;101(8):1003-21. doi: 10.1113/EP085714.

NEW FINDINGS: This review discusses the origins and development of microglia, and how stress, pain or inflammation in early life disturbs microglial function during critical developmental periods, leading to altered pain sensitivity and/or increased risk of chronic pain in later life. We highlight recent advances in understanding how disrupted microglial function impacts the developing nervous system and the consequences for pain processing and susceptibility for development of chronic pain in later life. The discovery of microglia is accredited to Pío del Río-Hortega, who recognized this 'third element' of CNS cells as being morphologically distinct from neurons and astrocytes. For decades after this finding, microglia were altogether ignored or relegated as simply being support cells. Emerging from virtual obscurity, microglia have now gained notoriety as immune cells that assume a leading role in the development, maintenance and protection of a healthy CNS. Pioneering studies have recently shed light on the origins of microglia, their role in the developing nervous system and the complex roles they play beyond the immune response. These studies reveal that altered microglial function can have a profoundly negative impact on the developing brain and may be a determinant in a range of neurodevelopmental disorders and neurodegenerative diseases. The realization that aberrant microglial function also critically underlies chronic pain, a debilitating disorder that afflicts over 1.5 billion people worldwide, was a major conceptual leap forward in the pain field. Adding to this advance is emerging evidence that early life noxious experiences can have a long-lasting impact on central pain processing and adult pain sensitivity. With microglia now coming of age, in this review we examine the association between adverse early life events, such as stress, injury or inflammation, and the influence of sex differences, on the role of microglia in pain physiology in adulthood.

EPIDEMIOLOGY STUDIES

[Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015.](#)

GBD 2015 Disease and Injury Incidence and Prevalence Collaborators.

Lancet. 2016 Oct 8;388(10053):1545-1602. doi: 10.1016/S0140-6736(16)31678-6.

BACKGROUND: Non-fatal outcomes of disease and injury increasingly detract from the ability of the world's population to live in full health, a trend largely attributable to an epidemiological transition in many countries from causes affecting children, to non-communicable diseases (NCDs) more common in adults. For the Global Burden of Diseases, Injuries, and Risk Factors Study 2015 (GBD 2015), we estimated the incidence, prevalence, and years lived with disability for diseases and injuries at the global, regional, and national scale over the period of 1990 to 2015. **METHODS:** We estimated incidence and prevalence by age, sex, cause, year, and geography with a wide range of updated and standardised analytical procedures. Improvements from GBD 2013 included the addition of new data sources, updates to literature reviews for 85 causes, and the identification and inclusion of additional studies published up to November, 2015, to expand the database used for estimation of non-fatal outcomes to 60 900 unique data sources. Prevalence and incidence by cause and sequelae were determined with DisMod-MR 2.1, an improved version of the DisMod-MR Bayesian meta-regression tool first developed for GBD 2010 and GBD 2013. For some causes, we used alternative modelling strategies where the complexity of the disease was not suited to DisMod-MR 2.1 or where incidence and prevalence needed to be determined from other data. For GBD 2015 we created a summary indicator that combines measures of income per capita, educational attainment, and fertility (the Socio-demographic Index [SDI]) and used it to compare observed patterns of health loss to the expected pattern for countries or locations with similar SDI scores. **FINDINGS:** We generated 9.3 billion estimates from the various combinations of prevalence, incidence, and YLDs for causes, sequelae, and impairments by age, sex, geography, and year. In 2015, two causes had acute incidences in excess of 1 billion: upper respiratory infections (17.2 billion, 95% uncertainty interval [UI] 15.4-19.2 billion) and diarrhoeal diseases (2.39 billion, 2.30-2.50 billion). Eight causes of chronic disease and injury each affected more than 10% of the world's population in 2015: permanent caries, tension-type headache, iron-deficiency anaemia, age-related and other hearing loss, migraine, genital herpes, refraction and accommodation disorders, and ascariasis. The impairment that affected the greatest number of people in 2015 was anaemia, with 2.36 billion (2.35-2.37 billion) individuals affected. The second and third leading impairments by number of individuals affected were hearing loss and vision loss, respectively. Between 2005 and 2015, there was little change in the leading causes of years lived with disability (YLDs) on a global basis. NCDs accounted for 18 of the leading 20 causes of age-standardised YLDs on a global scale. Where rates were decreasing, the rate of decrease for YLDs was slower than that of years of life lost (YLLs) for nearly every cause included in our analysis. For low SDI geographies, Group 1 causes typically accounted for 20-30% of total disability, largely attributable to nutritional deficiencies, malaria, neglected tropical diseases, HIV/AIDS, and tuberculosis. Lower back and neck pain was the leading global cause of disability in 2015 in most countries. The leading cause was sense organ disorders in 22 countries in Asia and Africa and one in central Latin America; diabetes in four countries in Oceania; HIV/AIDS in three southern

