



CUTTING EDGE

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COPCs Research Advances

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This e-newsletter - published by the CPRA to keep the medical-scientific and patient communities abreast of research advances on Chronic Overlapping Pain Conditions (COPCs) - contains abstracts of studies on the epidemiology, pathophysiology and clinical management of COPCs published between January and May 2019. Prior 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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NATIONAL MULTICENTER STUDIES

Genome-wide association reveals contribution of MRAS to painful temporomandibular disorder in males.

Smith SB, Parisien M, Bair E, Belfer I, Chabot-Dore AJ, Gris P, Khoury S, Tansley S, Torosyan Y, Zaykin DV, Bernhardt O, de Oliveira Serrano P, Gracely RH, Jain D, Jarvelin MR, Kaste LM, Kerr KF, Kocher T, Lahdesmaki R, Laniado N, Laurie CC, Laurie CA, Mannikko M, Meloto CB, Nackley AG, Nelson SC, Pesonen P, Ribeiro-Dasilva MC, Rizzatti-Barbosa CM, Sanders AE, Schwahn C, Sipila K, Sofer T, Teumer A, Mogil JS, Fillingim RB, Greenspan JD, Ohrbach R, Slade GD, Maixner W, Diatchenko L.

Pain. 2019 Mar;160(3):579-591. doi: 10.1097/j.pain.0000000000001438.

Painful temporomandibular disorders (TMDs) are the leading cause of chronic orofacial pain, but its underlying molecular mechanisms remain obscure. Although many environmental factors have been associated with higher risk of developing painful TMD, family and twin studies support a heritable genetic component as well. We performed a genome-wide association study assuming an additive genetic model of TMD in a discovery cohort of 999 cases and 2031 TMD-free controls from the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study. Using logistic models adjusted for sex, age, enrollment site,

and race, we identified 3 distinct loci that were significant in combined or sex-segregated analyses. A single-nucleotide polymorphism on chromosome 3 (rs13078961) was significantly associated with TMD in males only (odds ratio = 2.9, 95% confidence interval: 2.02-4.27, $P = 2.2 \times 10^{-8}$). This association was nominally replicated in a meta-analysis of 7 independent orofacial pain cohorts including 160,194 participants (odds ratio = 1.16, 95% confidence interval: 1.0-1.35, $P = 2.3 \times 10^{-2}$). Functional analysis in human dorsal root ganglia and blood indicated this variant is an expression quantitative trait locus, with the minor allele associated with decreased expression of the nearby muscle RAS oncogene homolog (MRAS) gene ($\beta = -0.51$, $P = 2.43 \times 10^{-4}$). Male mice, but not female mice, with a null mutation of *Mras* displayed persistent mechanical allodynia in a model of inflammatory pain. Genetic and behavioral evidence support a novel mechanism by which genetically determined MRAS expression moderates the resiliency to chronic pain. This effect is male-specific and may contribute to the lower rates of painful TMD in men.

Urologic chronic pelvic pain syndrome: Insights from the MAPP Research Network.

Clemens JQ, Mullins C, Ackerman AL, Bavendam T, van Bokhoven A, Ellingson BM, Harte SE, Kutch JJ, Lai HH, Martucci KT, Moldwin R, Naliboff BD, Pontari MA, Sutcliffe S, Landis JR; MAPP Research Network Study Group.

Nat Rev Urol. 2019 Mar;16(3):187-200. doi: 10.1038/s41585-018-0135-5.

Urologic chronic pelvic pain syndrome (UCPPS), which encompasses interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome, is characterized by chronic pain in the pelvic region or genitalia that is often accompanied by urinary frequency and urgency. Despite considerable research, no definite aetiological risk factors or effective treatments have been identified. The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network uses a novel integrated strategy to characterize UCPPS as a systemic disorder that potentially involves multiple aetiologies. The first phase, MAPP I, included >1,000 participants who completed an intensive baseline assessment followed by a 12-month observational follow-up period. MAPP I studies showed that UCPPS pain and urinary symptoms co-vary, with only moderate correlation, and should be evaluated separately and that symptom flares are common and can differ considerably in intensity, duration and influence on quality of life. Longitudinal clinical changes in UCPPS correlated with structural and functional brain changes, and many patients experienced global multisensory hypersensitivity. Additionally, UCPPS symptom profiles were distinguishable by biological correlates, such as immune factors. These findings indicate that patients with UCPPS have objective phenotypic abnormalities and distinct biological characteristics, providing a new foundation for the study and clinical management of UCPPS.

Symptom duration in patients with urologic chronic pelvic pain syndrome is not associated with pain severity, nonurologic syndromes and mental health symptoms: A Multidisciplinary Approach to the Study of Chronic Pelvic Pain Network Study.

Rodriguez LV, Stephens AJ, Clemens JQ, Buchwald D, Yang C, Lai HH, Krieger JN, Newcomb C, Bradley CS, Naliboff B; MAPP Research Network.

Urology. 2019 Feb;124:14-22. doi: 10.1016/j.urology.2018.11.015.

OBJECTIVE: To evaluate if patients with urologic chronic pelvic pain syndromes (UCPPS) with longer duration of symptoms experience more severe pain and urologic symptoms, higher rates of chronic overlapping pain conditions (COPC) and psychosocial comorbidities than those with a more recent onset of the condition. We evaluated cross-sectional associations between UCPPS symptom duration and (1) symptom severity, (2) presence of COPC, and (3) mental health comorbidities. **METHODS:** We analyzed baseline data from the Multidisciplinary Approach to the Study of Chronic Pelvic Pain. Symptom severity, COPC, and mental health comorbidities were compared between patients with symptom duration of < 2 vs ≥ 2 years. Symptom severity was assessed by the Genitourinary Pain Index, the Interstitial Cystitis Symptom and Problem Index, and Likert scales for pelvic pain, urgency, and frequency. Depression and anxiety were evaluated with the Hospital Anxiety and Depression Scale and stress with the Perceived Stress Scale. **RESULTS:** Males (but not females) with

UCPPS symptom duration ≥ 2 years had more severe symptoms than those with < 2 years. Participants with short (< 2 years) and longer (≥ 2 years) symptom duration were as likely to experience COPC. CONCLUSION: Longer UCPPS symptom duration was associated with more severe symptoms only in limited patient subpopulations. Symptom duration was not associated with risk for COPC or mental health comorbidities. Females with longer UCPPS duration had decreased distress, but the association was largely attributable to age.

