MEDICAL JOURNAL

FIBROMYALGIA
ABSTRACTS

NFA National Fibromyalgia Association

GREETINGS,

This booklet is a compilation of fibromyalgia scientific abstracts that have been specifically selected by the National Fibromyalgia Association (NFA) to portray the breadth of today's research. Since publication of the American College of Rheumatology's Fibromyalgia Diagnostic Criteria in 1990, research has escalated from less than 200 to more than 4,500 published papers. Through scientific scrutiny, fibromyalgia (FM) is emerging as a central nervous system disorder. Technology such as fMRI and SPECT scans are allowing scientists to see for the first time changes in the brain function of people affected by fibromyalgia.

The importance of quality scientific research is evident in the approval by the Food and Drug Administration (FDA) of medications such as Pregabalin (Lyrica) and Duloxetine (Cymbalta) in the treatment of FM. Others are in the process of being submitted to the FDA for approval. Although medications are just one part of a successful FM treatment regimen, the significance of the FDA approval cannot be overlooked.

There is a critical need for further fibromyalgia scientific research, which means that there is also a need for more clinical research locations. If you are interested in becoming a site for FM studies, please contact the NFA.

Visit www.FibromyalgiaHCP.org to find the most recent healthcare professional information and CME opportunities. Also, refer your fibromyalgia patients to the NFA website—www.FMaware.org—where they will find access to support group locations, information on the *Fibromyalgia AWARE* magazine, and other resources on how to live a better quality of life while experiencing the pain and fatigue of fibromyalgia.

Sincerely,

Rae Marie Gleason
Executive Director

I BACKGROUND

Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment.

Mease P.

J Rheumatol Suppl. 2005 Aug;75:6-21.

Fibromyalgia syndrome (FM) is a common chronic pain condition that affects at least 2% of the adult population in the USA and other regions in the world where FM is studied. Prevalence rates in some regions have not been ascertained and may be influenced by differences in cultural norms regarding the definition and attribution of chronic pain states.

Chronic, widespread pain is the defining feature of FM, but patients may also exhibit a range of other symptoms, including sleep disturbance, fatigue, irritable bowel syndrome, headache, and mood disorders. Although the etiology of FM is not completely understood, the syndrome is thought to arise from influencing factors such as stress, medical illness, and a variety of pain conditions in some, but not all patients, in conjunction with a variety of neurotransmitter and neuroendocrine disturbances. These include reduced levels of biogenic amines, increased concentrations of excitatory neurotransmitters, including substance P, and dysregulation of the hypothalamic-pituitary-adrenal axis. A unifying hypothesis is that FM results from sensitization of the central nervous system.

Establishing diagnosis and evaluating effects of therapy in patients with FM may be difficult because of the multifaceted nature of the syndrome and overlap with other chronically painful conditions. Diagnostic criteria, originally developed for research purposes, have aided our understanding of this patient population in both research and clinical settings, but need further refinement as our knowledge about chronic widespread pain evolves. Outcome measures, borrowed from clinical research in pain, rheumatology, neurology, and psychiatry, are able to distinguish treatment response in specific symptom domains. Further work is necessary to validate these measures in FM. In addition, work is under way to develop composite response criteria, intended to address the multidimensional nature of this syndrome.

A range of medical treatments, including antidepressants, opioids, nonsteroidal antiinflammatory drugs, sedatives, muscle relaxants, and antiepileptics, have been used to treat FM. Nonpharmaceutical treatment modalities, including exercise, physical therapy, massage, acupuncture, and cognitive behavioral therapy, can be helpful. Few of these approaches have been demonstrated to have clear-cut benefits in randomized controlled trials. However, there is now increased interest as more effective treatments are developed and our ability to accurately measure effect of treatment has improved. The multifaceted nature of FM suggests that multimodal individualized treatment programs may be necessary to achieve optimal outcomes in patients with this syndrome.

Fibromyalgia: more than just a musculoskeletal disease.

Clauw DJ.

Am Fam Physician. 1995 Sep 1; 52(3):843-51, 853-4.

Fibromyalgia is a common condition characterized by diffuse musculoskeletal pain and fatigue. The syndrome is defined by the presence of musculoskeletal tender points on physical examination. Additionally, persons with this syndrome have a high incidence of headaches, ocular and vestibular complaints, paresthesias, esophageal dysmotility, “allergic” symptoms, irritable bowl syndrome, genitourinary symptoms and affective disorders. Recent research has revealed a number of objective biochemical, hormonal and neurotransmitter abnormalities associated with fibromyalgia, making it a clearly identifiable condition. These abnormalities may clarify our understanding of the pathogenesis and treatment of fibromyalgia.

II BASIC SCIENCE

EPIDEMIOLOGY

Widespread pain and fibromyalgia in a biracial cohort of young women.

Gansky SA, Plesh O.

J Rheumatol. 2007 Apr;34(4):810-7.

OBJECTIVE: To assess the distribution of widespread pain, tenderpoints (TP), and fibromyalgia (FM) in young African American (AA) and Caucasian (C) women.

METHODS: A community population of 1334 young (21-26 yrs old) women (684 AA and 650 C) was surveyed and classified for body pain spread [chronic widespread pain (CWP), axial regional chronic pain (RCP), nonaxial RCP, or no pain]. Of these women, 53 were examined for TP based on American College of Rheumatology criteria.

RESULTS: Overall, 5.6% reported CWP, while 22% reported axial RCP, and 16% reported nonaxial RCP. From the CWP group, 57% were confirmed as FM cases. C women had significantly more TP and greater TP pain score than AA women (p <or= 0.005). Overall FM prevalence was 2.4% (95% confidence interval: 1.7-3.5%), with 3.0% in AA and 2.0% in C women. Increase in body pain and tenderness was significantly associated with decreased subjective socioeconomic status (SSS), worse self-reported health, greater impact of premenstrual symptoms on activities, and greater depressive symptoms. The effect of depressive symptoms on pain differed by race.

CONCLUSIONS: Widespread pain and tenderness is highly prevalent in these young women. Racial differences seem to exist; C women had significantly increased tenderness while AA women had more widespread pain. The association of depressive symptoms and pain was stronger in AA women. Racial differences emerged relatively early in these young women.

An internet survey of 2,596 people with fibromyalgia.

Bennett RM, Jones J, Turk DC, Russell IJ, Matallana L.

BMC Musculoskelet Disord. 2007 Mar;98:27.

BACKGROUND: This study explored the feasibility of using an Internet survey of people with fibromyalgia (FM), with a view to providing information on demographics, sources of information, symptoms, functionality, perceived aggravating factors, perceived triggering events, health care utilization, management strategies, and medication use.

METHODS: A survey questionnaire was developed by the National Fibromyalgia Association (NFA) in conjunction with a task force of "experts in the field". The questionnaire underwent several rounds of testing to improve its face validity, content validity, clarity and readability before it was mounted on the internet. The questionnaire consisted of 121 items and is available online at the website of the National Fibromyalgia Association.

RESULTS: The questionnaire was completed by 2,569 people. Most were from the United States, with at least one respondent from each of the 50 states. Respondents were predominantly middle-aged Caucasian females, most of whom had FM symptoms for > or = 4 years. The most common problems were morning stiffness, fatigue, non-restorative sleep, pain, concentration, and memory. Aggravating factors included: emotional distress, weather changes, insomnia, and strenuous activity. Respondents rated the most effective management modalities as rest, heat, pain medications, antidepressants, and hypnotics. The most commonly used medications were: acetaminophen, ibuprofen, naproxen, cyclobenzaprine, amitriptyline, and aspirin. The medications perceived to be the most effective were: hydrocodone preparations, aprazolam, oxycodone preparations, zolpidem, cyclobenzaprine, and clonazepam.

CONCLUSION: This survey provides a snap-shot of FM at the end of 2005, as reported by a self-selected population of people. This descriptive data has a heuristic function, in that it identifies several issues for further research, such as the prescribing habits of FM health care providers, the role of emotional precipitants, the impact of obesity, the significance of low back pain and the nature of FM related stiffness.

The prevalence and characteristics of fibromyalgia in the general population.

Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L.

Arthritis Rheum. 1995 Jan;38(1):19-28.

OBJECTIVE: To determine the prevalence and characteristics of fibromyalgia in the general population.

METHODS: A random sample of 3,006 persons in Wichita, KS, were characterized according to the presence of no pain, non-widespread pain, and widespread pain. A subsample of 391 persons, including 193 with widespread pain, were examined and interviewed in detail.

RESULTS: The prevalence of Fibromyalgia was 2.0% (95% confidence interval [95% CI] 1.4, 2.7) for both sexes, 3.4% (95% CI 2.3, 4.6) for women, and 0.5% (95% CI 0.0, 1.0) for men. The prevalence of the syndrome increased with age, with highest values attained between 60 and 79 years (> 7.0% in women). Demographic, psychological, dolorimetry, and symptom factors were associated with fibromyalgia.

CONCLUSION: Fibromyalgia is common in the population, and occurs often in older persons. Characteristic features of fibromyalgia—pain threshold and symptoms—are similar in community and clinic populations, but overall severity, pain, and functional disability are more severe in the clinic population.

ETIOLOGY

GENETICS

Family study of fibromyalgia.

Arnold LM, Hudson JI, Hess EV, Ware AE, Fritz DA, Auchenbach MB, Starck LO, Keck PE Jr.

Arthritis Rheum. 2004 Mar;50(3):944-52.

OBJECTIVE: To assess for familial aggregation of fibromyalgia (FM) and measures of tenderness and pain, and for familial coaggregation of FM and major mood disorder (major depressive disorder or bipolar disorder).

METHODS: Probands meeting the American College of Rheumatology criteria for FM and control probands with rheumatoid arthritis (RA) and no lifetime diagnosis of FM were recruited from consecutive referrals to 2 community-based rheumatology practices. Probands were ages 40-55 years and had at least 1 first-degree relative age 18 years or older who was available for interview and examination. All probands and interviewed relatives underwent a dolorimeter tender point examination and a structured clinical interview. Interviewed relatives were asked about first-degree relatives who were not available for interview, using a structured family interview. Logistic and linear regression models, adjusting for the correlation of observation within families, were applied to study the aggregation and coaggregation effects.

RESULTS: Information was collected for 533 relatives of 78 probands with FM and 272 relatives of 40 probands with RA. FM aggregated strongly in families: the odds ratio (OR) measuring the odds of FM in a relative of a proband with FM versus the odds of FM in a relative of a proband with RA was 8.5 (95% confidence interval [95% CI] 2.8-26, P = 0.0002). The number of tender points was significantly higher, and the total myalgic score was significantly lower in the relatives of probands with FM compared with the relatives of probands with RA. FM coaggregated significantly with major mood disorder: the OR measuring the odds of major mood disorder in a relative of a proband with FM versus the odds of major mood disorder in a relative of a proband with RA was 1.8 (95% CI 1.1-2.9, P = 0.013).

CONCLUSION: FM and reduced pressure pain thresholds aggregate in families, and FM coaggregates with major mood disorder in families. These findings have important clinical and theoretical implications, including the possibility that genetic factors are involved in the etiology of FM and in pain sensitivity. In addition, mood disorders and FM may share some of these inherited factors.

Significance of catechol-O-methyltransferase gene polymorphism in fibromyalgia syndrome.

Gursoy S, Erdal E, Herken H, Madenci E, Alasehirli B, Erdal N.

Rheumatol Int. 2003 May;23(3):104-7.

Fibromyalgia syndrome (FS) is associated with a neuroendocrinal disorder characterized by abnormal function of the hypothalamic-pituitary-adrenal (HPA) axis, including hyperactive adrenocorticotropic hormone (ACTH) release and adrenal hyporesponsiveness. Catechol-O-methyltransferase (COMT) enzyme inactivates catecholamines and catecholamine-containing drugs. Polymor-

phism in the gene encodes for the COMT enzyme.

For this study, the significance of COMT polymorphism was assessed in FS. There were three polymorphisms of the COMT gene: LL, LH, and HH. The analysis of COMT polymorphism was performed using polymerase chain reaction (PCR).

Sixty-one patients with FS and 61 healthy volunteers were included in the study. Although no significant difference was found between LL and LH separately, the LL and LH genotypes together were more highly represented in patients than controls (P=0.024). In addition, HH genotypes in patients were significantly lower than in the control groups (P=0.04). There was no significant difference between COMT polymorphism and psychiatric status of the patients as assessed by several psychiatric tests (P>0.05).

In conclusion, COMT polymorphism is of potential pharmacological importance regarding individual differences in the metabolism of catechol drugs and may also be involved in the pathogenesis and treatment of FS through adrenergic mechanisms as well as genetic predisposition to FS.

Possible association of fibromyalgia with a polymorphism in the serotonin transporter gene regulatory region.

Offenbaecher M, Bondy B, de Jonge S, Glatzeder K, Kruger M, Schoeps P, Ackenheil M.