sub-Saharan African countries; collective violence and legal intervention in two north African and Middle Eastern countries; iron-deficiency anaemia in Somalia and Venezuela; depression in Uganda; onchocerciasis in Liberia; and other neglected tropical diseases in the Democratic Republic of the Congo. INTERPRETATION: Ageing of the world's population is increasing the number of people living with sequelae of diseases and injuries. Shifts in the epidemiological profile driven by socioeconomic change also contribute to the continued increase in years lived with disability (YLDs) as well as the rate of increase in YLDs. Despite limitations imposed by gaps in data availability and the variable quality of the data available, the standardised and comprehensive approach of the GBD study provides opportunities to examine broad trends, compare those trends between countries or subnational geographies, benchmark against locations at similar stages of development, and gauge the strength or weakness of the estimates available.

[Prevalence of chronic pain in a large integrated healthcare delivery system in the U.S.A.](#)

Lamerato LE, Dryer RD, Wolff GG, Hegeman-Dingle R, Mardekian J, Park PW, Zlateva G.

Pain Pract. 2016 Sep;16(7):890-8. doi: 10.1111/papr.12334.

BACKGROUND: There is a paucity of published data on the prevalence of chronic pain conditions within large, integrated healthcare organizations in the U.S.A. Such data are essential to inform the development of appropriate treatment programs. METHODS: Twenty-five selected pain conditions were used to identify patients receiving care within the Henry Ford Health System (HFHS) who were enrolled in the Health Alliance Plan (HAP), a subsidiary of HFHS. Patients aged ≥ 18 years, enrolled in HAP in 2010, and having ≥ 2 encounters, ≥ 30 days apart, with an ICD-9-CM diagnosis code for a pain condition of interest during 2010 were counted. Variables included in the study were as follows: age, gender, body mass index (BMI), and Charlson comorbidity conditions and index score. RESULTS: Altogether, 14,784 persons (11.6% of the total adult population) met the criteria for having a chronic pain condition. Overall, the study population was 64.4% female and had mean age (SD) of 61.2 (15.6) years and mean BMI of 31.4 (7.2) kg/m². Musculoskeletal pain conditions were the most common diagnoses, comprising 75.4% of all pain diagnoses. Diabetes and chronic pulmonary disease were the most common medical comorbidities. CONCLUSIONS: In this comprehensive analysis of 2 years of data from a large, vertically integrated metropolitan health system, chronic pain was identified in 12% of adult patients. Approximately 75% of chronic pain conditions were musculoskeletal. The triad of age ≥ 60 years, BMI ≥ 30 , and female sex were the most salient demographic characteristics of patients with chronic pain conditions. These diagnostic and demographic data may be used to inform treatment program development.

[A systematic review and meta-analysis of the global burden of chronic pain without clear etiology in low-and middle-income countries: Trends in heterogeneous data and a proposal for new assessments methods.](#)

Jackson T, Thomas S, Stabile V, Shotwell M, Han X, McQueen K.

Anesth Analg. 2016 Sep;123(3):739-48. doi: 10.1213/ANE.0000000000001389.