A longitudinal analysis of urologic chronic pelvic pain syndrome flares in the MAPP Research Network.

Sutcliffe S, Gallop R, Lai HH, Andriole GL, Bradley CS, Chelimsky G, Chelimsky T, Clemens JQ, Colditz GA, Erickson B, Griffith JW, Kim J, Krieger JN, Labus J, Naliboff BD, Rodriguez LV, Sutherland SE, Taple BJ, Landis JR; MAPP Research Network.

BJU Int. 2019 Apr 23. doi: 10.1111/bju.14783. [Epub ahead of print]

OBJECTIVE: To describe the frequency, intensity, and duration of urologic chronic pelvic pain syndrome symptom exacerbations ("flares"), as well as risk factors for these features, in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Epidemiology and Phenotyping longitudinal study. PARTICIPANTS AND METHODS: Current flare status ("urologic or pelvic pain symptoms that are much worse than usual") was ascertained at each bi-weekly assessment. Flare characteristics, including start date, and current intensity of pelvic pain, urgency, and frequency (scales of 0-10), were assessed for participants' first three flares and at three randomly selected times when they did not report a flare. Generalized linear and mixed effects models were used to investigate flare risk factors. RESULTS: Of the 385 eligible participants, 24.2% reported no flares, 22.9% reported 1 flare, 28.3% 2-3 flares, and 24.6% ≥ 4 flares, up to a maximum of 18 during the 11-month follow-up (median incidence rate=0.13/bi-weekly assessment, range=0.00-1.00). Pelvic pain (mean=2.63 point increase) and urologic symptoms (mean=1.72) were both significantly worse during most flares (60.6%), with considerable within-participant variability (26.2-37.8%). Flare duration varied from 1-150 days (94.3% within-participant variability). In adjusted analyses, flares were more common, symptomatic, and/or longer-lasting in female participants and those with worse non-flare symptoms, bladder hypersensitivity, and chronic overlapping pain conditions. CONCLUSION: In this foundational flare study, we found that pelvic pain and urologic symptom flares were common, but variable in frequency and manifestation. We also identified sub-groups of participants with more frequent, symptomatic, and/or longer-lasting flares for targeted flare management/prevention and further study.

Management of symptom flares and patient-reported flare triggers in interstitial cystitis/bladder pain syndrome (IC/BPS)-Findings from one site of the MAPP Research Network.

Lai HH, Vetter J, Song J, Andriole GL, Colditz GA, Sutcliffe S.

Urology. 2019 Apr;126:24-33. doi: 10.1016/j.urology.2019.01.012.

OBJECTIVE: To document patient-reported interstitial cystitis/bladder pain syndrome (IC/BPS) flare management strategies and triggers. MATERIALS AND METHODS: Twenty-four male and 29 female participants enrolled at the Washington University site of the MAPP Research Network completed a questionnaire on strategies they utilized to manage flares and factors they believed triggered their flares (eg, specific food items, physical activities, sexual activities, infections, and stress). Participants were also asked about the diurnal timing of their flares. RESULTS: A total of 96.2% of participants reported having ever experienced a symptom flare. Participants treated or managed their flares using a wide variety of strategies, ranging from common strategies, such as drinking additional water or fluid (74.5%), to less common strategies, such as acupuncture/acupressure (5.9% of participants). Participants also reported a wide range of perceived flare triggers, including previously reported factors (citrus fruits, tomatoes, spicy food, alcoholic and caffeinated beverages, driving/sitting in forms of transportation, urinary tract infections, stress, and tight clothing), as well as some less common, previously undocumented factors (eg, certain foods,

nongenitourinary infections, wearing high-heeled shoes/boots or perfume, hair dye, and toothpaste). In general, female participants and those with somatic sensory hypersensitivity reported greater numbers of therapies and triggers. Finally, flares were reported most commonly in the afternoon or evening. CONCLUSION: IC/BPS participants reported diverse flare management strategies and numerous perceived triggers. These findings, together with those from the small body of literature to date, provide a wide array of candidates and hypotheses for future global and tailored flare management and prevention interventions.

PATHOPHYSIOLOGY STUDIES

Altered gray matter volume in sensorimotor and thalamic regions associated with pain in localized provoked vulvodynia: A voxel-based morphometry study.

Bhatt RR, Gupta A, Rapkin A, Kilpatrick LA, Hamadani K, Pazmany E, Van Oudenhove L, Stains J, Aerts L, Enzlin P, Tillisch K, Mayer EA, Labus JS. Pain. 2019 Feb 25. doi: 10.1097/j.pain.0000000000001532.

Multimodal neuroimaging studies provide support for a role of alterations in sensory processing circuits and endogenous pain modulatory systems in provoked vestibulodynia (PVD). In this study we tested the hypotheses that PVD compared to healthy controls (HCs) would demonstrate gray matter volume (GMV) alterations in regions associated with sensorimotor, corticothalamic, and basal ganglia circuits. We also tested the replicability of previously reported gray matter increases in basal ganglia and hippocampal volumes in PVD versus HCs. Additionally, disease-specificity of GMV alterations were examined by comparing PVD to another chronic pain disorder. Finally we examine whether GMV alterations are correlated with symptom measures. Structural magnetic resonance imaging was obtained in 119 premenopausal women (45 PVD, 45 HCs, 29 irritable bowel syndrome (IBS)). A voxel-based morphometry analysis was applied to determine group differences in the hypothesized regions of interest. Compared to HCs, PVD women exhibited greater GMV in the basal ganglia, hippocampus, and sensorimotor cortices. Compared to IBS patients, women with PVD had greater GMV in the hippocampus, and sensorimotor network, but lower GMV in the thalamus and precentral gyrus. Regional gray matter volume alterations were associated with patient reports of pain during intercourse and muscles tenderness. The current findings provide further evidence that GMV is increased in PVD compared to HCs in several regions of the sensorimotor network and the hippocampus in PVD patients. In addition, GMV distinct alterations in the sensorimotor network were identified between two pelvic pain disorders, PVD compared to irritable bowel syndrome.