Arthritis Rheum. 1999 Nov;42(11):2482-8.

OBJECTIVE: To analyze the genotypes of the promoter region of the serotonin transporter gene (5-HTT) in patients with fibromyalgia (FM).

METHODS: Genomic DNA from 62 patients meeting the American College of Rheumatology 1990 criteria for FM and 110 healthy controls was analyzed by polymerase chain reaction. Additionally, the psychopathologic state of 52 of the FM patients was evaluated using the Beck Depression Inventory (BDI) and the Symptom Checklist-90-Revised (SCL-90-R).

RESULTS: The 5-HTTLPR genotypes in FM patients versus controls were distributed as follows: L/L 27% versus 34%, L/S 42% versus 50%, and S/S 31% versus 16%. FM patients with the S/S genotype had higher mean scores on the BDI and the SCL-90-R compared with those in the L/L and L/S groups.

CONCLUSION: A higher frequency of the S/S genotype of 5-HTT was found in FM patients compared with healthy controls. The S/S subgroup exhibited higher mean levels of depression and psychological distress. These results support the notion of altered serotonin metabolism in at least a subgroup of patients with FM.

Fibromyalgia syndrome (FM) and nonarticular tenderness in relatives of patients with FM.

Buskila D, Neumann L.

J Rheumatol. 1997 May;24(5):941-4.

OBJECTIVE: To determine the prevalence of fibromyalgia (FM) and to assess nonarticular tenderness in relatives of patients with FM.

METHODS: Thirty female patients with FM randomly chosen from 117 of their close relatives (parents, brothers, sisters, children, husbands) were assessed for nonarticular tenderness. A count of 18 tender points was conducted by thumb palpation, and tenderness thresholds were assessed by dolorimetry at 9 tender sites. FM was diagnosed according to the 1990 American College of Rheumatology criteria.

RESULTS: The prevalence of FM among blood relatives of patients with FM was 26%, and among their husbands 19%. FM prevalence in male relatives was 14%, and in female relatives 41%. The mean tender point counts of male and female young relatives was significantly higher than that of controls: 6.1 vs 0.2 ($p < 0.01$), and 4.4 vs 0.4 ($p < 0.01$) respectively. Similarly, adult relatives had considerably higher mean tender point counts than controls: 4.0 vs 0.04 ($p < 0.01$) and 10.3 vs 0.28 ($p < 0.01$) respectively, for males and females.

CONCLUSION: Relatives of patients with FM have a higher prevalence of FM and are more tender than the general population, as recently reported and shown in a healthy control group. This finding can be attributed to genetic and environmental factors.

TRAUMA

Fibromyalgia after motor vehicle collision: evidence and implications.

McLean SA, Williams DA, Clauw DJ.

Traffic Inj Prev. 2005 Jun;6(2):97-104.

OBJECTIVE: Assess currently available evidence regarding the ability of a motor vehicle collision (MVC) to trigger the development of fibromyalgia (FM).

METHODS: Consensus standards developed by the American College of Rheumatology Environmental Disease Study Group were used to assess the ability of an MVC to trigger FM.

RESULTS: Increasing evidence suggests that FM and related disorders are characterized by abnormalities in central nervous system function related to sensory processing, autonomic regulation, and neuroendocrine function. MVC trauma appears capable of triggering FM, but generally not through direct biomechanical injury. Instead, the evidence suggests that MVC trauma can act as a "stressor," which in concert with other factors, such as an individual's biologic vulnerability, psychosocial factors, cultural factors, and so on, may result in the development of chronic widespread pain and other somatic symptoms. MVC trauma is only one of many stressors which can trigger such disorders, and the environment within which the stressor is experienced (biological and psychosocial) may largely determine whether there is an adverse physiologic result or not.

CONCLUSIONS: The evidence that MVC trauma may trigger FM meets established criteria for determining causality, and has a number of important implications, both for patient care, and for research into the pathophysiology and treatment of these disorders.

Increased rates of fibromyalgia following cervical spine injury. A controlled study of 161 cases of traumatic injury.

Buskila D, Neumann L, Vaisberg G, Alkalay D, Wolfe F.

Arthritis Rheum. 1997 Mar;40(3):446-52.

OBJECTIVE: To study the relationship between cervical spine injury and the development of fibromyalgia syndrome (FMS).

METHODS: One hundred two patients with neck injury and 59 patients with leg fractures (control group) were assessed for nonarticular tenderness and the presence of FMS. A count of 18 tender points was conducted by thumb palpation; and tenderness thresholds were assessed by dolorimetry at 9 tender sites. All patients were interviewed about the presence and severity of neck and FMS-related symptoms. FMS was diagnosed using the American College of Rheumatology 1990 criteria. Additional questions assessed measures of physical functioning and quality of life (QOL).

RESULTS: Although no patient had a chronic pain syndrome prior to the trauma, FMS was diagnosed following injury in 21.6% of those with neck injury versus 1.7% of the control patients with lower extremity fractures (P = 0.001). Almost all symptoms were more common and severe in the group with neck injury. FMS was noted at a mean of 3.2 months (SD 1.1) after the trauma. Neck injury patients with FMS (n = 22) had more tenderness, had more severe and prevalent FMS-related symptoms, and reported lower QOL and more impaired physical functioning than did those without FMS (n = 80). In spite of the injury or the presence of FMS, all patients were employed at the time of examination. Twenty percent of patients with neck injury and 24% of patients with leg fractures filed an insurance claim. Claims were not associated with the presence of FMS, increased FMS symptoms, pain, or impaired functioning.

CONCLUSION: FMS was 13 times more frequent following neck injury than following lower extremity injury. All patients continued to be employed, and insurance claims were not increased in patients with FMS.

CERVICAL ABNORMALITIES/CHIARI I

Positional cervical spinal cord compression and fibromyalgia: a novel comorbidity with important diagnostic and treatment implications.

Holman AJ.

J Pain. 2008 Jul;9(7):613-22.

The variable presentation and treatment response of fibromyalgia (FM) may be related to comorbidities, including positional cervical cord compression (PC3). Prevalence of PC3 among routine referrals for rheumatology consultation was assessed over 2 random months (January and February 2006) from a 4-year experience of 1100 patients. PC3 was defined as cord abutment, compression or flattening with a spinal canal diameter of <10 mm by magnetic resonance sagittal flexion, neutral, and extension images.

Of 107 referrals, 53 had FM, 32 had a connective tissue disease (CTD) without FM, and 22 had chronic widespread pain (CWP) without FM criteria. The dynamic cervical spine images were obtained in 70 patients: 49 of 53 with FM, 20 of 22 with CWP and 1 of 32 with CTD, based on history and examination. Among those who received magnetic resonance imaging [MRI], 52 patients met PC3 criteria (71% of FM group [35/49], 85% of CWP group [17/20]). Two patients had a Chiari malformation (FM), 1 had multiple sclerosis (CWP), and 1 had multiple myeloma (CWP). Extension views were required for diagnosis for 37 of these 52 (71%) subjects, as well as for 8 patients who also had cervical spinal cord flattening. The pilot data suggest that further evaluation of PC3 in a controlled trial is warranted among patients with FM and CWP.

PERSPECTIVE: Fibromyalgia is complex and poorly understood. Recognition of unsuspected, comorbid cervical cord compression may provide new insight into its variable presentation, leading to novel treatment considerations. Also, dissemination of this dynamic MRI protocol may promote further study of this emerging concept of cervical cord irritation.

Treatment of cervical myelopathy in patients with the fibromyalgia syndrome: outcomes and implications.

Heffez DS, Ross RE, Shade-Zeldow Y, Kostas K, Morrissey M, Elias DA, Shepard A.

Eur Spine J. 2007 Sep;16(9):1423-33.

Some patients with fibromyalgia also exhibit the neurological signs of cervical myelopathy. We sought to determine if treatment of cervical myelopathy in patients with fibromyalgia improves the symptoms of fibromyalgia and the patients' quality of life.

A non-randomized, prospective, case control study comparing the outcome of surgical (n = 40) versus non-surgical (n = 31) treatment of cervical myelopathy in patients with fibromyalgia was conducted. Outcomes were compared using SF-36, screening test for somatization, HADS, MMPI-2 scale 1 (Hypochondriasis), and self reported severity of symptoms 1 year after treatment. There was no significant difference in initial clinical presentation or demographic characteristics between the patients treated by surgical decompression and those treated by non-surgical means.

There was a striking and statistically significant improvement in all symptoms attributed to the fibromyalgia syndrome in the surgical patients but not in the non-surgical patients at 1 year following the treatment of cervical myelopathy (P </= 0.018-0.001, Chi-square or Fisher's exact test). At the 1 year follow-up, there was a statistically significant improvement in both physical and mental quality of life as measured by the SF-36 score for the surgical group as compared to the non-surgical group (Repeated Measures ANOVA P < 0.01). There was a statistically significant improvement in the scores from Scale 1 of the MMPI-2 and the screening test for somatization disorder, and the anxiety and depression scores exclusively in the surgical patients (Wilcoxon signed rank, P < 0.001).

The surgical treatment of cervical myelopathy due to spinal cord or caudal brainstem compression in patients carrying the diagnosis of fibromyalgia can result in a significant improvement in a wide array of symptoms usually attributed to fibromyalgia with attendant measurable improvements in the quality of life. We recommend detailed neurological and neuroradiological evaluation of patients with fibromyalgia in order to exclude compressive cervical myelopathy, a potentially treatable condition.

Clinical evidence for cervical myelopathy due to Chiari malformation and spinal stenosis in a non-randomized group of patients with the diagnosis of fibromyalgia.

Heffez DS, Ross RE, Shade-Zeldow Y, Kostas K, Shah S, Gottschalk R, Elias DA, Shepard A, Leurgans SE, Moore CG.

Eur Spine J. 2004 Oct;13(6):516-23.

OBJECTIVE: While patients with fibromyalgia report symptoms consistent with cervical myelopathy, a detailed neurological evaluation is not routine. We sought to determine if patients with fibromyalgia manifest objective neurological signs of cervical myelopathy.

METHODS: Two hundred and seventy patients, 18 years and older, who carried the diagnosis of fibromyalgia but who had no previously recognized neurological disease underwent detailed clinical neurological and neuroradiological evaluation for the prevalence of objective evidence of cervical myelopathy and radiological evidence of cerebellar tonsillar herniation (Chiari 1 malformation) or cervical spinal canal stenosis.

RESULTS: Patients were primarily women (87%), of mean age 44 years, who had been symptomatic for 8 years (standard deviation, 6.3 years). The predominant complaints were neck/back pain (95%), fatigue (95%), exertional fatigue (96%), cognitive impairment (92%), instability of gait (85%), grip weakness (83%), paresthesiae (80%), dizziness (71%) and numbness (69%). Eighty-eight percent of patients reported worsening symptoms with neck extension. The neurological examination was consistent with cervical myelopathy: upper thoracic spinothalamic sensory level (83%), hyperreflexia (64%), inversion of the radial periosteal reflex (57%), positive Romberg sign (28%), ankle clonus (25%), positive Hoffman sign (26%), impaired tandem walk (23%), dysmetria (15%) and dysdiadochokinesia (13%). MRI and contrast-enhanced CT imaging of the cervical spine revealed stenosis. The mean antero-posterior (AP) spinal canal diameter at C2/3, C3/4, C4/5, C5/6, C6/7 and C7/T1 was 13.5 mm, 11.8 mm, 11.5 mm, 10.4 mm, 11.3 mm and 14.5 mm respectively, (CT images). In 46% of patients, the AP spinal diameter at C5/6 measured 10 mm, or less, with the neck positioned in mild extension, i.e., clinically significant spinal canal stenosis. MRI of the brain revealed tonsillar ectopia >5 mm in 20% of patients (mean=7.1+/-1.8 mm), i.e., Chiari 1 malformation.

CONCLUSION: Our findings indicate that some patients who carry the diagnosis of fibromyalgia have both signs and symptoms consistent with cervical myelopathy, most likely resulting from spinal cord compression. We recommend detailed neurological evaluation of patients with fibromyalgia in order to exclude cervical myelopathy, a potentially treatable condition.

Functional abnormalities of the cervical cord and lower medulla and their effect on pain: observations in chronic pain patients with incidental mild Chiari I malformation and moderate to severe cervical cord compression.

Thimineur M, Kitaj M, Kravitz E, Kalizewski T, Sood P.

Clin J Pain. 2002 May-Jun;18(3):171-9.

OBJECTIVE: Abnormalities of central sensory processing may play a role in the pathogenesis of chronic pain. The Chiari I malformation is a congenital hindbrain anomaly characterized by protrusion of the cerebellar tonsils into the upper cervical canal, with variable effects on the lower brain stem and cervical cord. The purpose of this study was to compare sensory function and pain among patients with chronic pain who had these disorders incidentally diagnosed, to assess the effect on pain in these patients in comparison with those without central nervous system disease.