BACKGROUND: The global burden of chronic pain is projected to be large and growing, in concert with the burden of noncommunicable diseases. This is the first systematic review and meta-analysis of the prevalence of chronic pain without clear etiology in general, elderly, and working populations of low- and middle-income countries (LMICs). **METHODS:** We collected and reported data using Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines, excluding acute pain or pain associated with a concurrent medical condition. One hundred nineteen publications in 28 LMICs were identified for systematic review; the 68 reports that focused on general adult populations (GP), elderly general populations (EGP), or workers (W) were evaluated using mixed-effects regression meta-analysis. **RESULTS:** Average chronic pain prevalence is reported as a percentage of the population, with 95% confidence interval for each pain type and population (GP, EGP, and W; NA is equal to not available): unspecified chronic pain (34[26-42], 62[41-81], and NA); low back pain (21[15-27], 28[16-42], and 52[26-77]); headache (42[27-58], 30[19-43], and 51[13-88]); chronic daily headache (5[3-7], 5[1-12], and 10[0-33]); chronic migraine (GP 12[6-19]); chronic tension type headache (GP 8[3-15]); musculoskeletal pain (25[19-33], 44[28-62], and 79[60-94]); joint pain (14[11-18], 34[16-54], and NA); chronic pelvic/prostatitis pain (GP 4[0-14]); temporomandibular disorder (35[4-78], 8[0-24], and NA); abdominal pain (EGP 17[6-32]); fibromyalgia (Combined GP, EGP, W 6[5-7]); and widespread pain (7[1-18], 19[8-32], and NA). Chronic low back pain and musculoskeletal pain were 2.50 (1.21-4.10) and 3.11 (2.13-4.37) times more prevalent among W, relative to a GP. Musculoskeletal, joint, and unspecified pain were 1.74 (1.03-2.69), 2.36 (1.09-4.02), and 1.83 (1.13-2.65) times more prevalent among the EGP, relative to a GP. There was significant heterogeneity among studies for all pain types ($I^2 > 90\%$). **CONCLUSIONS:** Chronic pain is prevalent in LMICs, and where there was sufficient evidence, generally more prevalent in EGP and W. This meta-analysis reveals the spectrum of chronic pain without clear etiology in LMICs. Steps should be taken to reduce heterogeneity in the assessment of global chronic pain. Possible actions may include standardization of chronic pain definition, widespread adoption of validated questionnaires across cultures, attention to inequitably burdened populations, and inclusion of queries regarding known associations of chronic pain with social and psychological factors that, in combination, increase the global burden of noncommunicable disease and disability.

[Myogenic temporomandibular disorders: Clinical systemic comorbidities in a female population sample.](#)

de-Pedro-Herráez M, Mesa-Jiménez J, Fernández-de-Las-Peñas C, de-la-Hoz-Aizpurua JL.

Med Oral Patol Oral Cir Bucal. 2016 Oct 1:0. [Epub ahead of print]

BACKGROUND: Myogenic temporomandibular disorders (MTMD) frequently coexist with other clinical conditions in the same individual. In the last decades, several authors have analyzed these comorbidities looking for the origin of this overlapping. **Objectives:** The aim of this study was to perform a comparative analysis between a group of patients with MTMD and a control group of dental patients without dysfunctional pathology to assess whether there are significant differences in the presence of systemic medical comorbidities between the two groups. **Material and Methods:**

Retrospective epidemiological analysis, based on medical questionnaires in a group of 31 patients, women, aged from 24 to 58 (average 39.96 years), diagnosed with MTMD (Masticatory Myofascial Pain), with a control group with the same number of individuals, gender and age range to evaluate if there is a significant statistical difference in the presence of medical comorbidities in this group of patients with MTMD and if they are in a higher risk of suffering different pathological conditions. Results: It was found that the group affected by MTMD presented many more associated medical conditions than the control group: health changes during the last year, medical evaluations and treatments, presence of pain, sinus disease, tinnitus, headache, joint pain, ocular disorders, fatigue, dizziness, genitourinary disorders and xerostomia among others; and they were also in a higher risk to suffer other pathological entities as headaches and articular pain. Conclusions: These results reinforce our hypothesis that MTMD belong to a group of medical conditions triggered by a loss of equilibrium of the individual's Psycho-Neuro-Endocrine-Immune (PNEI) Axis that produces alterations in the response against external stimuli in some genetically predisposed individuals. It is, therefore, necessary to change the way of diagnosing and managing these individual's medical conditions, being mandatory to look from a more multidisciplinary perspective than the one we are currently offering.

[Women with endometriosis have higher comorbidities: Analysis of domestic data in Taiwan.](#)

Teng SW, Horng HC, Ho CH, Yen MS, Chao HT, Wang PH; Taiwan Association of Gynecology Systematic Review Group.

J Chin Med Assoc. 2016 Aug 20. pii: S1726-4901(16)30123-X. doi: 10.1016/j.jcma.2016.04.006. [Epub ahead of print]

Endometriosis, defined by the presence of viable extrauterine endometrial glands and stroma, can grow or bleed cyclically, and possesses characteristics including a destructive, invasive, and metastatic nature. Since endometriosis may result in pelvic inflammation, adhesion, chronic pain, and infertility, and can progress to biologically malignant tumors, it is a long-term major health issue in women of reproductive age. In this review, we analyze the Taiwan domestic research addressing associations between endometriosis and other diseases. Concerning malignant tumors, we identified four studies on the links between endometriosis and ovarian cancer, one on breast cancer, two on endometrial cancer, one on colorectal cancer, and one on other malignancies, as well as one on associations between endometriosis and irritable bowel syndrome, one on links with migraine headache, three on links with pelvic inflammatory diseases, four on links with infertility, four on links with obesity, four on links with chronic liver disease, four on links with rheumatoid arthritis, four on links with chronic renal disease, five on links with diabetes mellitus, and five on links with cardiovascular diseases (hypertension, hyperlipidemia, etc.). The data available to date support that women with endometriosis might be at risk of some chronic illnesses and certain malignancies, although we consider the evidence for some comorbidities to be of low quality, for example, the association between colon cancer and adenomyosis/endometriosis. We still believe that the risk of comorbidity might be higher in women with endometriosis than that we supposed before. More research is needed to determine whether women with endometriosis are really at risk of these comorbidities.