Clinical features contributing to cortical thickness changes in chronic migraine - a pilot study.

Woldeamanuel YW, DeSouza DD, Sanjanwala BM, Cowan RP. Headache. 2019 Feb;59(2):180-191. doi: 10.1111/head.13452.

OBJECTIVES: The objectives of this cross-sectional pilot study were threefold: to identify regions of cortical thickness that differentiate chronic migraine (CM) from controls, to assess group differences in interregional cortical thickness covariance, and to determine group differences in associations between clinical variables and cortical thickness.

BACKGROUND: Cortical thickness alterations in relation to clinical features have not been adequately explored in CM. Assessment of this relationship can be useful to describe cortical substrates for disease progression in migraine and to identify clinical variables that warrant management emphasis. **METHODS:** Thirty CM cases (mean age 40 years; male-to-female 1:4) and 30 sex-matched healthy controls (mean age 40 years) were enrolled. Participants completed self-administered and standardized questionnaires assessing headache-related clinical features and common psychological comorbidities. T1-weighted brain images were acquired on a 3T MRI. A whole-brain cortical thickness analysis was performed. Additionally, correlations between all brain regions were assessed to examine interregional cortical thickness covariance. Interactions were analyzed to identify clinical variables that were

significantly associated with cortical thickness. RESULTS: The whole brain cortical thickness analysis revealed no significant differences between CM patients and controls. However, significant associations between clinical features and cortical thickness were observed for the patients only. These associations included the right superior temporal sulcus ($R^2 = 0.72$, $P = .001$) and the right insula ($R^2 = 0.71$, $P = .002$) with distinct clinical variables ie, longer history of CM, posttraumatic stress disorder (PTSD), sleep quality, pain self-efficacy, and somatic symptoms. Higher interregional cortical covariance was found in CM compared to controls (OR = 3.1, CI 2.10-4.56, $P < .0001$), such that cortical thickness between regions tended to be more correlated in patients, particularly in the temporal and frontal lobes. CONCLUSION: CM patients have significantly greater cortical covariance compared to controls. Cortical thickness in CM patients was predominantly accounted for by CM duration, PTSD, and poor sleep quality, while improved pain self-efficacy buffered cortical thickness. While it is important to address all CM features and comorbidities, it may be useful to emphasize optimizing the management of certain clinical features that contribute to cortical abnormalities including managing PTSD, early management to shorten duration of CM, and improving pain self-efficacy and sleep quality.

Widespread mechanical pain hypersensitivity in patients with chronic migraine and temporomandibular disorders: relationship and correlation between psychological and sensorimotor variables.

Garrigos-Pedron M, La Touche R, Navarro-Desentre P, Gracia-Naya M, Segura-Orti E. Acta Odontol Scand. 2019 Apr;77(3):224-231. doi: 10.1080/00016357.2018.1538533.

OBJECTIVE: This study aimed to assess mechanical hyperalgesia in the trigeminal and extra-trigeminal regions in patients with chronic migraine (CM) and temporomandibular disorders (TMD) in comparison to asymptomatic subjects and to determine the association between sensorimotor variables and psychological and disability variables and evaluate the prediction of a sensorimotor variables through psychological and disability variables in patients with CM and TMD. MATERIAL AND METHODS: A total of 52 subjects with concomitant CM and TMD and 30 asymptomatic subjects were included in the study. The pressure pain threshold (PPT), maximal mouth opening (MMO) and a series of self-reported factors were compared. RESULTS: There were 52 CM and TMD (92.3% women and 7.7% men; age = 26.2 +/- 9.5) and 30 asymptomatic subjects (80% women and 20% men; age = 47.4 +/- 10). Differences were found between patients with CM and TMD and asymptomatic participants ($p < 0.01$) when comparing the PPTs in the trigeminal and extra-trigeminal regions. The PPT for the trigeminal region was predicted by depressive symptoms (variance of 18%) as well as disability and craniofacial pain (variance of 20%). The extra-trigeminal region PPT was predicted by depressive symptoms (variance of 10%), and pain-free MMO was predicted by disability and craniofacial pain (variance of 24%). CONCLUSIONS: This study suggests that patients with CM and TMD present with generalized mechanical hyperalgesia. In addition, an association between sensorimotor, psychological and disability variables was observed.

Migraine associated with gastrointestinal disorders: A pathophysiological explanation.

Talafi Noghani M, Namdar H.

Med Hypotheses. 2019 Apr;125:90-93. doi: 10.1016/j.mehy.2019.02.041.

BACKGROUND: Migraine is a highly prevalent, disabling, and costly disorder worldwide. From a long time ago, headaches have been known to be associated with gastrointestinal (GI) disorders. Headaches originating from gastric complaints were appreciated by Persian Medicine (PM) scholars. Today, functional GI disorders are shown to have high comorbidity with migraines; however, a causal relationship is not accepted today and pathophysiological explanations for this comorbidity are scarce. Therefore, based on the PM philosophy and the existing evidence, we aimed to propose an explanation for the comorbidity of migraine and GI disorders. SUMMARY: Noxious stimuli from the GI tract are relayed to the nucleus tractus solitarius (NTS) in the brain stem, which is located close to the trigeminal nucleus caudalis (TNC). TNC has shown projections to (NTS) through which frequent GI stimuli may antidromically reach the TNC and finally result in neurogenic

inflammation. In addition, immune products, particularly histamine, are released in the submucosa of the GI tract and absorbed into the systemic circulation, which renders migraineurs more prone to attacks.

Voluntary wheel running reveals sex-specific nociceptive factors in murine experimental autoimmune encephalomyelitis.

Mifflin KA, Yousuf MS, Thorburn KC, Huang J, Perez-Munoz ME, Tenorio G, Walter J, Ballanyi K, Drohomysky PC, Dunn SE, Kerr BJ. Pain. 2019 Apr;160(4):870-881. doi: 10.1097/j.pain.0000000000001465.