DESIGN: Retrospective study in which pain, mood, and sensory function in 32 patients with chronic pain who had mild Chiari I malformation were compared with that in 53 patients with chronic pain who had moderate to severe compression of the cervical spinal cord and 52 patients with chronic pain who had no apparent central nervous system disorder. Data had been collected previously as part of standard clinical assessments, including clinical neurological examinations, quantitative sensory testing, pain drawings, and psychometric testing with the Symptom Checklist 90.

PATIENTS: All subjects were patients of a hospital-based pain management practice who had been accepted for treatment over a 5-year period.

RESULTS: Both the Chiari I and cervical compression groups had long tract signs evident on clinical neurological examination. Quantitative sensory testing indicated elevations in the trigeminal territory among patients with Chiari I malformation and on the neck, hands, and feet in both the Chiari I and cervical compression groups. The extent of

pain and mood disturbance was greatest in the Chiari I group and least in the group with no central nervous system disorder. Complex regional pain syndrome, fibromyalgia, and temporal mandibular joint disorder were more common among the Chiari I malformation group than among the other groups.

CONCLUSIONS: Quantitative sensory analysis indicates sensory dysfunction associated with Chiari I malformation and cervical cord compression. The pattern of sensory abnormality is consistent with medullary dysfunction among the patients with Chiari I malformation and cervical cord dysfunction among cord compression patients. There were differences in the types and extent of pain and the associated disorders of mood observed among the cohorts defined above. These differences may be partly due to the presence and location of central sensory dysfunction.

ADVERSE EARLY LIFE EVENTS/STRESS

Childhood trauma and diurnal cortisol disruption in fibromyalgia syndrome.

Weissbecker I, Floyd A, Dedert E, Salmon P, Sephton S.

Psychoneuroendocrinology. 2006 Apr;31(3):312-24.

Adults with fibromyalgia syndrome report high rates of childhood trauma. Neuroendocrine abnormalities have also been noted in this population. Exploratory analyses tested relationships between retrospective reports of childhood trauma and diurnal salivary cortisol patterns among 85 women with fibromyalgia.

Subjects with fibromyalgia completed self-reports of childhood physical, sexual and emotional abuse, as well as emotional and physical neglect. Recent major life events, current perceptions of stress, and depressive symptoms were also assessed. Salivary cortisol was collected six times per day for two consecutive days to assess diurnal rhythm, awakening response and mean cortisol levels. Hierarchical regression analyses were performed, controlling for age, relevant medications, life events, perceived stress, and depressive symptoms.

Childhood physical abuse predicted flattened diurnal cortisol rhythms as well as greater cortisol responses to awakening. Sexual abuse was a second predictor of increased awakening cortisol responses. Patients with a history of trauma had markedly low levels of cortisol at the time of first awakening, partly explaining the results.

These findings suggest that severe traumatic experiences in childhood may be a factor of adult neuroendocrine dysregulation among fibromyalgia sufferers. Trauma history should be evaluated and psychosocial intervention may be indicated as a component of treatment for fibromyalgia.

Sexual and physical abuse in women with fibromyalgia syndrome: a test of the trauma hypothesis.

Ciccone DS, Elliott DK, Chandler HK, Nayak S, Raphael KG.

Clin J Pain. 2005 Sep-Oct;21(5):378-86.

OBJECTIVES: According to the trauma hypothesis, women with fibromyalgia syndrome (FMS) are more likely to report a history of sexual and/or physical abuse than women without FMS. In this study, we rely on a community sample to test this hypothesis and the related prediction that women with FMS are more likely to have posttraumatic stress disorder than women without FMS.

METHODS: Eligibility for the present study was limited to an existing community sample in which FMS and major depressive disorder were prevalent. The unique composition of the original sample allowed us to recruit women with and without FMS from the community. A total of 52 female participants were enrolled in the present FMS group and 53 in the control (no FMS) group. Sexual and physical abuse were assessed retrospectively using a standardized telephone interview.

RESULTS: Except for rape, sexual and physical abuse were reported equally often by women in the FMS and control groups. Women who reported rape were 3.1 times more likely to have FMS than women who did not report rape ($P<0.05$). There was no evidence of increased childhood abuse in the FMS group. Women with FMS were more likely to have posttraumatic stress disorder symptoms (intrusive thoughts and arousal) as well as posttraumatic stress disorder diagnosis ($P<0.01$).

DISCUSSION: With the exception of rape, no self-reported sexual or physical abuse event was associated with FMS in this community sample. In accord with the trauma hypothesis, however, posttraumatic stress disorder was more prevalent in the FMS group. Chronic stress in the form of posttraumatic stress disorder but not major depressive disorder may mediate the relationship between rape and FMS.

Hypothalamic-pituitary-adrenal stress axis function and the relationship with chronic widespread pain and its antecedents.

McBeth J, Chiu YH, Silman AJ, Ray D, Morriss R, Dickens C, Gupta A, Macfarlane GJ.

Arthritis Res Ther. 2005;7(5):R992-R1000.

In clinic studies, altered hypothalamic-pituitary-adrenal (HPA) axis function has been associated with fibromyalgia, a syndrome characterised by chronic widespread body pain. These results may be explained by the associated high rates of psychological distress and somatisation. We address the hypothesis that the latter, rather than the pain, might explain the HPA results.

A population study ascertained pain and psychological status in subjects aged 25 to 65 years. Random samples were selected from the following three groups: satisfying criteria for chronic widespread pain; free of chronic widespread pain but with strong evidence of somatisation ('at risk'); and a reference group. HPA axis function was assessed from measuring early morning and evening salivary cortisol levels, and serum cortisol after physical (pain pressure threshold exam) and chemical (overnight 0.25 mg dexamethasone suppression test) stressors. The relationship between HPA function with pain and the various psychosocial scales assessed was modelled using appropriate regression analyses, adjusted for age and gender.

In all 131 persons with chronic widespread pain (participation rate 74%), 267 'at risk' (58%) and 56 controls (70%) were studied. Those in the chronic widespread pain and 'at risk' groups were, respectively, 3.1 (95% CI (1.3, 7.3)) and 1.8 (0.8, 4.0) times more likely to have a saliva cortisol score in the lowest third. None of the psychosocial factors measured were, however, associated with saliva cortisol scores. Further, those in the chronic widespread pain (1.9 (0.8, 4.7)) and 'at risk' (1.6 (0.7, 3.6)) groups were also more likely to have the highest serum cortisol scores. High post-stress serum cortisol was related to high levels of psychological distress (p = 0.05, 95% CI (0.02, 0.08)). After adjusting for levels of psychological distress, the association between chronic widespread pain and post-stress cortisol scores remained, albeit slightly attenuated.

This is the first population study to demonstrate that those with established, and those psychologically at risk of, chronic widespread pain demonstrate abnormalities of HPA axis function, which are more marked in the former group. Although some aspects of the altered function are related to the psychosocial factors measured, we conclude that the occurrence of HPA abnormality in persons with chronic widespread pain is not fully explained by the accompanying psychological stress.

Perceived physical and emotional trauma as precipitating events in fibromyalgia. Associations with health care seeking and disability status but not pain severity.

Aaron LA, Bradley LA, Alarcón GS, Triana-Alexander M, Alexander RW, Martin MY, Alberts KR.

Arthritis Rheum. 1997 Mar;40(3):453-60.

OBJECTIVE: We examined relationships between perceived physical and emotional trauma that occur prior to, or that initiate, pain onset and health care seeking for fibromyalgia syndrome (FMS). We also assessed associations between perceived trauma and levels of health care usage, symptom severity, functional disability, and receipt of disability compensation among patients with FMS.

METHODS: We evaluated these variables using interviews and standardized instruments in a consecutive series of FMS patients and community residents who met the American College of Rheumatology criteria for FMS but had not sought medical care ("nonpatients").

RESULTS: Emotional trauma was associated with status as an FMS patient independently of demographics, physical trauma, and sexual/physical abuse (P = 0.007). Among patients, emotional trauma was related to a high number of physician visits (P = 0.013), functional disability ratings (P = 0.012), and fatigue (P = 0.029), but physical trauma was associated with receipt of disability compensation (P = 0.019). Trauma history was not related to pain severity or pain thresholds.

CONCLUSION: Perception of physical trauma is a greater determinant of disability compensation for FMS than is perceived emotional trauma, symptom severity, or functional disability. Effort should be devoted to understanding the social and legal factors underlying this observation, as well as to reducing high health care usage among FMS patients with emotional trauma.

INFECTION

Higher prevalence of fibromyalgia in patients infected with human T cell lymphotropic virus type I.

Cruz BA, Catalan-Soares B, Proietti F.

J Rheumatol. 2006 Nov;33(11):2300-3.

OBJECTIVE: Inflammatory rheumatic conditions including rheumatoid arthritis and Sjögren's syndrome have been reported in individuals infected with human T cell lymphotropic virus type I (HTLV-I). Other chronic lymphotropic virus infections such as hepatitis C and human immunodeficiency virus are associated with fibromyalgia (FM). There are no reports about the association between HTLV-I infection and FM. We evaluated the association between FM and HTLV-I infection.

METHODS: We conducted a case-control study with prevalent cases. Ex-blood donation candidates with HTLV-I infection from a blood bank cohort, and healthy blood donors as a control group, were submitted to rheumatologic evaluation to compare the prevalence of FM. The following covariables were also evaluated: other rheumatic diseases, age, sex, personal income, level of education, and depression.

RESULTS: One hundred individuals with HTLV-I infection and 62 non-infected blood donors were studied. Thirty-eight (38%) HTLV-I infected individuals and 3 (4.8%) individuals from the control group presented the diagnosis of FM (OR 12.05, 95% CI 3.53-41.17). Other rheumatic diseases were also more prevalent in the infected group (37% vs 12.9%; OR 3.80, 95% CI 1.63-8.86). In multivariate analysis adjusted by the covariables, the association between HTLV-I and FM was statistically significant (OR 9.14, 95% CI 2.42-34.52).

CONCLUSION: Our study shows a greater prevalence of FM in HTLV-I infected individuals, suggesting that FM may be associated with this viral infection.

Fibromyalgia frequency in hepatitis B carriers.

Adak B, Tekeoglu I, Ediz L, Budancamanak M, Yazgan T, Karahocagil K, Demirel A.

J Clin Rheumatol. 2005 Jun;11(3):157-9.

BACKGROUND: Fibromyalgia (FM) is characterized by diffuse musculoskeletal pain, fatigue, morning stiffness, and sleep disturbance. Chronic viral infections may trigger FM symptoms.

OBJECTIVES: In this study, we aimed to evaluate whether there was an association between HBsAg seropositivity and fibromyalgia syndrome.

METHODS: Fifty hepatitis B carriers (HBsAg positivity and anti-HBs negativity in sera for at least 6 months) and 50 age- and sex-matched HbsAg-negative control subjects were enrolled in this study. The hepatitis B carriers with normal or slightly elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were recruited from the infectious diseases outpatient clinic and the control group was recruited from the physical medicine and rehabilitation outpatient clinic. The relationship between groups was calculated by independent Student t test, chi-squared test, and Fisher exact test for comparing proportions. Alpha criterion for significance was set at $P < 0.05$. RESULTS: There was no statistically significant difference between the groups according to sex, mean age, body mass index, serum ALT, and AST levels ($P > 0.05$). FM syndrome and FM-associated symptoms were much more prevalent in the hepatitis B group ($P < 0.001$).

CONCLUSION: The present study suggests that chronic hepatitis B carriage appears to increase the risk of FM and many of the typically associated symptoms. Whether this association is related to altered liver function, viral infection, concerns associated with chronic disease, or other factors, physicians should be aware of this apparent association.

A prospective study of tender points and fibromyalgia during and after an acute viral infection.

Rea T, Russo J, Katon W, Ashley RL, Buchwald D.

Arch Intern Med. 1999 Apr 26;159(8):865-70.

BACKGROUND: Tender points (TPs) and fibromyalgia (FM) may be precipitated by infections, but the frequency, associated characteristics, and predictors of these outcomes are unknown.

OBJECTIVES: To determine if acute infectious mononucleosis (AIM) is associated with the development of TPs or FM acutely or during the subsequent 6 months; if demographic, clinical, or psychosocial features predict TPs or FM; and if TPs or FM correlate with nonrecovery.

METHODS: A total of 150 subjects diagnosed as having AIM were assessed with physical examinations (including palpation of 18 TPs), laboratory tests, and measures of psychosocial and somatic functioning at enrollment and at 2 and 6 months. Subjects also completed a structured psychiatric interview at the initial evaluation.