[Somatic comorbidity in women with overactive bladder syndrome.](#)

Altman D, Iliadou AN, Lundholm C, Milsom I, Pedersen NL.

J Urol. 2016 Aug;196(2):473-7. doi: 10.1016/j.juro.2016.02.076.

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

[Benign joint hypermobility minimally impacts autonomic abnormalities in pediatric subjects with chronic functional pain disorders.](#)

Chelimsky G, Kovacic K, Simpson P, Nugent M, Basel D, Banda J, Chelimsky T.

J Pediatr. 2016 Oct;177:49-52. doi: 10.1016/j.jpeds.2016.06.091.

OBJECTIVE: To determine if children with benign joint hypermobility (BJH) syndrome and chronic functional pain disorders have more autonomic dysfunction. **STUDY DESIGN:** Retrospective chart review study of pediatric patients seen in the pediatric neurogastroenterology and autonomic clinic who underwent autonomic testing and had either a Beighton score of ≥ 6 and met Brighton criteria for BJH (with BJH) or a score of ≤ 2 (no BJH). **RESULTS:** Twenty-one female subjects (10 without BJH) met inclusion criteria; 64% of BJH had diagnosis confirmed by genetics consultation. We evaluated for postural tachycardiasyndrome, syncope, orthostatic intolerance, and orthostatic hypotension. None of these diagnoses, as well as baseline heart rate, peak heart rate in first 20 minutes of head up tilt ($P=.35$ and $P=.61$, respectively), and sudomotor index (suggestive of autonomic neuropathy) ($P=.58$), showed differences between the groups. Age of onset of symptoms was also similar ($P=.61$) (BJH vs without BJH: median [range]: 15.6 years [12.9-17.5] vs 15.4 years [11.1-18.2]). There was no difference between groups in complaints of migraine, chronic nausea, chronic fatigue, lightheadedness, dizziness, fainting >3 times/lifetime, delayed onset of sleep, irritable bowel syndrome, dyspepsia, abdominal migraine, functional abdominal pain,

constipation, or fibromyalgia. CONCLUSIONS: Children with chronic functional pain disorders and BJH have autonomic testing findings and comorbid features compared with a similar cohort of subjects without BJH, suggesting that BJH is not the driver of the autonomic and comorbid disorders.

[Migraine patients have a higher prevalence of PTSD symptoms in comparison to chronic tension-type headache and healthy subjects: A case-control study.](#)

Zarei MR, Shabani M, Chamani G, Abareghi F, Razavinasab M, Nazeri M.
Acta Odontol Scand. 2016 Sep 20;1-3. [Epub ahead of print]

OBJECTIVE: Headache is one of the most common disorders and has a heavy socioeconomic burden on both patients and society. Previous studies have demonstrated a high prevalence of psychological issues (e.g. depression and anxiety) in headache and especially migraine patients. The current study was designed to evaluate the prevalence of post-traumatic stress disorder (PTSD) symptomatology in chronic migraine (CM), chronic tension-type headache (CTTH) and healthy subjects. MATERIAL AND METHODS: CM and CTTH subjects were selected consecutively from patients referring to the department of neurology clinic at Shafa Hospital, Kerman University of Medical Sciences, Kerman, Iran. PTSD symptomatology was assessed using PTSD checklist civilian version-Persian edition (PCL-C). Control subjects were enrolled from the family members of headache patients who did not have any history of headache. Chi-square test was used to analyse data and $p < .05$ was considered statistically significant. RESULTS: Of the 60 control subjects, 5 had a PTSD symptomatology (8.3%); this prevalence was 13.3% for CTTH and 40% for CM groups. CM patients had a significantly higher prevalence of PTSD symptomatology in comparison to CTTH and control subjects ($p < .05$). With reference to gender, most of the subjects with PTSD symptomatology were female. CONCLUSION: Results of the current study demonstrated that CM patients have a higher prevalence of PTSD symptomatology compared to another chronic headache condition (CTTH) and healthy subjects, which should be considered while treating CM patients. Further studies in larger populations are demanded.