Multiple sclerosis (MS) is an inflammatory, neurodegenerative autoimmune disease associated with sensory and motor dysfunction. Although estimates vary, ~50% of patients with MS experience pain during their disease. The mechanisms underlying the development of pain are not fully understood, and no effective treatment for MS-related pain is available. Previous work from our laboratory demonstrated that voluntary exercise (wheel running) can reduce nociceptive behaviours at the disease onset in female mice with experimental autoimmune encephalomyelitis (EAE), an animal model used to study the immunopathogenesis of MS. However, given the established sex differences in the underlying mechanisms of chronic pain and MS, we wanted to investigate whether wheel running would also be effective at preventing nociceptive behaviours in male mice with EAE. C57BL/6 mice of both sexes were given access to running wheels for 1 hour/day until the disease onset, when nociceptive behaviour was assessed using von Frey hairs. Daily running effectively reduced nociceptive behaviour in female mice, but not in male mice. We explored the potential biological mechanisms for these effects and found that the reduction in nociceptive behaviour in female mice was associated with reduced levels of inflammatory cytokines from myelin-reactive T cells as well as reduced dorsal root ganglia excitability as seen by decreased calcium responses. These changes were not seen in male mice. Instead, running increased the levels of inflammatory cytokines and potentiated Ca responses in dorsal root ganglia cells. Our results show that voluntary wheel running has sex-dependent effects on nociceptive behaviour and inflammatory responses in male and female mice with EAE.

EPIDEMIOLOGY STUDIES

Provoked vestibulodynia in women with pelvic pain.

Bao C, Noga H, Allaire C, Williams C, Bedaiwy MA, Sadownik LA, Brotto LA, Smith KB, Yong PJ. Sex Med. 2019 Apr 3. pii: S2050-1161(19)30030-3. doi: 10.1016/j.esxm.2019.03.002.

INTRODUCTION: Pelvic pain and vulvar pain are common conditions in women. In this study, we sought to characterize the clinical picture of patients with concurrent pelvic pain and provoked vestibulodynia (PVD). **AIM:** To analyze the association between sexual/clinical characteristics and a diagnosis of PVD among women with pelvic pain. **METHODS:** Cross-sectional analysis of a prospective registry at a tertiary referral center for pelvic pain and endometriosis, involving consecutive non-menopausal sexually active patients 18-49 years-old seen by a single gynecologist from January 2016-December 2017. The sample was divided into 2 groups: pelvic pain with PVD; and pelvic pain alone (without PVD). **MAIN OUTCOME MEASURES:** Superficial dyspareunia and deep dyspareunia on a 11-point numeric rating scale, and the sexual quality-of-life subscale of the Endometriosis Health Profile-30 (0-100%). **RESULTS:** There were 129 patients that met study criteria: one third with pelvic pain and PVD (n = 42) and two-thirds with pelvic pain alone (without PVD) (n = 87). Women with pelvic pain and PVD had significantly more severe superficial dyspareunia $\geq 7/10$ (OR = 12.00 (4.48-32.16), $P < .001$), more severe deep dyspareunia $\geq 7/10$ (OR = 4.08 (1.83-9.10), $P = .001$), and poorer sexual quality of life (Endometriosis Health Profile-30 $\geq 50\%$) (OR = 4.39 (1.67-11.57), $P = .002$), compared with the group with pelvic pain alone. Women with pelvic pain and PVD also had more anxiety, depression, and catastrophizing, more frequent tenderness of the bladder and pelvic floor, and more common diagnosis of painful

bladder syndrome. On the other hand, there were no significant differences between the 2 groups in terms of dysmenorrhea, chronic pelvic pain, abdominal wall allodynia, positive Carnett test for abdominal wall pain, functional quality of life, endometriosis, and irritable bowel syndrome. CONCLUSIONS: In the pelvic pain population, PVD may be associated with more negative impact on dyspareunia, sexual quality of life, and bladder/pelvic floor function, but it may not significantly impact abdominopelvic pain or day-to-day function in general.

Comorbidity between fibromyalgia and temporomandibular disorders: a systematic review.

Ayouni I, Chebbi R, Hela Z, Dhidah M.

Oral Surg Oral Med Oral Pathol Oral Radiol. 2019 Feb 28. pii: S2212-4403(19)30156-7.

OBJECTIVE: Fibromyalgia (FM) is characterized by bodywide diffuse and chronic musculoskeletal pain, which, in some patients, can include pain in the masticatory muscles and temporomandibular joints; those patients are defined as having temporomandibular disorders (TMDs). The purpose of this systematic review is to study the association between FM and TMD, as well as the prevalence and characteristics of TMD in patients with FM or the features and prevalence of FM in patients with TMD. STUDY DESIGN: Our bibliographic search was conducted from January 1, 2005, to May 31, 2018, in the MEDLINE database by using its free search engine PubMed and the keywords "fibromyalgia," "temporomandibular joint disorder," and "orofacial pain." RESULTS: Of the 185 studies found in this search, only 19 met the inclusion criteria. These studies showed a high prevalence of TMD in patients with FM. Muscle pain, temporomandibular joint pain, and muscle tenderness on palpation are the most common symptoms. These results suggest an association between TMD and FM; FM can be an etiologic or aggravating factor for TMD, or it may represent a general vulnerability to pain disorders. Besides, the 2 pathologies may share some regional or central mechanisms in common. CONCLUSIONS: The high prevalence of TMD in patients with FM emphasizes the need to consider the signs and symptoms of TMD in the diagnosis of FM to improve pain management in these patients.

Burden of migraine in Finland: Health care resource use, sick-leaves and comorbidities in occupational health care.

Korolainen MA, Kurki S, Lassenius MI, Toppila I, Costa-Scharplatz M, Purmonen T, Nissila M. J Headache Pain. 2019 Feb 12;20(1):13. doi: 10.1186/s10194-019-0964-5.