RESULTS: At presentation and at 2 and 6 months, the mean TP counts were 7.5, 4.6, and 3.0, respectively; at these time points, 19%, 3%, and 1% of subjects also met modified criteria for FM. Tender points and degree of pain diminished over time following AIM. Acutely, TPs were associated only with higher temperature (P<.001). Baseline features that predicted more TPs at 2 and 6 months were female sex, older age, less family social support, and more TPs at presentation. Neither initial laboratory tests nor psychiatric disease or distress predicted TPs. Differences between those who had and had not recovered at 6 months were found for the mean number of TPs (P<.008), the proportion of subjects with 11 or more TPs (P<.002), and the degree of pain.

CONCLUSIONS: Tender points are a common, transient finding associated with AIM, but FM is an unusual long-term outcome. Demographic, social, and physical examination features predicted TPs.

PATHOPHYSIOLOGY

CENTRAL SENSITIZATION

A psychophysical study of auditory and pressure sensitivity in patients with fibromyalgia and healthy controls.

Geisser ME, Glass JM, Rajcevska LD, Clauw DJ, Williams DA, Kileny PR, Gracely RH.

J Pain. 2008 May;9(5):417-22.

Fibromyalgia (FM) is characterized by widespread tenderness. Studies have also reported that persons with FM are sensitive to other stimuli, such as auditory tones. We hypothesized that subjects with FM would display greater sensitivity to both pressure and auditory tones and report greater sensitivity to sounds encountered in daily activities.

FM subjects (n = 30) and healthy control subjects (n = 28) were administered auditory tones and pressure using the same psychophysical methods to deliver the stimuli and a common way of scaling responses. Subjects were also administered a self-report questionnaire regarding sensitivity to everyday sounds. Participants with FM displayed significantly greater sensitivity to all levels of auditory stimulation (Ps < .05). The magnitude of difference between FM patients' lowered auditory sensitivity (relative to control subjects) was similar to that seen with pressure, and pressure and auditory ratings were significantly correlated in both control subjects and subjects with FM. FM patients also were more sensitive to everyday sounds (t = 8.65, P < .001). These findings support that FM is associated with a global central nervous system augmentation in sensory processing. Further research is needed to examine the neural substrates associated with this abnormality and its role in the etiology and maintenance of FM.

PERSPECTIVE: Muscle tenderness is the hallmark of FM, but the findings of this study and others suggest that persons with FM display sensitivity to a number of sensory stimuli. These findings suggest that FM is associated with a global central nervous system augmentation of sensory information. These findings may also help to explain why persons with FM display a number of comorbid physical symptoms other than pain.

PERIPHERAL TISSUES

A subset of fibromyalgia patients have findings suggestive of chronic inflammatory demyelinating polyneuropathy and appear to respond to IVIg.

Caro XJ, Winter EF, Dumas AJ.

Rheumatology (Oxford). 2008 Feb;47(2):208-11.

OBJECTIVES: The aetiopathogenesis of the fibromyalgia syndrome (FMS) remains unknown. Recent reports, however, suggest that a subgroup of FMS subjects has an immune-mediated disease. Therefore, our primary objective was to study FMS subjects for evidence of an immune-mediated demyelinating polyneuropathy. Our secondary objective was to determine the effects of treating these FMS subjects with the immune modulator, intravenous immunoglobulin (IVIg).

METHODS: Fifty-eight FMS subjects, 26 rheumatic non-FMS subjects and 52 non-rheumatic non-FMS subjects were studied. Subjective measures of paraesthesias, weakness, stocking hypaesthesia, pain, fatigue and stiffness were made. Objective measures of tenderness, proximal muscle strength and electrodiagnostic (EDX) evidence of polyneuropathy and demyelination were also made. Eleven other FMS subjects underwent sural nerve biopsy.

RESULTS: Paraesthesias, subjective weakness and stocking hypaesthesia were more common in FMS than in rheumatic non-FMS ($P \leq 0.0001$). Proximal muscle strength was less in FMS than in rheumatic non-FMS ($P \leq 0.0001$). EDX demonstrated a distal demyelinating polyneuropathy, suggestive of chronic inflammatory demyelinating polyneuropathy (CIDP), in 33% of FMS subjects. No rheumatic non-FMS subject had polyneuropathy ($P = 0.005$), or demyelination ($P = 0.05$). Fifteen FMS/CIDP subjects were subsequently treated with IVIg (400 mg/kg each day for 5 days). Pain ($P = 0.01$), tenderness ($P = 0.001$) and strength ($P = 0.04$) improved significantly. Fatigue and stiffness trended towards improvement.

CONCLUSIONS: A significant subset of FMS subjects have clinical and EDX findings suggestive of CIDP. IVIg treatment shows promise in treating this subset. These observations have implications for better understanding and treating some FMS patients.

Overall fibromyalgia pain is predicted by ratings of local pain and pain-related negative affect—possible role of peripheral tissues.

Staud R, Vierck CJ, Robinson ME, Price DD.

Rheumatology (Oxford). 2006 Nov;45(11):1409-15.

OBJECTIVES: Despite variable numbers and intensities of local pain areas, fibromyalgia (FM) patients can provide overall clinical pain ratings. We hypothesized that the overall clinical pain is largely determined by the pain intensity of local body areas. Thus, we assessed the role of local body pains as predictors of overall clinical pain in FM patients.

METHODS: Ratings of overall clinical pain intensity and pain-related negative affect (PRNA) were obtained from 277 FM patients. In addition, the patients identified painful body areas by shading a body pain diagram and rated the intensity of each pain area using a mechanical visual analogue scale (VAS). Hierarchical regression analyses were used to examine predictors of overall clinical FM pain intensity including PRNA, number of local pain areas, and maximal/average intensity of local pain areas.

RESULTS: The average overall clinical pain rating of all FM patients was 4.6 (S.D. 2.3) VAS. The PRNA accounted for 19%, number of painful body areas for 9% and maximal/average local pain for 27% of the variance of overall clinical FM pain (P-values < 0.001). The combination of all factors predicted 55% of the variance in overall clinical pain intensity of FM patients.

CONCLUSION: Peripheral factors (maximal/average local pain and number of painful body areas) predicted most of the variance of overall clinical FM pain, suggesting that the input of pain by the peripheral tissues is clinically relevant. About 19% of the pain variance was predicted by PRNA. Thus, peripheral pain and negative affect appear to be particularly relevant for overall FM pain and may represent important targets for future therapies.

SLEEP

The significance of the sleeping-waking brain for the understanding of widespread musculoskeletal pain and fatigue in fibromyalgia syndrome and allied syndromes.

Moldofsky, H.

Joint Bone Spine. 2008 Jul;75(4):397-402.

The clinical focus of rheumatologists on the widespread pain and numerous tender points in specific anatomic regions in their patients who show no evidence for disease pathology has lead to the characterization of such peripheral symptoms as a specific disorder of the musculoskeletal system, now commonly known as fibromyalgia. This rheumatologic diagnostic entity has resulted in relative inattention to an understanding of their patients' common complaints of unrefreshing sleep, chronic fatigue and psychological distress. Experimental evidence from humans and animal studies indicate that there is an inter-relationship of disturbances in the physiology of the sleeping-waking brain with the widespread musculoskeletal pain, chronic fatigue, and psychological distress in patients with hitherto unexplained pain/fatigue illnesses, e.g., fibromyalgia and chronic fatigue syndromes. The emerging knowledge of the dysfunction of the nervous system in such patients has lead to the study of novel medications that affect neurotransmitter functions, e.g., pregabalin, serotonin/noradrenaline compounds and sodium oxybate that are shown to improve many of the symptoms of such patients.

Musculosketal symptoms and non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy subjects.

Moldofsky H, Scarisbrick P, England R, Smythe H.

Psychosom Med. 1975 Jul-Aug;37(4):341-51.

In sleep studies of (a) patients with the "fibrositis syndrome" and (b) healthy subjects undergoing stage 4 sleep deprivation, we observed in both groups the anomalous presence of alpha-rhythms in the non-rapid-eye-movement (NREM) sleep EEG. This phenomenon has been termed alpha-delta sleep. In the healthy subjects stage 4 deprivation was accompanied by the temporary appearance of muscoloskeletal and mood symptoms comparable to the symptoms seen chronically in the patients. It is suggested that the external arousing stimulus, which induced alpha-delta sleep in the subjects, is paralleled in the patients by an internal arousing mechanism. Such a mechanism, acting in competition with the NREM sleep system, would impair the presumed restorative function of NREM sleep and lead to the development of symptoms. It is proposed that the "fibrositis" symptom complex be considered a "non-restorative sleep syndrome". Evidence froms presented in support of the hypothesis that a disorder of serotonin metabolism serves as a basis for both the EEG sleep disturbance and the symptoms.

CEREBROSPINAL FLUID ABNORMALITIES

Cerebrospinal fluid corticotropin-releasing factor concentration is associated with pain but not fatigue symptoms in patients with fibromyalgia.

McLean SA, Williams DA, Stein PK, Harris RE, Lyden AK, Whalen G, Park KM, Liberzon I, Sen A, Gracely RH, Baraniuk JN, Clauw DJ.

Neuropsychopharmacology. 2006 Dec; 31(12):2776-82.

Previous studies have identified stress system dysregulation in fibromyalgia (FM) patients; such dysregulation may be involved in the generation and/or maintenance of pain and other symptoms. Corticotropin-releasing factor (CRF) is the principal known central nervous system mediator of the stress response; however, to date no studies have examined cerebrospinal fluid (CSF) CRF levels in patients with FM.

The relationship between CSF CRF level, heart rate variability (HRV), and pain, fatigue, and depressive symptoms was examined in patients with FM. Among participants (n=26), CSF CRF levels were associated with sensory pain symptoms (r=0.574, p=0.003) and affective pain symptoms (r=0.497, p=0.011), but not fatigue symptoms. Increased HRV was also strongly associated with increased CSF CRF and FM pain. In multivariate analyses adjusting for age, sex, and depressive

symptoms, the association between CSF CRF and sensory pain symptoms (t=2.54, p=0.027) persisted. Women with FM who reported a history of physical or sexual abuse had lower CSF CRF levels than women who did not report such a history. CSF CRF levels are associated with both pain symptoms and variation in autonomic function in FM.

Differences in CSF CRF levels among women with and without a self-reported history of physical or sexual abuse suggest that subgroups of FM patients may exist with different neurobiological characteristics. Further studies are needed to better understand the nature of the association between CSF CRF and pain symptoms in FM.

Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome.

Russell IJ, Orr MD, Littman B, Vipraio GA, Alboukrek D, Michalek JE, Lopez Y, MacKillip F.

Arthritis Rheum. 1994 Nov;37(11):1593-601.

OBJECTIVE: To measure, and seek clinical correlates with, levels of substance P (SP) in the cerebrospinal fluid (CSF) of fibromyalgia syndrome (FMS) patients.

METHODS: CSF from 32 FMS patients and 30 normal control subjects was tested for SP by radioimmunoassay. Clinical measures included tender point examination and standardized questionnaires.

RESULTS: CSF SP levels were 3-fold higher in FMS patients than in normal controls ($P < 0.001$), but they correlated only weakly with tenderness found on examination.

CONCLUSION: SP is significantly elevated in FMS CSF, but other abnormalities must exist in FMS to more fully explain the symptoms.

Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis.

Russell IJ, Vaeroy H, Javors M, Nyberg F.

Arthritis Rheum. 1992 May;35(5):550-6.

OBJECTIVE: To compare the levels of biogenic amines in the cerebrospinal fluid (CSF) of primary fibromyalgia syndrome (PFS) patients with those in the CSF of controls.

METHODS: Metabolites of serotonin, norepinephrine, and dopamine were identified in CSF, using high performance liquid chromatography with coulometric detection.

RESULTS: CSF levels of metabolites from all 3 neurotransmitters were lower in PFS patients than in controls.

CONCLUSION: A low rate of turnover of several neurotransmitters supports the proposed hypothesis of a metabolic defect in PFS and suggests that the defect occurs at a neuroregulatory level.

AUTONOMIC DYSFUNCTION

Autonomic activation and pain in response to low-grade mental stress in fibromyalgia and shoulder/neck pain patients.

Nilsen KB, Sand T, Westgaard RH, Stovner LJ, White LR, Bang Leistad R, Helde G, Rø M.

Eur J Pain. 2007 Oct;11(7):743-55.

OBJECTIVE: Psychosocial stress is a risk factor for musculoskeletal pain, but how stress affects musculoskeletal pain is poorly understood. We wanted to examine the relationship between low-grade autonomic activation and stress-related pain in patients with fibromyalgia and localised chronic shoulder/neck pain.

METHODS: Twenty-three female patients with fibromyalgia, 29 female patients with chronic shoulder-neck pain, and 35 healthy women performed a stressful task lasting 60min. With a blinded study design, we recorded continuous blood pressure, heart rate, finger skin blood flow and respiration frequency before (10min), during (60min) and after (30min) the stressful task. The physiological responses were compared with subjective reports of pain.