[Co-occurrence of pain symptoms and somatosensory sensitivity in burning mouth syndrome: A systematic review.](#)

Moisset X, Calbacho V, Torres P, Gremeau-Richard C, Dallel R.
PLoS One. 2016 Sep 22;11(9):e0163449. doi: 10.1371/journal.pone.0163449.

BACKGROUND: Burning mouth syndrome (BMS) is a chronic and spontaneous oral pain with burning quality in the tongue or other oral mucosa without any identifiable oral lesion or laboratory finding. Pathogenesis and etiology of BMS are still unknown. However, BMS has been associated with other chronic pain syndromes including other idiopathic orofacial pain, the dynias group and the family of central sensitivity syndromes. This would imply that BMS shares common mechanisms with other cephalic and/or extracephalic chronic pains. The primary aim of this systematic review was to determine whether BMS is actually associated with other pain syndromes, and to analyze cephalic and extracephalic somatosensory sensitivity in these patients.

METHODS: This report followed the PRISMA Statement. An electronic search was performed until January 2015 in PubMed, Cochrane library, Wiley and Science Direct. Searched terms included "burning mouth syndrome OR stomatodynia OR glossodynia OR burning tongue OR oral burning". Studies were selected according to predefined inclusion criteria (report of an association between BMS and other pain(s) symptoms or of cutaneous cephalic and/or extracephalic quantitative sensory testing in BMS patients), and a descriptive analysis conducted. **RESULTS:** The search retrieved 1512 reports. Out of these, twelve articles met criteria for co-occurring pain symptoms and nine studies for quantitative sensory testing (QST) in BMS patients. The analysis reveals that in BMS patients co-occurring pain symptoms are rare, assessed by only 0.8% (12 of 1512) of the retrieved studies. BMS was associated with headaches, TMD, atypical facial pain, trigeminal neuralgia, post-herpetic facial pain, back pain, fibromyalgia, joint pain, abdominal pain, rectal pain or vulvodynia. However, the prevalence of pain symptoms in BMS patients is not different from that in the age-matched general population. QST studies reveal no or inconsistent evidence of abnormal cutaneous cephalic and extracephalic somatosensory sensitivity. **CONCLUSIONS:** There is no evidence for a high rate of other pain symptoms or somatosensory impairments co-occurring with BMS. These results thus suggest that BMS rather depends on specific mechanisms, likely at the trigeminal level. Nevertheless, more thoroughly conducted research is required to draw definitive conclusion.

[DSM-5 insomnia and short sleep: Comorbidity landscape and racial disparities.](#)

Kalmbach DA, Pillai V, Arnedt JT, Drake CL.

Sleep. 2016 Sep 9. pii: sp-00284-16. [Epub ahead of print]

STUDY OBJECTIVES: We estimated rates of cardiometabolic disease, pain conditions, and psychiatric illness associated with Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) insomnia disorder (current and in remission) and habitual short sleep (fewer than 6 h), and examined the roles of insomnia and short sleep in racial disparities in disease burden between black and non-Hispanic white Americans. **METHODS:** This epidemiological survey study was cross-sectional. The community-based sample consisted of 3,911 subjects ($46.0 \text{ y} \pm 13.3$; 65.4% female; 25.0% black) across six sleep groups based on DSM-5 insomnia classification (never vs. remitted vs. current) and self-reported habitual sleep duration (normal vs. short). Vascular events, cardiometabolic disease, pain conditions, and psychiatric symptoms were self-reported. **RESULTS:** Short sleeping insomniacs were at elevated risk for myocardial infarction, stroke, treated hypertension, diabetes, chronic pain, back pain, depression, and anxiety, independent of sex, age, and obesity. Morbidity profiles for insomniacs with normal sleep duration and former insomniacs, irrespective of sleep duration, were similar with elevations in treated hypertension, chronic pain, depression, and anxiety. Regarding racial disparities, cardiometabolic and psychiatric illness burden was greater for blacks, who were more likely to have short sleep and the short sleep insomnia phenotype. Evidence suggested that health disparities may be attributable in part to race-related differences in sleep. **CONCLUSIONS:** Insomnia disorder with short sleep is the most severe phenotype of insomnia and comorbid with many cardiometabolic and psychiatric illnesses, whereas morbidity profiles are highly similar

between insomniacs with normal sleep duration and former insomniacs. Short sleep endemic to black Americans increases risk for the short sleep insomnia phenotype and likely contributes to racial disparities in cardiometabolic disease and psychiatric illness.