BACKGROUND: The highest prevalence of migraine is detected among people who are of working age. The aim of this study was to assess the burden of migraine in an occupational health care setting using real world data collected as a part of routine clinical practice. METHODS: This retrospective register study included migraineurs using occupational health care at the private health care provider Terveystalo. An age and gender matched control population was established for comparison. Electronic medical records were assessed for overall and migraine related health care visits, sick-leaves and comorbidities. Stratification to acute and prophylactic treatment groups along with prophylactic treatment lines was based on prescriptions. RESULTS: Among the 369,383 individuals in the study cohort, 7.4% women and 2.1% men were identified having a diagnosis of migraine. Prophylactic medication was prescribed to 13% of migraine patients and exclusively acute medication to 37%. Although migraine related visits and sick-leave days were significantly lower than overall visits or sick-leave days, both increased by prophylactic treatment line. The number of visits rose from 13.8 to 26.2 and sick-leave days from 16.8 to 30.4 per patient-year, in those without prophylaxis vs. ≥ 3 prophylactic treatments. Moreover, migraine patients had 1.7-fold increase in visits and 1.8-fold increase in sick leave days on average per patient-year, when compared to the control population. Depression and anxiety were 1.8-fold more common among patients with migraine, and the frequency also increase by treatment line. CONCLUSIONS: Migraine burden increased by each failed treatment line and was associated with increased comorbidity. In addition, migraine patients had significantly higher extent of visits and sick-leave days as well as extent of comorbidities when compared to their age- and gender-matched counterparts.

Factors associated with migraine in the general population of Spain: Results from the European Health Survey 2014.

Roy R, Sanchez-Rodriguez E, Galan S, Racine M, Castarlenas E, Jensen MP, Miro J. Pain Med. 2019 Mar 1;20(3):555-563. doi: 10.1093/pm/pny093.

OBJECTIVE: To identify the modifiable and nonmodifiable variables that are associated with and might moderate the presence of migraine in the general population. DESIGN: Nationally representative cross-sectional survey. SETTING: Noninstitutionalized population of Spain. SUBJECTS: Individuals aged 15 years or older (n=22,842). METHODS: A secondary analysis of data from the second wave of the European Health Interview Survey conducted in Spain (2014/2015). We estimated the prevalence of migraine and its distribution according to the study variables, and then built a multivariate logistic model encompassing age, sex, depression severity, chronic anxiety, body mass index, physical activity, smoking status, alcohol use, and perceived social support to predict migraine. RESULTS: The one-year prevalence of migraine was 8%. The final multivariate model (Wald $\chi^2 = 693.00$, $df=15$, $p<0.001$) retained depression severity, chronic anxiety, exercising several times a month or week, and alcohol use as predictors of migraine (odds ratios = 2.1-3.5 for positive associations, odds ratios = 0.4-0.9 for negative associations). CONCLUSIONS: Raising awareness among clinicians regarding the fact that many of the variables that potentially contribute to the presence of migraine are modifiable (e.g., psychological problems and lifestyle behaviors) might intensify resources dedicated to assessing and impacting these factors in order to potentially prevent the frequency and severity of migraine.

Painful temporomandibular disorder is associated with migraine in adolescents: A case-control study.

Fernandes G, Arruda MA, Bigal ME, Camparis CM, Goncalves DAG. J Pain. 2019 Mar 29. pii: S1526-5900(19)30699-6. doi: 10.1016/j.jpain.2019.03.010.

Some types of primary headaches and temporomandibular disorders (TMD) are comorbid in adults and highly prevalent in adolescents. Herein, we investigated the association of painful TMD with specific headache diagnoses (migraine, tension-type headache) and with headache frequency in adolescents. We also explored the association of headache diagnosis with the number of painful sites in the trigeminal area. Painful TMD was assessed using the Research Diagnostic Criteria for TMD. We conducted a case-control study of adolescents from 13-15 years old who were recruited among participants in a previous epidemiological study conducted in Araraquara, SP, Brazil. Headaches were classified according to the Second Edition of the International Classification for Headache Disorders. Logistic, multinomial logistic and linear regression models were used to test associations. Of 149 individuals, 55.7% presented painful TMD. Adolescents with painful TMD (cases) were more likely to have migraine compared with those without TMD (controls) [OR= 3.0 (95% CI: 1.47-6.19); $p=0.033$]. Significant differences were not observed for probable TTH ($p=0.307$) and TTH ($p=0.834$). Painful TMD was also associated with an increase in headache frequency (linear-by-linear association=8.051; $p=0.005$). Only migraine was associated with a greater number of painful sites on palpation in the trigeminal area ($p= 0.001$). Migraine and frequency of headache were associated with painful TMD in adolescents. PERSPECTIVE: Migraine and headache frequency were strongly associated with painful TMD in adolescents, and causality must be determined. For now, the presence of one condition should raise suspicion of the other and warrants collaboration between orofacial pain specialists and neurologists.

Joint hypermobility among female patients presenting with chronic myofascial pelvic pain.

Hastings J, Forster JE, Witzeman K. PMR. 2019 Feb 6. doi: 10.1002/pmrj.12131. [Epub ahead of print]

BACKGROUND: Female chronic pelvic pain is estimated to affect up to 24% of adult women, many of whom have a component of myofascial pelvic pain. Although an association of joint hypermobility and pelvic pain has been hypothesized, limited data are available that

estimate the prevalence of joint hypermobility in this population. OBJECTIVE: To estimate the prevalence of generalized hypermobility spectrum disorder (G-HSD) among female patients with chronic myofascial pelvic pain and examine the association between G-HSD and other frequent pelvic pain-associated complaints. STUDY DESIGN: Retrospective case control. SETTING: Tertiary referral center within a university-affiliated public health system. PATIENTS: Adult women who were diagnosed with myofascial pelvic pain during a 1-year period (n=77 with G-HSD and n=241 without G-HSD). METHODS: Data were abstracted via chart review of patients meeting inclusion criteria. OUTCOMES: The primary outcome of this study was the prevalence of G-HSD among patients with persistent myofascial pelvic pain. Secondary outcomes included the prevalence of dyspareunia, provoked vestibulodynia, stress urinary incontinence, irritable bowel syndrome, hip pain, low back pain, and fibromyalgia in patients with persistent myofascial pelvic pain with and without G-HSD. RESULTS: Twenty-four percent (n=77;95% CI:19.6, 29.4) of myofascial pelvic pain patients also met criteria for G-HSD. After adjusting for confounders, the odds in favor of having G-HSD was 3.55 higher (95% CI: 1.50, 8.40)(p=0.004) in females with dyspareunia; 7.46 higher (95% CI: 2.41, 23.1) (p<0.001) with low back pain; 3.76 higher (95% CI: 1.35, 10.5) (p=0.02) with stress urinary incontinence; 4.72 higher (95% CI: 2.00, 11.2) (p<0.001) with irritable bowel syndrome; and 3.12 higher (95% CI: 1.36, 7.13) (p=0.007) with hip pain. There was no significant association identified between provoked vestibulodynia or fibromyalgia and G-HSD. CONCLUSION: The estimated prevalence of G-HSD is higher in chronic myofascial pelvic pain patients than in the general population with statistically significant associations with several comorbid conditions. Characterizing these associations is the first step in developing effective, evidence-based screening recommendations. LEVEL OF EVIDENCE: III.