RESULTS: The increase in diastolic blood pressure and heart rate in response to the stressful task were smaller in fibromyalgia patients compared with the healthy controls. Furthermore, fibromyalgia patients had reduced finger skin blood flow at the end of the stressful task compared to healthy controls. We also found an inverse relationship between the heart rate response and development and recovery of the stress-related pain in fibromyalgia patients.

CONCLUSION: We found abnormal cardiovas-

cular responses to a 60min long stressful task in fibromyalgia patients. Furthermore, we found a negative association between the heart rate response and the pain which developed during the stressful task in the fibromyalgia group, possibly a result of reduced stress-induced analgesia for fibromyalgia patients.

Dysautonomia in fibromyalgia syndrome: sympathetic skin responses and RR interval analysis.

Ulas UH, Unlu E, Hamamcioglu K, Odabasi Z, Cakci A, Vural O.

Rheumatol Int. 2006 Mar;26(5):383-7.

This study was planned to investigate the dysfunction of the autonomic nervous system in fibromyalgia syndrome (FM) using sympathetic skin responses (SSR) and RR interval analysis.

Thirty-four FM and 22 healthy subjects were recruited for the study. They were questioned for symptoms that are characteristic for FM and medical outcome study short form-36 (SF-36) was used to determine the quality of life of the subjects. Tender points were counted and the disease duration was noted. SSR was recorded from palm and sole with stimulation of contralateral median and tibial nerves respectively. R-R interval variation was evaluated at rest (R%) and during deep breathing (DR%).

The mean ages of the patients were 37+/- 10.2 and 37+/-10.6, respectively. The mean tender point count was 14.9+/-2.3 and the disease duration was 16.6+/-12.1 months. The symptoms were discrepant in FM ($P<0.001$). The scores of the eight items of SF-36 in FMS patients were significantly lower than the control group ($P<0.001$). We could not elicit SSR in five FM patients (15%) from the sole and in two patients (6%) from the palm. The latencies of SSR recorded from both palms and soles of FM patients were significantly longer than healthy subjects ($P<0.001$). The mean amplitude of SSR recorded from both palm and sole was not statistically different from control subjects ($P>0.05$). RRIV obtained from FM and the control subjects at rest and during deep breathing showed that the decrease in DR% was significant compared to normal subjects ($P<0.001$).

As a result, we can state that sympathetic as well as parasympathetic nervous system dysfunction occurs in FM patients and this abnormality could be determined by SSR and RRIV analysis.

Abnormalities of cardiovascular neural control and reduced orthostatic tolerance in patients with primary fibromyalgia.

Furlan R, Colombo S, Perego F, Atzeni F, Diana A, Barbic F, Porta A, Pace F, Malliani A, Sarzi-Puttini P.

J Rheumatol. 2005 Sep;32(9):1787-93.

OBJECTIVE: Fibromyalgia (FM) is a syndrome characterized by widespread musculoskeletal pain. Symptoms of orthostatic intolerance may also be present, suggesting underlying abnormalities of cardiovascular neural regulation. We tested the hypothesis that FM is characterized by sympathetic overactivity and alterations in cardiovascular autonomic response to gravitational stimulus.

METHODS: Sixteen patients with primary FM and 16 healthy controls underwent electrocardiography examination, finger blood pressure, respiration, and muscle sympathetic nerve activity (MSNA) recordings at rest and during stepwise tilt test, up to 75 degrees . The autonomic profile was assessed by MSNA, plasma catecholamine, and spectral indices of cardiac sympathetic (LFRR in normalized units, NU) and vagal (HFRR both in absolute and NU) modulation and of sympathetic vasomotor control (LFSAP) computed by spectrum analysis of RR and systolic arterial pressure (SAP) variability. Arterial baroreflex function was evaluated by the SAP/RR spontaneous-sequences technique, the index a, and the gain of MSNA/diastolic pressure relationship during stepwise tilt test.

RESULTS: At rest, patients showed higher values of heart rate, MSNA, LFRR NU, LF/HF, LFSAP, and reduced HFRR than controls. During tilt test, lack of increase of MSNA, less decrease of HFRR, and excessive rate (44%) of syncope were found in patients, suggesting reduced capability to enhance the sympathetic activity to vessels and withdraw the vagal modulation to sino-atrial node. Baroreflex function was similar in both groups.

CONCLUSION: Patients with FM have an overall enhancement of cardiovascular sympathetic activity while recumbent. Lack of increased sympathetic discharge to vessels and decreased cardiac vagal activity characterize their autonomic profile during tilt test, and might account for the excessive rate of syncope.

Circadian studies of autonomic nervous

Balance in patients with fibromyalgia: a heart rate variability analysis.

Martínez-Lavin M, Hermosillo AG, Rosas M, Soto ME.

Arthritis Rheum. 1998 Nov;41(11):1966-71.

OBJECTIVE: To determine the accumulated 24-hour cardiovascular autonomic modulation and its circadian variations in patients with fibromyalgia, by means of heart rate variability analysis.

METHODS: Thirty patients with fibromyalgia and 30 age- and sex-matched controls were studied prospectively. Assessments included a 24-hour ambulatory recording of heart rate variability, time-domain analysis of the accumulated 24-hour R-R interval variations, and power spectral analysis to determine the sympatho/ vagal balance at different hours (calculated as the power spectral density of the low-frequency [0.04-0.15-Hz] sympathetic band divided by the power of the high-frequency [0.15-0.50-Hz] parasympathetic band).

RESULTS: Fibromyalgia patients had diminished accumulated 24-hour heart rate variability, manifested by a decreased standard deviation of all R-R intervals (mean +/- SD 126 +/- 35 ms, versus 150 +/- 33 ms in controls; P =0.008) and a decreased ratio of pairs of adjacent R-R intervals differing by >50 ms (mean +/- SD 12.0 +/- 9.0% versus 20.1 +/- 18.0%; P = 0.031). Patients lost the circadian variations of sympatho/vagal balance, with nocturnal values significantly higher than those of controls at time 0 (mean +/- SD 3.5 +/- 3.2 versus 1.2 +/- 1.0; P = 0.027) and at 3 hours (3.3 +/- 3.0 versus 1.6 +/- 1.4; P = 0.01).

CONCLUSION: Individuals with fibromyalgia have diminished 24-hour heart rate variability due to an increased nocturnal predominance of the low-frequency band oscillations consistent with an exaggerated sympathetic modulation of the sinus node. This abnormal chronobiology could explain the sleep disturbances and fatigue that occur in this syndrome. Spectral analysis of heart rate variability may be a useful test to identify fibromyalgia patients who have dysautonomia.

NEUROENDOCRINE DYSFUNCTION

HPA axis reactivity and lymphocyte glucocorticoid sensitivity in fibromyalgia syndrome and chronic pelvic pain.

Wingenfeld K, Heim C, Schmidt I, Wagner D, Meinlschmidt G, Hellhammer DH.

Psychosom Med. 2008 Jan;70(1):65-72.

OBJECTIVE: Chronic pelvic pain (CPP) and fibromyalgia syndrome (FMS) have been associated with hypothalamic-pituitary-adrenal (HPA) axis alterations, i.e., mild hypocortisolism and enhanced feedback sensitivity. We tested the hypothesis of reduced cortisol release in response to a psychosocial stressor and pharmacological stimulation. Furthermore, glucocorticoid (GC) sensitivity was evaluated.

METHODS: Plasma total and salivary-free cortisol concentrations were measured in response to a standardized social laboratory stressor, the Trier Social Stress Test, and to adrenocorticotropin (ACTH) (1-24) stimulation. In the Trier Social Stress Test, we additionally measured ACTH. GC sensitivity was measured by dexamethasone inhibition of lipopolysaccharide-induced interleukin-6 and tumor necrosis factor-alpha production in whole blood.

RESULTS: There were no HPA axis alterations in women with CPP (N = 18) in these tests. Patients with FMS (N = 17) showed lower total cortisol release in response to the social stressor and exogenous ACTH, but normal free cortisol and ACTH levels compared with controls (N = 24). GC sensitivity was similar in all groups.

CONCLUSIONS: Our results suggest normal HPA responses to stress and ACTH stimulation in patients with CPP but reduced adrenal reactivity in patients with FMS, namely in total cortisol release. Free cortisol on the other hand was unaltered, possibly reflecting an adaptation to reduced circulating total cortisol.

Growth hormone perturbations in fibromyalgia: a review.

Jones KD, Deodhar P, Lorentzen A, Bennett RM, Deodhar AA.

Semin Arthritis Rheum. 2007 Jun;36(6):357-79.

OBJECTIVE: Fibromyalgia (FM) is a syndrome characterized by chronic widespread pain, fatigue, disrupted sleep, depression, and physical deconditioning. In this article, we review the literature on the normal activity of the hypothalamic-pituitary-growth hormone-insulin-like growth factor-1 (HP-GH-IGF-1) axis and its perturbations in FM subjects.

METHODS: Studies included in this review were accessed through an English language search of Cochrane Collaboration Reviews. Keyword MeSH terms included "fibromyalgia," "growth hormone" (GH), or "insulin-like growth factor-1" (IGF-1).

RESULTS: Twenty-six studies enrolling 2006 subjects were reviewed. Overall, low levels of IGF-1 were found in a subgroup of subjects. Growth hormone stimulation tests often revealed a suboptimal response, which did not always correlate with IGF-1 levels. No consistent defects in pituitary function were found. Of the 3 randomized placebo controlled studies, only 9 months of daily injectable recombinant GH reduced FM symptoms and normalized IGF-1.

CONCLUSIONS: These studies suggest that pituitary function is normal in FM and that reported changes in the HP-GH-IGF-1 axis are most likely hypothalamic in origin. The therapeutic efficacy of supplemental GH therapy in FM requires further study before any solid recommendations can be made.

Neuroendocrine perturbations in fibromyalgia and chronic fatigue syndrome.

Neeck G, Crofford LJ.

Rheum Dis Clin North Am. 2000 Nov; 26(4):989-1002.

A large body of data from a number of different laboratories worldwide has demonstrated a general tendency for reduced adrenocortical responsiveness in CFS. It is still not clear if this is secondary to CNS abnormalities leading to decreased activity of CRH- or AVP-producing hypothalamic neurons. Primary hypofunction of the CRH neurons has been described on the basis of genetic and environmental influences. Other pathways could secondarily influence HPA axis activity, however. For example, serotonergic and noradrenergic input acts to stimulate HPA axis activity. Deficient serotonergic activity in CFS has been suggested by some of the studies as reviewed here.

In addition, hypofunction of sympathetic nervous system function has been described and could contribute to abnormalities of central components of the HPA axis. One could interpret the clinical trial of glucocorticoid replacement in patients with CFS as confirmation of adrenal insufficiency if one were convinced of a positive therapeutic effect. If patient symptoms were related to impaired activation of central components of the axis, replacing glucocorticoids would merely exacerbate symptoms caused by enhanced negative feedback. Further study of specific components of the HPA axis should ultimately clarify the reproducible abnormalities associated with a clinical picture of CFS.

In contrast to CFS, the results of the different hormonal axes in FMS support the assumption that the distortion of the hormonal pattern observed can be attributed to hyperactivity of CRH neurons. This hyperactivity may be driven and sustained by stress exerted by chronic pain originating in the musculoskeletal system or by an alteration of the CNS mechanism of nociception. The elevated activity of CRH neurons also seems to cause alteration of the set point of other hormonal axes. In addition to its control of the adrenal hormones, CRH stimulates somatostatin secretion at the hypothalamic level, which, in turn, causes inhibition of growth hormone and thyroid-stimulating hormone at the pituitary level. The suppression of gonadal function may also be attributed to elevated CRH because of its ability to inhibit hypothalamic luteinizing hormone-releasing hormone release; however, a remote effect on the ovary by the inhibition of follicle-stimulating hormone-stimulated estrogen production must also be considered. Serotonin (5-HT) precursors such as tryptophan (5-HTP), drugs that release 5-HT, or drugs that act directly on 5-HT receptors stimulate the HPA axis, indicating a stimulatory effect of serotonergic input on HPA axis function. Hyperfunction of the HPA axis could also reflect an elevated serotonergic tonus in the CNS of FMS patients.

The authors conclude that the observed pattern of hormonal deviations in patients with FMS is a CNS adjustment to chronic pain and stress, constitutes a specific entity of FMS, and is primarily evoked by activated CRH neurons.

Secretory pattern of GH, TSH, thyroid hormones, ACTH, cortisol, FSH, and LH in patients with fibromyalgia syndrome following systemic injection of the relevant hypothalamic-releasing hormones.

Riedel W, Layka H, Neeck G.

Z Rheumatol. 1998;57 Suppl 2:81-7.