[Reporting of sex effects by systematic reviews on interventions for depression, diabetes and chronic pain.](#)

Duan-Porter W, Goldstein KM, McDuffie JR, Hughes JM, Clowse ME, Klap RS, Masilamani V, Allen LaPointe NM, Nagi A, Gierisch JM, Williams JW Jr. *Ann Intern Med.* 2016 Aug 2;165(3):184-93. doi: 10.7326/M15-2877.

Systematic reviews (SRs) have the potential to contribute uniquely to the evaluation of sex and gender differences (termed "sex effects"). This article describes the reporting of sex effects by SRs on interventions for depression, type 2 diabetes mellitus, and chronic pain conditions (chronic low back pain, knee osteoarthritis, and fibromyalgia). It includes SRs published since 1 October 2009 that evaluate medications, behavioral interventions, exercise, quality improvement, and some condition-specific treatments. The reporting of sex effects by primary randomized, controlled trials is also examined. Of 313 eligible SRs (86 for depression, 159 for type 2 diabetes mellitus, and 68 for chronic pain), few (n = 29) reported sex effects. Most SRs reporting sex effects used metaregression, whereas 9 SRs used subgroup analysis or individual-patient data meta-analysis. The proportion of SRs reporting the sex distribution of primary studies varied from a low of 31% (n = 8) for low back pain to a high of 68% (n = 23) for fibromyalgia. Primary randomized, controlled trials also infrequently reported sex effects, and most lacked an adequate sample size to examine them. Therefore, all SRs should report the proportion of women enrolled in primary studies and evaluate sex effects using appropriate methods whenever power is adequate.

FUNCTIONAL STATUS/QUALITY OF LIFE STUDIES

[Affect and low back pain: More to consider than the influence of negative affect alone.](#)

Hassett AL, Goesling J, Mathur SN, Moser SE, Brummett CM, Silille KT. *Clin J Pain.* 2016 Oct;32(10):907-14. doi: 10.1097/AJP.0000000000000350.

OBJECTIVES: Affect balance style, a measure of trait positive affect (PA) and negative affect (NA), is predictive of pain and functioning in fibromyalgia and healthy individuals. The purpose of this study was to evaluate the distribution of affect balance styles and the relationship between these styles and clinical factors in low back pain. **METHODS:** In this cross-sectional study, patients with low back pain (N=443) completed questionnaires and were categorized as having 1 of 4 distinct affect balance styles: Healthy (high levels of PA and low levels of NA), Low (low PA/low NA), Reactive (high PA/high NA), and Depressive (low PA/high NA). Comparisons between groups were made in regard to pain, functioning, and psychiatric comorbidity. **RESULTS:** High NA was observed in 63% (n=281), whereas low PA was present in 81% (n=359). We found that having a Depressive style was associated with greater pain severity, increased odds for comorbid fibromyalgia, and worse functioning compared with having a Healthy or Low style. Yet, those with a Low style were at increased risk for depression compared

with a Healthy style, whereas patients with a Reactive style had similar levels of pain, functioning, and depression as those with a Healthy affective style. **CONCLUSIONS:** Our study revealed that there are important differences between trait affect balance styles in regard to pain, mood, and functioning in low back pain. Findings related to Reactive and Low affective styles suggest that relationships between affect, pain, and disability in low back pain extend beyond considering NA alone.

[Self-regulatory fatigue: A missing link in understanding fibromyalgia and other chronic pain multi-symptom illnesses.](#)

Nes LS, Ehlers SL, Whipple MO, Vincent A.

Pain Pract. 2016 Sep 2. doi: 10.1111/papr.12480. [Epub ahead of print]

OBJECTIVE: Patients with chronic multi-symptom illnesses such as fibromyalgia syndrome (FMS) are experiencing a multitude of physical and mental challenges. Facing such challenges may drain capacity to self-regulate, and research suggests patients with these illnesses may experience self-regulatory fatigue (SRF). This study sought to examine whether SRF can be associated with quality of life (QoL) in patients with FMS. **METHODS:** Patients (N=258) diagnosed with FMS completed self-report measures related to demographics, SRF (Self-Regulatory Fatigue 18 [SRF-18]), anxiety (Generalized Anxiety Disorder questionnaire [GAD-7]), depression (Patient Health Questionnaire [PHQ-9]), physical fatigue (Multidimensional Fatigue Inventory [MFI]), symptoms related to FMS (Fibromyalgia Impact Questionnaire [FIQ]), and QoL (36-Item Short-Form Health Survey [SF-36]). **RESULTS:** Hierarchical regressions showed higher SRF to be associated with lower QoL in terms of lower overall physical QoL, with subscales related to physical functioning, role limitations-physical, bodily pain, and general health (all P 's>0.001), as well as lower overall mental QoL, with subscales related to vitality, social functioning, role limitations-emotional, and mental health (all P 's>0.001). Including traditional predictors such as anxiety, depression, physical fatigue, and FMS-related symptoms as covariates in the analyses reduced the link between SRF and QoL somewhat, but the associations remained generally strong, particularly for SRF and mental QoL. **CONCLUSION:** This is the first study to show higher SRF relating to lower QoL for patients with FMS. Results suggest that SRF is distinct from anxiety, depression, and fatigue, and predicts QoL above and beyond these traditional factors in the area of chronic multi-symptom illnesses such as FMS. SRF may be a "missing link" in understanding the complex nature of chronic multi-symptom illnesses.