Gender differences in the prevalence of chronic pain and leisure time physical activity among US adults: A NHANES Study.

Umeda M, Kim Y.

Int J Environ Res Public Health. 2019 Mar 19;16(6). pii: E988. doi: 10.3390/ijerph16060988.

Gender disparities in chronic pain are well documented in the literature. However, little is known regarding the relationship between physical activity (PA) and gender disparities in chronic pain. This study described gender differences in prevalence of chronic pain and PA, and identified a type of leisure time PA that individuals frequently chose in a nationally representative sample of US adults (N = 14,449). Data from the National Health Nutrition Examination Survey 1999-2004 were analyzed. Individuals were categorized into no chronic pain (NCP), localized chronic pain (LCP), and widespread chronic pain (WCP) groups based on responses to a pain questionnaire. A self-report PA questionnaire was used to estimate the time spent in different types of PA. Women showed higher prevalence of LCP and WCP compared to men. Men spent more hours per week for leisure time PA compared to women, but men and women showed similar prevalence of sufficient PA to meet a PA recommendation (≥ 150 min/week of moderate-to-vigorous intensity PA) across chronic pain categories. However, the prevalence of sufficient PA was substantially higher among men and women with NCP compared to men and women with LCP and WCP. Additionally, both men and women chose walking as the primary type of leisure time PA. Together, gender disparities exist in the prevalence of chronic pain and hours spent for leisure time PA. More research is needed to explore the role of increasing leisure time PA, such as walking, in reducing gender disparities in chronic pain.

Gender differences in the prevalence and characteristics of pain in Spain: Report from a population-based study.

Jimenez-Trujillo I, Lopez-de-Andres A, Del Barrio JL, Hernandez-Barrera V, Valero-de-Bernabe M, Jimenez-Garcia R.

Pain Med. 2019 Feb 21. pii: pnz004. doi: 10.1093/pm/pnz004.

OBJECTIVE: To assess the prevalence and characteristics of chronic neck pain, chronic low back pain, and migraine or frequent headaches among Spanish adults in 2014 according to gender, to identify predictors for each of these types of pains, and to compare the

prevalence with those found in 2009. DESIGN: Cross-sectional study. SETTING: Spain. METHODS: We used data collected from the 2014 European Health Interview Survey (n=22,842). Sociodemographic features, self-rated health status, lifestyle habits, comorbid conditions, pain characteristics, and self-reported use of medications were analyzed. RESULTS: The prevalence of all types of pain was significantly higher among women than men. For chronic neck pain, the figures were 25.68% vs 12.54%, for chronic low back pain, 27.03% vs 18.83%, and for migraine or frequent headaches, 15.93% vs 6.74%, in women and men, respectively. Predictors of these types of pain included female gender, advanced age, poor self-rated health, psychological distress, comorbidities, and obesity. The prevalence of neck pain and low back pain increased from 2009 to 2014 for both sexes, and the prevalence of migraine or frequent headaches remained stable over time. CONCLUSIONS: The prevalence and intensity of all the forms of chronic pain were higher among women. Women experiencing pain used prescribed medications for pain, anxiety, and/or depression and sleeping pills more than men. The prevalence of chronic neck and low back has increased in the last five years in Spain, and the prevalence of migraine or frequent headaches has remained stable.

Sex differences in prevalence, symptoms, impact, and psychiatric comorbidities in migraine and probable migraine: A population-based study.

Song TJ, Cho SJ, Kim WJ, Yang KI, Yun CH, Chu MK.
Headache. 2019 Feb;59(2):215-223. doi: 10.1111/head.13470.

OBJECTIVE: This study was conducted to investigate sex differences in the prevalence and clinical presentation of migraine and probable migraine in a general population-based sample. BACKGROUND: While there is research on sex differences in clinical characteristics and their impact on migraine headache, only few studies have investigated sex differences in probable migraine in population-based settings. Moreover, compared with Western countries, the prevalence of probable migraine in Asia is relatively high. This cross-sectional study was designed to investigate sex differences in the prevalence and clinical presentation of migraine and probable migraine in a general population-based sample. METHODS: We used the data of the Korean Headache-Sleep Study, which is a nationwide survey on headache and sleep. RESULTS: We interviewed 7430 people, and 3114 of them agreed to participate in our study (rejection rate, 58.1%). Among these people, 419 withdrew their participation during the interview. Ultimately, 2695 people completed our survey (cooperation rate, 36.3%). The prevalence of overall migraine and probable migraine was 350/1350 (25.9%) for women and 172/1345 (12.8%) for men ($P < .001$, respectively). The prevalence of migraine (107/1350 [7.9%] vs 36/1345 [2.7%], $P < .001$) and probable migraine (243/1350 [18.0%] vs 136/1345 [10.1%], $P < .001$) was significantly higher among women than among men. Headache frequency per month (median [interquartile range]) (1.0 [0.3-3.0] vs 0.8 [0.3-2.0], $P = .037$), the visual analog scale score for headache intensity (5.0 [4.0-7.0] vs 5.0 [3.0-6.0], $P = .019$), and the impact of headache {Headache Impact Test-6 score (47.0 [42.0-54.0] vs 44.0 [42.0-51.8], $P = .013$)} were significantly higher among women with probable migraine than men. Headache frequency per month (2.0 [0.4-4.0] vs 1.0 [0.3-2.0], $P = .073$), headache intensity (6.0 [5.0-8.0] vs 6.0 [4.2-7.0], $P = .281$), and the impact of headache (55.0 [48.0-61.0] vs 49.0 [46.3-60.8], $P = .225$) were not significantly different between women and men with migraine. Other comorbidities or associated symptoms, such as anxiety and depression, were not significantly different between women and men with migraine and probable migraine, except for nausea in probable migraine. CONCLUSION: Women experience more severe symptoms and a higher impact of headache than men among participants with probable migraine. Our findings suggest that women with PM need a more intensive evaluation and treatment than men with PM.