To study the hormonal perturbations in FMS patients we injected sixteen FMS patients and seventeen controls a cocktail of the hypothalamic releasing hormones: Corticotropin-releasing hormone (CRH), Thyrotropin-releasing hormone (TRH), Growth hormone-releasing hormone (GHRH), and Luteinizing hormone-releasing hormone (LHRH) and observed the hormonal secretion pattern of the pituitary together with the hormones of the peripheral endocrine glands.

We found in FMS patients elevated basal values of ACTH and cortisol, lowered basal values of insulin-like growth factor I (IGF-I) and of triiodothyronine (T3), elevated basal values of follicle-stimulating hormone (FSH) and lowered basal values of estrogen. Following injection of the four releasing-hormones, we found in FMS patients an augmented response of ACTH, a blunted response of TSH, while the prolactin response was exaggerated. The effects of LHRH stimulation were investigated in six FMS patients and six controls and disclosed a significantly blunted response of LH in FMS.

We explain the deviations of hormonal secretion in FMS patients as being caused by chronic stress, which, after being perceived and processed by the central nervous system (CNS), activates hypothalamic CRH neurons. CRH, on the one hand, activates the pituitary-adrenal axis, but also stimulates at the hypothalamic level somatostatin secretion which, in turn, causes inhibition of GH and TSH at the pituitary level. The suppression of gonadal function may also be attributed to elevated CRH by its ability to inhibit hypothalamic LHRH release, although it could act also directly on the ovary by inhibiting FSH-stimulated estrogen production.

We conclude that the observed pattern of hormonal deviations in FMS patients is a CNS adjustment to chronic pain and stress, constitutes a specific entity of FMS, and is primarily evoked by activated CRH neurons.

CYTOKINES

Cytokine patterns in fibromyalgia and their correlation with clinical manifestations.

Bazzichi L, Rossi A, Massimetti G, Giannaccini G, Giuliano T, De Feo F, Ciapparelli A, Dell'Osso L, Bombardieri S.

Clin Exp Rheumatol. 2007 Mar-Apr;25(2):225-30.

OBJECTIVE: To examine the possible role of the soluble factor in fibromyalgia (FM) by studying the correlation of cytokine levels with the patients' clinical and psychiatric profile.

METHODS: Eighty FM patients underwent clinical and psychiatric evaluations, and plasma levels of cytokines (IL-1, IL-6, IL-8, IL-10, TNF-alpha), aspecific markers of inflammation, rheumatoid factor (RF), anti-extractable nuclear antigen (ENA) antibodies, and anti-nuclear factor (FAN) were measured.

RESULTS: Higher levels of IL-10, IL-8 and TNF-alpha were found in FM patients than in controls. Significant correlations between the biochemical parameters and clinical data were found.

CONCLUSION: The higher levels of cytokines found in FM patients suggest the presence of an inflammatory response system (IRS) and highlight a parallel between the clinical symptoms and biochemical data. They support the hypothesis that cytokines may play a role in the clinical features of fibromyalgia. In addition, the similar cytokine patterns found in FM patients with different psychiatric profiles suggests that IRS impairment may play a specific role in the disease.

NEUROIMAGING

Hippocampus dysfunction may explain symptoms of fibromyalgia syndrome. A study with single-voxel magnetic resonance spectroscopy.

Emad Y, Ragab Y, Zeinhom F, El-Khouly G, Abou-Zeid A, Rasker JJ.

J Rheumatol. 2008 Jul;35(7):1371-7.

OBJECTIVE: (1) To investigate dysfunction of hippocampus in patients with fibromyalgia syndrome (FM) using proton magnetic resonance spectroscopy (1H-MRS), and to compare these findings with healthy controls. (2) To correlate levels of metabolites obtained with aspects of cognition, depression, and sleep symptoms in the patient group.

METHODS: The case-control study was performed in 15 female patients, who met American College of Rheumatology criteria for classification of FM, and 10 healthy age-matched female controls. Patients and controls were receiving no medications known to affect cognitive functioning or central nervous system metabolites before their participation in the study. In all patients and controls, 1H-MRS was used to assess N-acetylaspartate (NAA), choline (Cho), creatine (Cr), and their ratios from both hippocampi. Levels of metabolites and their ratios were determined and the findings compared between the groups. All patients and controls underwent psychological assessment to assess cognitive function, depression, and structured sleep interview with sleep diary; Fibromyalgia Impact Questionnaire (FIQ), number of tender points, and visual analog scale (VAS) for pain were assessed in all patients.

RESULTS: NAA levels of right and left hippocampi differed significantly between patients and controls ($p < 0.05$). Cho levels in the right hippocampus were higher in the patient group than in controls ($p = 0.005$), while no differences were found with respect to Cr levels in both hippocampi. NAA/Cho and NAA/Cr ratios differed significantly between patients and controls ($p < 0.05$), while the Cho/Cr ratio showed no differences. Significant correlations were found between language score and right Cho and right Cr levels ($p = 0.041$, $p = 0.006$, respectively), while no significant correlations were found between metabolites and their ratios with FIQ, VAS for pain, or number of tender points.

CONCLUSION: The hippocampus was dysfunctional in patients with FM, as shown by lower NAA levels compared to controls, representing neuronal or axonal metabolic dysfunction. As the hippocampus plays crucial roles in maintenance of cognitive functions, sleep regulation, and pain perception, we suggest that metabolic dysfunction of hippocampus may be implicated in the appearance of these symptoms associated with this puzzling syndrome.

Proton MR spectroscopy in the evaluation of cerebral metabolism in patients with fibromyalgia: comparison with healthy controls and correlation with symptom severity.

Petrou M, Harris RE, Foerster BR, McLean SA, Sen A, Clauw DJ, Sundgren PC.

AJNR Am J Neuroradiol. 2008 May;29(5):913-8.

BACKGROUND AND PURPOSE: Widespread pain sensitivity in patients with fibromyalgia (FM) suggests a central nervous system (CNS)-processing problem. Therefore, it is conceivable that metabolic alterations exist in pain-processing brain regions of people with FM compared with healthy controls (HC) and that such metabolic data could correlate with clinical symptoms. The purpose of this study was to test these hypotheses using proton MR spectroscopy ((1)H-MR spectroscopy).

MATERIALS AND METHODS: There were 21 patients with FM and 27 HC who underwent conventional structural MR imaging and additional 2D-chemical shift imaging (CSI) MR-spectroscopy sequences. For the 2D-CSI spectroscopy, larger volumes of interest (VOIs) were centered at the level of the basal ganglia and the supraventricular white matter. Within these larger areas, 16 smaller voxels were placed in a number of regions previously implicated in pain processing. N-acetylaspartate (NAA)/creatine(Cr), choline (Cho)/Cr and NAA/Cho ratios were calculated for each voxel. Subjects underwent clinical and experimental pain assessment.

RESULTS: Mean metabolite ratios and ratio variability for each region were analyzed by using repeated-measures analysis of variance (ANOVA). Correlations between clinical symptoms and metabolite ratios were assessed. Cho/Cr variability in the right dorsolateral prefrontal cortex (DLPFC) was significantly different in the 2 groups; a significant

correlation between Cho/Cr in this location and clinical pain was present in the FM group. Evoked pain threshold correlated significantly with NAA/Cho ratios in the left insula and left basal ganglia.

CONCLUSION: Our data suggest that there are baseline differences in the variability of brain metabolite relative concentrations between patients with FM and HC, especially in the right DLPFC. Furthermore, there are significant correlations between metabolite ratios and clinical and experimental pain parameters in patients with FM.

Dynamic levels of glutamate within the insula are associated with improvements in multiple pain domains in fibromyalgia.

Harris RE, Sundgren PC, Pang Y, Hsu M, Petrou M, Kim SH, McLean SA, Gracely RH, Clauw DJ.

Arthritis Rheum. 2008 Mar;58(3):903-7.

OBJECTIVE: Fibromyalgia (FM) is a chronic widespread pain condition that is thought to arise from augmentation of central neural activity. Glutamate (Glu) is an excitatory neurotransmitter that functions in pain-processing pathways. This study was carried out to investigate the relationship between changing levels of Glu within the insula and changes in multiple pain domains in patients with FM.

METHODS: Ten patients with FM underwent 2 sessions of proton magnetic resonance spectroscopy (H-MRS) and 2 sessions of functional magnetic resonance imaging (FMRI), each conducted before and after a nonpharmacologic intervention to reduce pain. During H-MRS, the anterior and posterior insular regions were examined separately using single-voxel spectroscopy. The levels of Glu and other metabolites were estimated relative to levels of creatine (Cr) (e.g., the Glu/Cr ratio). During FMRI, painful pressures were applied to the thumbnail to elicit neuronal activation. Experimental pressure-evoked pain thresholds and clinical pain ratings (on the Short Form of the McGill Pain Questionnaire [SF-MPQ]) were also assessed prior to each imaging session

RESULTS: Both experimental pain ($P = 0.047$ versus pretreatment) and SF-MPQ-rated clinical pain ($P = 0.043$ versus pretreatment) were reduced following treatment. Changes from pre- to posttreatment in Glu/Cr were negatively correlated with changes in experimental pain thresholds ($r = -0.95$, $P < 0.001$) and positively correlated with changes in clinical pain ($r = 0.85$, $P = 0.002$). Changes in the FMRI-determined blood oxygenation level-dependent effect (a measure of neural activation) were positively correlated with changes in Glu/Cr within the contralateral insula ($r = 0.81$, $P = 0.002$).

CONCLUSION: Changes in Glu levels within the insula are associated with changes in multiple pain domains in patients with FM. Thus, H-MRS data may serve as a useful biomarker and surrogate end point for clinical trials of FM.

Striatal grey matter increase in patients suffering from fibromyalgia—a voxel-based morphometry study.

Schmidt-Wilcke T, Luerding R, Weigand T, Jürgens T, Schuierer G, Leinisch E, Bogdahn U.

Pain. 2007 Nov;132 Suppl 1:S109-16.

Fibromyalgia (FM), among other chronic pain syndromes, such as chronic tension type headache and atypical face pain, is classified as a so-called dysfunctional pain syndrome. Patients with fibromyalgia suffer from widespread, "deep" muscle pain and often report concomitant depressive episodes, fatigue and cognitive deficits. Clear evidence for structural abnormalities within the muscles or soft tissue of fibromyalgia patients is lacking. There is growing evidence that clinical pain in fibromyalgia has to be understood in terms of pathological activity of central structures involved in nociception.

We applied MR-imaging and voxel-based morphometry, to determine whether fibromyalgia is associated with altered local brain morphology. We investigated 20 patients with the diagnosis of primary fibromyalgia and 22 healthy controls.

VBM revealed a conspicuous pattern of altered brain morphology in the right superior temporal gyrus (decrease in grey matter), the left posterior thalamus (decrease in grey matter), in the left orbitofrontal cortex (increase in grey matter), left cerebellum (increase in grey matter) and in the striatum bilaterally (increase in grey matter).

Our data suggest that fibromyalgia is associated with structural changes in the CNS of patients suffering from this chronic pain disorder. They might reflect either a consequence of chronic nociceptive input or they might be causative to the pathogenesis of fibromyalgia. The affected areas are known to be both, part of the somatosensory system and part of the motor system.

The effects of multidisciplinary therapy on positron emission tomography of the brain in fibromyalgia: a pilot study.

Walitt B, Roebuck-Spencer T, Esposito G, Atkins F, Bleiberg J, Foster G, Weinstein A.

Rheumatol Int. 2007 Sep;27(11):1019-24.

Aberrant central neurological functioning is believed to contribute to the abnormal sensations of fibromyalgia (FM). This pilot study sought to determine if alterations in regional brain metabolism from baseline occur in FM after undergoing a multidisciplinary therapeutic regimen.

Regional brain metabolic activity was estimated using (18)F-fluorodeoxyglucose positron emission tomography ((18)FDG PET). Nine participants with FM received an 8-week comprehensive treatment program. Serial testing with (18)FDG PET and the Fibromyalgia Impact Questionnaire were performed. Statistical analysis was performed using repeated Wilcoxon signed rank tests. A clinical improvement (FIQ median change 20.68, P = 0.005) was noted with treatment.

With treatment, increases in brain metabolism were noted in various components of the limbic system (P = 0.004-0.1). An increase in limbic metabolism was noted with concomitant symptomatic improvement, suggesting that the limbic system attenuates FM symptoms.

Decreased central mu-opioid receptor availability in fibromyalgia.

Harris RE, Clauw DJ, Scott DJ, McLean SA, Gracely RH, Zubieta JK.

J Neurosci. 2007 Sep 12;27(37):10000-6.

The underlying neurophysiology of acute pain is fairly well characterized, whereas the central mechanisms operative in chronic pain states are less well understood. Fibromyalgia (FM), a common chronic pain condition characterized by widespread pain, is thought to originate largely from altered central neurotransmission.