[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.

Pain Med. 2016 Sep 28. pii: pnw236. [Epub ahead of print]

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:** Five thousand two hundred twenty adults age 65 years 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, wide-spread 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.

[Distinctive personality profiles of fibromyalgia and chronic fatigue syndrome patients.](#)

Ablin JN, Zohar AH, Zarava-Blum R, Buskila D.

Peer J. 2016 Sep 13;4:e2421. doi: 10.7717/peerj.2421. eCollection 2016.

OBJECTIVE: The current study is an innovative exploratory investigation, aiming at identifying differences in personality profiles within Fibromyalgia Syndrome (FMS) and Chronic Fatigue Syndrome (CFS) patients. METHOD: In total, 344 participants (309 female, 35 male) reported suffering from FMS and/or CFS and consented to participate in the study. Participants were recruited at an Israeli FM/CFS patient meeting held in May 2013, and through an announcement posted on several social networks. Participants were asked to complete a research questionnaire, which included FMS criteria and severity scales, and measures of personality, emotional functioning, positivity, social support and subjective assessment of general health. In total, 204 participants completed the research questionnaire (40.7% attrition rate). RESULTS: A cluster analysis produced two distinct clusters, which differed significantly on psychological variables, but did not differ on demographic variables or illness severity. As compared to cluster number 2 (N=107), participants classified into cluster number 1 (N=97) showed a less adaptive pattern, with higher levels of Harm Avoidance and Alexithymia; higher prevalence of Type D personality; and lower levels of Persistence (PS), Reward dependence (RD), Cooperation, Self-directedness (SD), social support and positivity. CONCLUSION: The significant pattern of results indicates at least two distinct personality profiles of FM and CFS patients. Findings from this research may help improve the evaluation and treatment of FM and CFS patients, based on each patient's unique needs, psychological resources and weaknesses, as proposed by the current trend of personalized medicine.

CLINICAL STUDIES

[Fecal microbiota transplantation and its usage in neuropsychiatric disorders.](#)

Evrensel A, Ceylan ME.

Clin Psychopharmacol Neurosci. 2016 Aug 31;14(3):231-7. doi:

10.9758/cpn.2016.14.3.231.

Fecal microbiota transplantation has a 1700-year history. This forgotten treatment method has been put into use again during the last 50 years. The interest in microbiota-gut-brain axis and fecal microbiota transplantation is rapidly increasing. New evidence is obtained in the etiopathogenesis of neuropsychiatric disorders. There is a large number of experimental and clinical researches in the field of gut-brain axis. There is limited information on fecal microbiota transplantation. Despite this, initial results are promising. It is commonly used in the treatment of gastrointestinal diseases such as *Clostridium difficile* infection, Crohn's disease, ulcerative colitis. It is also experimentally used in the treatment of metabolic and autoimmune diseases. There are case reports that it is effective in the treatment of autism, Parkinson's disease, multiple sclerosis, chronic fatigue syndrome and irritable bowel syndrome. Its implementation is easy, and it is a cheap and reliable treatment method. However, the long-term risks are unknown. Additionally, standard application protocols have not yet been established. There are a lot of questions to be answered. A university in Turkey has got official permission this year, and started to apply fecal microbiota transplantation. In this review, neuropsychiatric areas of use of fecal microbiota transplantation have been discussed in the light of the current information.

[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. 2016 Sep 15. doi: 10.1002/ejp.935. [Epub ahead of print]

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.

[Current status of new antiepileptic drugs in chronic pain.](#)

Sidhu HS, Sadhotra A.

Front Pharmacol. 2016 Aug 25;7:276. doi: 10.3389/fphar.2016.00276. eCollection 2016.