CLINICAL STUDIES

Differences between palpation and static/dynamic tests to diagnose

painful temporomandibular disorders in patients with Lyme disease.

Osiewicz M, Manfredini D, Biesiada G, Czepiel J, Garlicki A, Pytko-Polonczyk J, Lobbezoo F. Clin Oral Investig. 2019 Apr 13. doi: 10.1007/s00784-019-02890-4.

OBJECTIVES: The aim was to determine the frequency of Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD)-based pain diagnoses and dynamic/static tests-based pain diagnoses, and to assess the agreement of palpation tests with static/dynamic tests. **MATERIALS AND METHODS:** Eighty-six (n=86) adult patients with Lyme disease (mean age 57.0 +/- 14.3 years; male/female ratio was 42/44) were examined according to techniques described in the RDC/TMD. Additionally, dynamic/static tests were performed. For RDC/TMD-based pain diagnoses and dynamic/static tests-based pain diagnoses, descriptive frequencies were calculated. Differences between the frequency of palpation-based diagnoses and of dynamic/static-based diagnoses as well as the agreement between pain diagnoses established with the two diagnostic approaches were assessed. **RESULTS:** RDC/TMD-based pain diagnoses were made in 61 patients for myofascial pain and in 11 patients for arthralgia and/or osteoarthritis. Based on dynamic/static tests, mainly myogenous pain was diagnosed in 6 patients, and a mainly arthrogeous pain in 5. The agreement of palpation tests with static/dynamic tests in Lyme disease population was poor. **CONCLUSION:** A high prevalence of TMD symptoms was found in patients with Lyme disease. The results suggest that using palpation tests alone could overestimate primary TMDs when comorbid conditions are present. **CLINICAL RELEVANCE:** Dynamic/static tests should be used as part of the routine TMD assessment. In case of Lyme disease as the actual cause of the facial pain, while the dentist might be suspecting TMD when dynamic/static TMD tests are negative, referral to an appropriate specialist for the diagnosis and treatment of Lyme disease needs to be made.

Migraine in patients with fibromyalgia and outcomes of greater occipital nerve blockage.

Yilmaz V, Aras B, Erturk FA, Cakc FA, Umay E.

Clin Neurol Neurosurg. 2019 Apr 9;181:54-57. doi: 10.1016/j.clineuro.2019.04.004.

OBJECTIVES: The aim of this study is to evaluate the efficacy of greater occipital nerve (GON) blockage in patients with migraine and fibromyalgia (FM) comorbidity. **PATIENTS AND METHOD:** 20 patients who were diagnosed as FM according to 2010 American College of Rheumatology (ACR) diagnostic criteria and migraine according to International Classification of Headache Disorders II criteria and did not receive any medication or GON block for both disorders were included for the study. GON blocks were repeated every week in the first month and repeated monthly for the following 2 months. The frequency and duration of the migraine attacks, pain severity with visual analogue scale (VAS), quality of life (QoL) with revised fibromyalgia impact questionnaire (FIQR) and migraine disability assessment questionnaire (MIDAS) before, 1st month and 3rd months after treatment were recorded and compared. **RESULTS:** 95% of 20 patients were female (n=19) and 5% was male (n=1). The affected site was left in 60% of the patients (n=12) and 40% was right (n=8). There was significant improvement in terms of all evaluation parameters both at 1st month and 3rd months after treatment compared to the baseline. Likely, all parameters were significantly improved at 3rd month compared to the 1st month. **CONCLUSIONS:** GON blockage reduces pain severity, headache frequency and duration and increases QoL in patients with migraine and FM comorbidity.

The diagnostic accuracy of headache measurement instruments: A systematic review and meta-analysis focusing on headaches associated with musculoskeletal symptoms.

van der Meer HA, Visscher CM, Vredeveld T, Nijhuis van der Sanden MW, Hh Engelbert R, Speksnijder CM.

Cephalalgia. 2019 Apr 18;333102419840777. doi: 10.1177/0333102419840777.

AIM: To systematically review the available literature on the diagnostic accuracy of questionnaires and measurement instruments for headaches associated with musculoskeletal symptoms. **DESIGN:** Articles were eligible for inclusion when the diagnostic

accuracy (sensitivity/specificity) was established for measurement instruments for headaches associated with musculoskeletal symptoms in an adult population. The databases searched were PubMed (1966-2018), Cochrane (1898-2018) and Cinahl (1988-2018). Methodological quality was assessed with the Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2) and COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist for criterion validity. When possible, a meta-analysis was performed. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) recommendations were applied to establish the level of evidence per measurement instrument. RESULTS: From 3450 articles identified, 31 articles were included in this review. Eleven measurement instruments for migraine were identified, of which the ID-Migraine is recommended with a moderate level of evidence and a pooled sensitivity of 0.87 (95% CI: 0.85-0.89) and specificity of 0.75 (95% CI: 0.72-0.78). Six measurement instruments examined both migraine and tension-type headache and only the Headache Screening Questionnaire - Dutch version has a moderate level of evidence with a sensitivity of 0.69 (95% CI 0.55-0.80) and specificity of 0.90 (95% CI 0.77-0.96) for migraine, and a sensitivity of 0.36 (95% CI 0.21-0.54) and specificity of 0.86 (95% CI 0.74-0.92) for tension-type headache. For cervicogenic headache, only the cervical flexion rotation test was identified and had a very low level of evidence with a pooled sensitivity of 0.83 (95% CI 0.72-0.94) and specificity of 0.82 (95% CI 0.73-0.91). DISCUSSION: The current review is the first to establish an overview of the diagnostic accuracy of measurement instruments for headaches associated with musculoskeletal factors. However, as most measurement instruments were validated in one study, pooling was not always possible. Risk of bias was a serious problem for most studies, decreasing the level of evidence. More research is needed to enhance the level of evidence for existing measurement instruments for multiple headaches.