We compare a sample of 17 FM patients and 17 age- and sex-matched healthy controls, using mu-opioid receptor (MOR) positron emission tomography. We demonstrate that FM patients display reduced MOR binding potential (BP) within several regions known to play a role in pain modulation, including the nucleus accumbens, the amygdala, and the dorsal cingulate. MOR BP in the accumbens of FM patients was negatively correlated with affective pain ratings. Moreover, MOR BP throughout the cingulate and the striatum was also negatively correlated with the relative amount of affective pain (McGill, affective score/sensory score) within these patients.

These findings indicate altered endogenous opioid analgesic activity in FM and suggest a possible reason for why exogenous opiates appear to have reduced efficacy in this population.

Fibromyalgia patients show an abnormal dopamine response to pain.

Wood PB, Schweinhardt P, Jaeger E, Dagher A, Hakyemez H, Rabiner EA, Bushnell MC, Chizh BA.

Eur J Neurosci. 2007 Jun;25(12):3576-82.

Fibromyalgia is characterized by chronic widespread pain and bodily tenderness and is often accompanied by affective disturbances. Accumulating evidence indicates that fibromyalgia may involve a dysfunction of modulatory systems in the brain. While brain dopamine is best known for its role in pleasure, motivation and motor control, recent evidence suggests that it is also involved in pain modulation. Because dopamine is implicated in both pain modulation and affective processing, we hypothesized that fibromyalgia may involve a disturbance of dopaminergic neurotransmission.

Fibromyalgia patients and matched healthy control subjects were subjected to deep muscle pain produced by injection of hypertonic saline into the anterior tibialis muscle. In order to determine the endogenous release of dopamine in response to painful stimulation, we used positron emission tomography to examine binding of [(11)C]-raclopride (D2/D3 ligand) in the brain during injection of painful hypertonic saline and nonpainful normal saline.

Fibromyalgia patients experienced the hypertonic saline as more painful than healthy control subjects. Control subjects released dopamine in the basal ganglia during the painful stimulation, whereas fibromyalgia patients did not. In control subjects, the amount of dopamine release correlated with the amount of perceived pain but in fibromyalgia patients no such correlation was observed.

These findings provide the first direct evidence that fibromyalgia patients have an abnormal dopamine response to pain. The disrupted dopaminergic reactivity in fibromyalgia patients could be a critical factor underlying the widespread pain and discomfort in fibromyalgia and suggests that the therapeutic effects of dopaminergic treatments for this intractable disorder should be explored.

Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain?

Kuchinad A, Schweinhardt P, Seminowicz DA, Wood PB, Chizh BA, Bushnell MC.

J Neurosci. 2007 Apr 11;27(15):4004-7.

Fibromyalgia is an intractable widespread pain disorder that is most frequently diagnosed in women. It has traditionally been classified as either a musculoskeletal disease or a psychological disorder. Accumulating evidence now suggests that fibromyalgia may be associated with CNS dysfunction.

In this study, we investigate anatomical changes in the brain associated with fibromyalgia. Using voxel-based morphometric analysis of magnetic resonance brain images, we examined the brains of 10 female fibromyalgia patients and 10 healthy controls.

We found that fibromyalgia patients had significantly less total gray matter volume and showed a 3.3 times greater age-associated decrease in gray matter than healthy controls. The longer the individuals had had fibromyalgia, the greater the gray matter loss, with each year of fibromyalgia being equivalent to 9.5 times the loss in normal aging. In addition, fibromyalgia patients demonstrated significantly less gray matter density than healthy controls in several brain regions, including the cingulate, insular and medial frontal cortices, and parahippocampal gyri.

The neuroanatomical changes that we see in fibromyalgia patients contribute additional evidence of CNS involvement in fibromyalgia. In particular, fibromyalgia appears to be associated with an acceleration of age-related changes in the very substance of the brain. Moreover, the regions in which we demonstrate objective changes may be functionally linked to core features of the disorder including affective disturbances and chronic widespread pain.

(99m)Tc-ECD brain perfusion SPECT in hyperalgesic fibromyalgia.

Guedj E, Taieb D, Cammilleri S, Lussato D, de Laforte C, Niboyet J, Mundler O.

Eur J Nucl Med Mol Imaging. 2007 Jan; 34(1):130-4.

PURPOSE: Neuro-imaging studies with (99m)Tc-HMPAO SPECT in fibromyalgia (FM) patients have reported only limited subcortical hypoperfusion. (99m)Tc-ECD SPECT is known to provide better evaluation of areas of high cerebral blood flow and regional metabolic rate. We evaluated a homogeneous group of hyperalgesic patients with FM using (99m)Tc-ECD SPECT. The aim of this study was to investigate brain processing associated with spontaneous pain in FM patients.

METHODS: Eighteen hyperalgesic FM women (mean age 49 years, range 25-63 years; American College of Rheumatology criteria) and ten healthy women matched for age were enrolled in the study. A voxel-by-voxel group analysis was performed using SPM2 ($p<0.05$, corrected for multiple comparisons). Visual Analogue Scale score for pain was 82+/-4 at the time of the SPECT study.

RESULTS: Compared with control subjects, we observed individual brain SPECT abnormalities in FM patients, confirmed by SPM2 analysis, with hyperperfusion of the somatosensory cortex and hypoperfusion of the frontal, cingulate, medial temporal and cerebellar cortices.

CONCLUSION: In the present study, performed without noxious stimuli in hyperalgesic FM patients, we found significant hyperperfusion in regions of the brain known to be involved in the sensory dimension of pain processing and significant hypoperfusion in areas assumed to be associated with the affective-attentional dimension. As current pharmacological and non-pharmacological therapies act differently on the two components of pain, we hypothesise that SPECT could be a valuable and readily available tool to guide individual therapeutic strategy and provide objective follow-up of pain processing recovery under treatment.

Reduced presynaptic dopamine activity in fibromyalgia syndrome demonstrated with positron emission tomography: a pilot study.

Wood PB, Patterson JC 2nd, Sunderland JJ, Tainter KH, Glabus MF, Lilien DL.

J Pain. 2007 Jan;8(1):51-8.

Although the pathophysiology underlying the pain of fibromyalgia syndrome (FMS) remains unknown, a variety of clinical and investigational findings suggests a dysregulation of dopaminergic neurotransmission. We therefore investigated presynaptic dopaminergic function in 6 female FMS patients in comparison to 8 age- and gender-matched controls as assessed by positron emission tomography with 6-[(18)F]fluoro-L-DOPA as a tracer.

Semiquantitative analysis revealed reductions in 6-[(18)F]fluoro-L-DOPA uptake in several brain regions, indicating a disruption of presynaptic dopamine activity wherein dopamine plays a putative role in natural analgesia. Although the small sample size makes these findings preliminary, it appears that FMS might be characterized by a disruption of dopaminergic neurotransmission.

PERSPECTIVE: An association between FMS and reduced dopamine metabolism within the pain neuromatrix provides important insights into the pathophysiology of this mysterious disorder.

Functional imaging of pain in patients with primary fibromyalgia.

Cook DB, Lange G, Ciccone DS, Liu WC, Steffener J, Natelson BH.

J Rheumatol. 2004 Feb;31(2):364-78.

OBJECTIVE: To examine the function of the nociceptive system in patients with fibromyalgia (FM) using functional magnetic resonance imaging (fMRI).

METHODS: Two groups of women, 9 with FM and 9 pain-free, volunteered to participate. In Experiment 1, we assessed psychophysical responses to painful stimuli and prepared participants for fMRI testing. For Experiment 2, subjects underwent fMRI scanning while receiving painful and nonpainful heat stimuli. Conventional and functional MR images were acquired using a 1.5 T MR scanner. Scanning occurred over 5 conditions. Condition 1 served as a practice session (no stimuli). Conditions 2 and 5 consisted of nonpainful warm stimuli. Conditions 3 and 4 consisted of an absolute thermal pain stimulus (47 degrees C) and a perceptually equivalent pain stimulus delivered in counterbalanced order.

RESULTS: Experiment 1 indicated that subjects with FM were significantly more sensitive to experimental heat pain than controls ($p < 0.001$). In Experiment 2, fMRI data indicated that the FM group exhibited greater activity than controls over multiple brain regions in response to both nonpainful and painful stimuli ($p < 0.01$). Specifically, in response to nonpainful warm stimuli, FM subjects had significantly greater activity than controls in prefrontal, supplemental motor, insular, and anterior cingulate cortices ($p < 0.01$). In response to painful stimuli, FM subjects had greater activity in the contralateral insular cortex ($p < 0.01$). Data from the practice session indicated brain activity in pain-relevant areas for the FM group but not for controls.

CONCLUSION: Our results provide further evidence for a physiological explanation for FM pain.

Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia.

Gracely RH, Petzke F, Wolf JM, Clauw DJ.

Arthritis Rheum. 2002 May;46(5):1333-43.

OBJECTIVE: To use functional magnetic resonance imaging (fMRI) to evaluate the pattern of cerebral activation during the application of painful pressure and determine whether this pattern is augmented in patients with fibromyalgia (FM) compared with controls.

METHODS: Pressure was applied to the left thumbnail beds of 16 right-handed patients with FM and 16 right-handed matched controls. Each FM patient underwent fMRI while moderately painful pressure was being applied. The functional activation patterns in FM patients were compared with those in controls, who were tested under 2 conditions: the "stimulus pressure control" condition, during which they received an amount of pressure similar to that delivered to patients, and the "subjective pain control" condition, during which the intensity of stimulation was increased to deliver a subjective level of pain similar to that experienced by patients.

RESULTS: Stimulation with adequate pressure to cause similar pain in both groups resulted in 19 regions of increased regional cerebral blood flow in healthy controls and 12 significant regions in patients. Increased fMRI signal occurred in 7 regions common to both groups, and decreased signal was observed in 1 common region. In contrast, stimulation of controls with the same amount of pressure that caused pain in patients resulted in only 2 regions of increased signal, neither of which coincided with a region of activation in patients. Statistical comparison of the patient and control groups receiving similar stimulus pressures revealed 13 regions of greater activation in the patient group. In contrast, similar stimulus pressures produced only 1 region of greater activation in the control group.

CONCLUSION: The fact that comparable subjectively painful conditions resulted in activation patterns that were similar in patients and controls, whereas similar pressures resulted in no common regions of activation and greater effects in patients, supports the hypothesis that FM is characterized by cortical or subcortical augmentation of pain processing.

Regional cerebral blood flow in fibromyalgia: single-photon-emission computed tomography evidence of reduction in the pontine tegmentum and thalami.

Kwiatek R, Barnden L, Tedman R, Jarrett R, Chew J, Rowe C, Pile K.

Arthritis Rheum. 2000 Dec;43(12):2823-33.

OBJECTIVE: To determine whether regional cerebral blood flow (rCBF) is abnormal in any cerebral structure of women with fibromyalgia (FM), following a report that rCBF is reduced in the thalami and heads of caudate nuclei in FM.

METHODS: Seventeen women with FM and 22 healthy women had a resting single-photon-emission computed tomography (SPECT) brain scan to assess rCBF and a T1-weighted magnetic resonance imaging (MRI) scan to enable precise anatomic localization. Additionally, all participants underwent 2 manual tender point examinations and completed a set of questionnaires evaluating clinical features. SPECT scans were analyzed for differences in rCBF between groups using statistical parametric mapping (SPM) and regions of interest (ROIs) manually drawn on coregistered MRI.

RESULTS: Compared with control subjects, the rCBF in FM patients was significantly reduced in the right thalamus (P = 0.006), but not in the left thalamus or head of either caudate nucleus. SPM analysis indicated a statistically significant reduction in rCBF in the inferior pontine tegmentum (corrected P = 0.006 at the cluster level and corrected P = 0.023 for voxel of maximal significance), with consistent findings from ROI analysis (P = 0.003). SPM also detected a reduction in rCBF on the perimeter of the right lentiform nucleus. No correlations were found with clinical features or indices of pain threshold.

CONCLUSION: Our finding of a reduction in thalamic rCBF is consistent with findings of functional brain imaging studies of other chronic clinical pain syndromes, while our finding of reduced pontine tegmental rCBF is new. The pathophysiologic significance of these changes in FM remains to be elucidated.

III TREATMENT

RX, CONTROLLED DATA

PREGABALIN

A 14-week, randomized, double-blinded, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia.

Arnold LM, Russell IJ, Diri EW, Duan WR, Young, Jr, JP, Sharma U, Martin SA, Barrett JA, Haig G.

J Pain. 2008 Sep;9(9):792-805.