Antiepileptic drugs (AEDs) are extensively used worldwide to treat a wide range of disorders other than epilepsy, such as neuropathic pain, migraine, and bipolar disorder. Due to this situation more than 20 new third-generation AEDs have been introduced in the market recently. The future design of new AEDs must also have potential to help in the non-epileptic disorders. The wide acceptance of second generation AEDs for the management of various non-epileptic disorders has caused the emergence of generics in the market. The wide use of approved AEDs outside epilepsy is based on both economic and scientific reasons. Bipolar disorders, migraine prophylaxis, fibromyalgia, and neuropathic pain represent the most attractive indication expansion opportunities for anticonvulsant developers, providing blockbuster revenues. Strong growth in non-epilepsy conditions will see Pfizer's Lyrica become the market leading brand by 2018. In this review, we mainly focus on the current status of new AEDs in the treatment of chronic pain and migraine prophylaxis. AEDs have a strong analgesic potential and this is demonstrated by the wide use of carbamazepine in trigeminal neuralgia and sodium valproate in migraine prophylaxis. At present, data on the new AEDs for non-epileptic conditions are inconclusive. Not all AEDs are effective in the management of neuropathic pain and migraine. Only those AEDs whose mechanisms of action are match with pathophysiology of the disease, have potential to show efficacy in non-epileptic disorder. For this better understanding of the pathophysiology of the disease and mechanisms of action of new AEDs are essential requirement before initiating pre-clinical and clinical trials. Many new AEDs show good results in the animal model and open-label studies but fail to provide strong evidence at randomized, placebo-controlled trials. The final decision regarding the clinical efficacy of the particular AEDs in a specific non-epileptic disorder should be withdrawal from randomized placebo trials rather than open-label studies; otherwise this may lead to off-label uses of drug. The purpose of the present review is to relate the various mechanisms of action of new AEDs to pathophysiological mechanisms and clinical efficacy in neuropathic pain and migraine.

[How to early recognize mood disorders in primary care: A nationwide, population-based, cohort study.](#)

Castellini G, Pecchioli S, Cricelli I, Mazzoleni F, Cricelli C, Ricca V, Hudziak JJ, Brignoli O, Lapi F.

Eur Psychiatry. 2016 Sep;37:63-9. doi: 10.1016/j.eurpsy.2016.04.003.

BACKGROUND: Mood disorders are managed predominantly in primary care. However, general practitioners' (GPs) ability to detect and diagnose patients with

mood disorders is still considered unsatisfactory. The aim of the present study was to identify predictors for the early recognition of depressive disorder (DD) and bipolar disorder (BD) in general practice. METHODS: A cohort of 1,144,622 patients (605,285 women, 539,337 men) was investigated, using the Health Search IMS Health Longitudinal Patient Database. Predictors of DD or BD were identified at baseline encompassing somatization-related features, lifestyle variables, medical and psychiatric comorbidities. Patients were followed up as long as the following events occurred: diagnoses of DD or BD, death, end of the registration with the GP, end of the study period. RESULTS: We found an incidence rate of DD or BD of 53.61 and 1.5 per 10,000 person-years, respectively. For both the conditions, the incidence rate grew with age. Most of the lifestyle variables and medical comorbidities increased the risk of mood disorders. The strongest effect was found for migraine/headache (HR [95% CI]=1.32 [1.26-1.38]), fatigue (1.32 [1.25-1.39]) irritable bowel syndrome (1.15 [1.08-1.23]), and pelvic inflammation disease (1.28 [1.18-1.38]). CONCLUSIONS: Several predictors, in particular somatic symptoms, could be interpreted as an early sign of a mood disorder, and represent a valid indication for the GPs diagnostic process of mental disorders.

[Temporomandibular disorders and headache.](#)

Graff-Radford SB, Abbott JJ.

Oral Maxillofac Surg Clin North Am. 2016 Aug;28(3):335-49. doi: 10.1016/j.coms.2016.03.004.

Temporomandibular disorders (TMD) and primary headaches can be perpetual and debilitating musculoskeletal and neurological disorders. The presence of both can affect up to one-sixth of the population at any one time. Initially, TMDs were thought to be predominantly musculoskeletal disorders, and migraine was thought to be solely a cerebrovascular disorder. The further understanding of their pathophysiology has helped to clarify their clinical presentation. This article focuses on the role of the trigeminal system in associating TMD and migraine. By discussing recent descriptions of prevalence, diagnosis, and treatment of headache and TMD, we will further elucidate this relationship.

[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. 2016 Aug 19:1-22. [Epub ahead of print]

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.

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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.

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