Small fiber polyneuropathy is prevalent in patients experiencing complex chronic pelvic pain.

Chen A, De E, Argoff C.

Pain Med. 2019 Mar 1;20(3):521-527. doi: 10.1093/pm/pny001.

OBJECTIVE: To demonstrate the prevalence of small fiber polyneuropathy (SFPN) in patients with refractory chronic pelvic pain (CPP). DESIGN: Retrospective study of prospective database. SUBJECTS: Participants were complex CPP patients recruited from subspecialty referral clinics defined as those who were refractory to initial treatment and/or exhibited comorbid pain syndromes at initial presentation. METHODS: Comprehensive treatment history for CPP was obtained, and participants referred as above; 3-mm punch biopsies were obtained of the lower extremity and sent to diagnostic reference labs to evaluate for SFPN. The reported lab sensitivity and specificity for SFPN are 78-92% and 65-90%, respectively. RESULTS: Twenty-five of 39 patients (64%) were positive for SFPN. Comorbid conditions noted in our population included gastroesophageal reflux disease (46%), migraine (38%), irritable bowel syndrome (33%), lower back pain (33%), fibromyalgia (38%), endometriosis (15%), interstitial cystitis (18%), vulvodynia (5%), and other chronic pain syndromes (36%). CONCLUSIONS: The prevalence of SFPN in our specialty referral patients with complex CPP is remarkably high vs published general population prevalence data (53/100,000). Identification of SFPN in this complex population shifts the focus from undefined syndromes to symptom complexes with linked potentially treatable mechanisms (e.g., SFPN, central sensitization). Most CPP patients with SFPN are undiagnosed. Considering the diagnosis may expand treatment options beyond conventional or so-called adjuvant analgesics. Treatment may expand to therapies such as IV lidocaine, IVIG, or other immunomodulatory options. In addition, the value to the patient of receiving a diagnosis for a multisystem or refractory pain syndrome, often attributed to negative psychologic factors, cannot be underestimated. Identifying SFPN should be contemplated in CPP patients who present with multisystem pain or who have not responded to initial evaluation and management.

Muscle tenderness score in temporomandibular disorders patients: A case-control study.

Almoznino G, Zini A, Zakuto A, Zlutzky H, Bekker S, Shay B, Haviv Y, Sharav Y, Benoliel R.

BACKGROUND: The total tenderness score (TTS) is commonly used in headache practice and contributes valuable information. **OBJECTIVE:** To assess muscle tenderness scores in patients diagnosed with Temporomandibular disorders (TMD) and analyse their associations with various demographic and clinical parameters. **METHODS:** Masticatory (MTS), cervical (CTS) and TTSs were analysed in this case-control study among 192 TMD patients and 99 controls. The study included a questionnaire and a clinical examination following RDC/TMD guidelines. Data were analysed using: Pearson's chi-square, analysis of variance, t test and Bonferroni post hoc. To examine the factors associated with MTS score in a multivariate manner, a conceptual hierarchical multiple regression model was adopted. **RESULTS:** Masticatory and TTS differed between TMD sub-groups and controls. Muscle tenderness was positively associated with: female sex, whiplash history, parafunction, co-morbid pains such as headaches and body pain, pain intensity, onset, frequency and duration. In the conceptual hierarchical multiple regression model, pain onset, frequency and duration, co-morbid pains were mediators in the relationship between TMD diagnosis and MTS. **CONCLUSION:** Muscle tenderness scores were positively associated with TMD disease characteristics and co-morbid pain conditions, which may reflect associations with disease severity. MTS differed between TMD populations and may be used in routine patient workup, to assess MMD severity and changes over time as well as treatments response and as a research tool. MTS can be used as a common methodology to describe both headaches and masticatory muscle disorders and to facilitate interprofessional research and crosstalk between a headache and oro-facial pain practitioners.

Which examination tests detect differences in cervical musculoskeletal impairments in people with migraine? A systematic review and meta-analysis.

Szikszay TM, Hoenick S, von Korn K, Meise R, Schwarz A, Starke W, Luedtke K. Phys Ther. 2019 Jan 28. doi: 10.1093/ptj/pzz007. [Epub ahead of print]

BACKGROUND: Most patients with migraine report associated neck pain. Whether neck pain is a symptom of migraine or an indicator for associated cervical musculoskeletal impairment has not yet been determined. Physical examination tests to detect cervical impairments in people with headache have been suggested, but results have not been evaluated systematically and combined in meta-analyses. **PURPOSE:** The purpose of this study was to identify musculoskeletal impairments in people with migraine and people who were healthy (healthy controls) by reviewing published data on physical examination results. **DATA SOURCES:** PubMed, CINAHL, Web of Science, and the Cochrane Register of Clinical Trials were searched for studies published prior to December 2017. **STUDY SELECTION:** Publications investigating physical examination procedures that are feasible for use in a physical therapy setting for patients with migraine and healthy controls were independently selected by 2 researchers. **DATA EXTRACTION:** One researcher extracted the data into predesigned data extraction tables. Entries were checked for correctness by a second researcher. The Downs and Black Scale was used for risk-of-bias assessment by 2 reviewers independently. **DATA SYNTHESIS:** Thirty-five studies (involving 1033 participants who were healthy [healthy controls] and 1371 participants with migraine) were included in the qualitative synthesis, and 18 were included in the meta-analyses (544 healthy controls and 603 participants with migraine). Overall, studies were rated as having a low to moderate risk of bias. Included studies reported 20 different test procedures. Combined mean effects indicated that 4 of the tests included in the meta-analyses distinguished between patients and controls: range of cervical motion, flexion-rotation, pressure pain thresholds, and forward head posture in a standing position. **LIMITATIONS:** Manual joint testing and evaluation of trigger points were the 2 most frequently investigated tests not included in the meta-analyses because of heterogeneity of reporting and procedures. **CONCLUSIONS:** Three tests confirmed the presence of musculoskeletal impairments in participants with migraine when combined in meta-analyses. Pressure pain thresholds added information on sensory processing. Additional tests might be useful but require standardized protocols and reporting.

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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