The purpose of the study was to assess the efficacy and safety of pregabalin monotherapy in patients with fibromyalgia in a randomized, double-blinded, placebo-controlled trial. After 1 week of single-blinded administration of placebo, 750 patients meeting American College of Rheumatology criteria for fibromyalgia were randomly assigned to pregabalin (300 mg/d, 450 mg/d, 600 mg/d) or placebo, administered twice daily for 14 weeks. The primary outcome variable was comparison of end point mean pain scores, derived from daily diary ratings of pain intensity (0 to 10 scale), between each of the pregabalin groups and the placebo group. If positive, additional primary efficacy parameters included the Patient Global Impression of Change (PGIC) and the Fibromyalgia Impact Questionnaire (FIQ) total score. Compared with placebo-treated patients, mean changes in pain scores at the end point in pregabalin-treated patients were significantly greater ($P < .001$: 300 mg/d, -0.71; 450 mg/d, -0.98; 600 mg/d, -1.00). Compared with placebo, significantly more pregabalin-treated patients reported improvement on PGIC ($P < .01$ for all 3 pregabalin doses) and significant improvements in total FIQ score for the 450 mg/d ($P = .004$) and the 600 mg/d ($P = .003$) doses. Compared with placebo, all 3 doses of pregabalin were associated with significant improvement in sleep. The most commonly reported pregabalin-related adverse events were dizziness and somnolence, which tended to be dose-related.

PERSPECTIVE: This randomized, placebo-controlled trial of 300, 450, and 600 mg/d of pregabalin monotherapy demonstrated that all 3 doses were efficacious for up to 14 weeks for the treatment of fibromyalgia and were well tolerated by most patients. These results provide evidence that pregabalin is an important treatment option for patients with fibromyalgia.

Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6-month, double-blind, placebo-controlled trial with pregabalin.

Crofford LJ, Mease PJ, Simpson SL, Young JP Jr, Martin SA, Haig GM, Sharma U.

Pain. 2008 Jun;136(3):419-31.

This was a multicenter, double-blind (DB), placebo-controlled, randomized discontinuation trial to evaluate the efficacy of pregabalin monotherapy for durability of effect on fibromyalgia (FM) pain. The trial included a 6-week open-label (OL) pregabalin-treatment period followed by 26-week DB treatment with placebo or pregabalin. Adults with FM and 40-mm score on 100-mm pain visual analog scale (VAS) were eligible.

During OL weeks 1-3, patients received escalating dosages of pregabalin to determine their optimal dosages. During OL weeks 4-6, patients received their optimal fixed dosages (300, 450, 600mg/d). To be randomized, patients must have had 50% decrease in pain VAS and a self-rating of "much" or "very much" improved on Patient Global Impression of Change (PGIC) at the end of OL. Double-blind treatment was with placebo or the patient's optimal fixed dosage of pregabalin. Primary outcome was time to loss of therapeutic response (LTR), defined as <30% reduction in pain (from OL baseline) or worsening of FM. A total of 1051 patients entered OL; 287 were randomized to placebo, 279 to pregabalin. Time to LTR was longer for pregabalin versus placebo ($P<.0001$). Kaplan-Meier estimates of time-to-event showed half the placebo group had LTR by Day 19; half the pregabalin group still had not lost response by trial end. At the end of DB, 174 (61%) placebo patients met LTR criteria versus 90 (32%) pregabalin patients.

Pregabalin was well tolerated, though 178 (17%) discontinued during OL for treatment-related adverse events (AE), and more pregabalin than placebo patients discontinued for AEs during DB. In those who respond, pregabalin demonstrated durability of effect for relieving FM pain.

DULOXETINE

Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: Results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial.

Russell IJ, Mease PJ, Smith TR, Kajdasz DK, Wohlreich MM, Detke MJ, Walker DJ, Chappell AS, Arnold LM.

Pain. 2008 Jun;136(3):432-44.

The primary objectives of this study were to assess the efficacy and safety of duloxetine for reducing pain severity in fibromyalgia patients with or without current major depressive disorder.

This was a 6-month, multicenter, randomized, double-blind, placebo-controlled study. In total, 520 patients meeting American College of Rheumatology criteria for fibromyalgia were randomly assigned to duloxetine (20 mg/day, 60 mg/day, or 120 mg/day) or placebo, administered once daily, for 6 months (after 3 months, the duloxetine 20-mg/day group titrated to 60 mg/day). The co-primary outcome measures were the Brief Pain Inventory (BPI) average pain severity score and Patient Global Impressions of Improvement (PGI-I) score. Safety was assessed via treatment-emergent adverse events, and changes in vital sign, laboratory, and ECG measures.

Compared with placebo-treated patients, those patients treated with duloxetine 120 mg/day improved significantly more on the co-primary outcome measures at 3 months (change in BPI score [-2.31 vs -1.39, P<0.001] and PGI-I [2.89 vs 3.39, P=0.004]) and at 6 months (change in BPI [-2.26 vs -1.43, P=0.003] and PGI-I [2.93 vs 3.37, P=0.012]). Compared with placebo, treatment with duloxetine 60 mg/day also significantly improved the co-primary measures at 3 months and BPI at 6 months. Duloxetine was efficacious in patients both with and without major depressive disorder. There were no clinically significant differences between treatment groups in changes in vital signs, laboratory measures, or ECG measures.

Study results demonstrated that duloxetine at doses of 60 mg/day and 120 mg/day appears to be safe and efficacious in patients with fibromyalgia.

A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder.

Arnold LM, Rosen A, Pritchett YL, D'Souza DN, Goldstein DJ, Iyengar S, Wernicke JF.

Pain. 2005 Dec 15;119(1-3):5-15.

This was a 12-week, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, in 354 female patients with primary fibromyalgia, with or without current major depressive disorder.

Patients (90% Caucasian; mean age, 49.6 years; 26% with current major depressive disorder) received duloxetine 60 mg once daily (QD) (N=118), duloxetine 60 mg twice daily (BID) (N=116), or placebo (N=120). The primary outcome was the Brief Pain Inventory average pain severity score. Response to treatment was defined as >or=30% reduction in this score.

Compared with placebo, both duloxetine-treated groups improved significantly more (P<0.001) on the Brief Pain Inventory average pain severity score. A significantly higher percentage of duloxetine-treated patients had a decrease of >or=30% in this score (duloxetine 60 mg QD (55%; P<0.001); duloxetine 60 mg BID (54%; P=0.002); placebo (33%). The treatment effect of duloxetine on pain reduction was independent of the effect on mood and the presence of major depressive disorder. Compared with patients on placebo, patients treated with duloxetine 60 mg QD or duloxetine 60 mg BID had significantly greater improvement in remaining Brief Pain Inventory pain severity and interference scores, Fibromyalgia Impact Questionnaire, Clinical Global Impression of Severity, Patient Global Impression of Improvement, and several quality-of-life measures. Both doses of duloxetine were safely administered and well tolerated.

In conclusion, both duloxetine 60 mg QD and duloxetine 60 mg BID were effective and safe in the treatment of fibromyalgia in female patients with or without major depressive disorder.

A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder.

Arnold LM, Lu Y, Crofford LJ, Wohlreich M, Detke MJ, Iyengar S, Goldstein DJ.

Arthritis Rheum. 2004 Sep;50(9):2974-84.

OBJECTIVE: To assess the efficacy and safety of duloxetine, a serotonin and norepinephrine reuptake inhibitor, in subjects with primary fibromyalgia, with or without current major depressive disorder.

METHODS: This study was a randomized, double-blind, placebo-controlled trial conducted in 18 outpatient research centers in the US. A total of 207 subjects meeting the American College of Rheumatology criteria for primary fibromyalgia were enrolled (89% female, 87% white, mean age 49 years, 38% with current major depressive disorder). After single-blind placebo treatment for 1 week, subjects were randomly assigned to receive duloxetine 60 mg twice a day (n = 104) or placebo (n = 103) for 12 weeks. Co-primary outcome measures were the Fibromyalgia Impact Questionnaire (FIQ) total score (score range 0-80, with 0 indicating no impact) and FIQ pain score (score range 0-10). Secondary outcome measures included mean tender point pain threshold, number of tender points, FIQ fatigue, tiredness on awakening, and stiffness scores, Clinical Global Impression of Severity (CGI-Severity) scale, Patient Global Impression of Improvement (PGI-Improvement) scale, Brief Pain Inventory (short form), Medical Outcomes Study Short Form 36, Quality of Life in Depression Scale, and Sheehan Disability Scale.

RESULTS: Compared with placebo-treated subjects, duloxetine-treated subjects improved significantly more (P = 0.027) on the FIQ total score, with a treatment difference of -5.53 (95% confidence interval -10.43, -0.63), but not significantly more on the FIQ pain score (P = 0.130). Compared with placebo-treated subjects, duloxetine-treated subjects had significantly greater reductions in Brief Pain Inventory average pain severity score (P = 0.008), Brief Pain Inventory average interference from pain score (P = 0.004), number of tender points (P = 0.002), and FIQ stiffness score (P = 0.048), and had significantly greater improvement in mean tender point pain threshold (P = 0.002), CGI-Severity (P = 0.048), PGI-Improvement (P = 0.033), and several quality-of-life measures. Duloxetine treatment improved fibromyalgia symptoms and pain severity regardless of baseline status of major depressive disorder. Compared with placebo-treated female subjects (n = 92), duloxetine-treated female subjects (n = 92) demonstrated significantly greater improvement on most efficacy measures, while duloxetine-treated male subjects (n = 12) failed to improve significantly on any efficacy measure. The treatment effect on significant pain reduction in female subjects was independent of the effect on mood or anxiety. Duloxetine was safely administered and well tolerated.

CONCLUSION: In this randomized, controlled, 12-week trial (with a 1-week placebo lead-in phase), duloxetine was an effective and safe treatment for many of the symptoms associated with fibromyalgia in subjects with or without major depressive disorder, particularly for women, who had significant improvement across most outcome measures.

MILNACIPRAN

Efficacy of milnacipran in patients with fibromyalgia.

Gendreau RM, Thorn MD, Gendreau JF, Kranzler JD, Ribeiro S, Gracely RH, Williams DA, Mease PJ, McLean SA, Clauw DJ.

J Rheumatol. 2005 Oct;32(10):1975-85.

OBJECTIVE: Fibromyalgia (FM) is a common musculoskeletal condition characterized by widespread pain, tenderness, and a variety of other somatic symptoms. Current treatments are modestly effective. Arguably, the best studied and most effective compounds are tricyclic antidepressants (TCA). Milnacipran, a nontricyclic compound that inhibits the reuptake of both serotonin and norepinephrine, may provide many of the beneficial effects of TCA with a superior side effect profile.

METHODS: One hundred twenty-five patients with FM were randomly assigned in a 3:3:2 ratio to receive milnacipran twice daily, milnacipran once daily, or placebo for 3 months in a double-blind dose-escalation trial; 92% of twice-daily and 81% of once-daily participants achieved dose escalation to the target milnacipran dose of 200 mg.

RESULTS: The primary endpoint was reduction of pain. Both the once- and twice-daily groups showed statistically significant improvements in pain, as well as improvements in global well be-

ing, fatigue, and other domains. Response rates for patients receiving milnacipran were equal in patients with and without comorbid depression, but placebo response rates were considerably higher in depressed patients, leading to significantly greater overall efficacy in the nondepressed group.

CONCLUSION: In this Phase II study, milnacipran led to statistically significant improvements in pain and other symptoms of FM. The effect sizes were equal to those previously found with TCA, and the drug was generally well tolerated.

PRAMIPEXOLE

A randomized, double-blind, placebo-controlled trial of pramipexole, a dopamine agonist, in patients with fibromyalgia receiving concomitant medications.

Holman AJ, Myers RR.

Arthritis Rheum. 2005 Aug;52(8):2495-505.

OBJECTIVE: To assess the efficacy and safety of pramipexole, a dopamine 3 receptor agonist, in patients with fibromyalgia.

METHODS: In this 14-week, single-center, double-blind, placebo-controlled, parallel-group, escalating-dose trial, 60 patients with fibromyalgia were randomized 2:1 (pramipexole:placebo) to receive 4.5 mg of pramipexole or placebo orally every evening. The primary outcome was improvement in the pain score (10-cm visual analog scale [VAS]) at 14 weeks. Secondary outcome measures were the Fibromyalgia Impact Questionnaire (FIQ), the Multidimensional Health Assessment Questionnaire (MDHAQ), the pain improvement scale, the tender point score, the 17-question Hamilton Depression Inventory (HAM-d), and the Beck Anxiety Index (BAI). Patients with comorbidities and disability were not excluded. Stable dosages of concomitant medications, including analgesics, were allowed.

RESULTS: Compared with the placebo group, patients receiving pramipexole experienced gradual and more significant improvement in measures of pain, fatigue, function, and global status. At 14 weeks, the VAS pain score decreased 36% in the pramipexole arm and 9% in the placebo arm (treatment difference -1.77 cm). Forty-two percent of patients receiving pramipexole and 14% of those receiving placebo achieved > or =50% decrease in pain. Secondary outcomes favoring pramipexole over placebo included the total FIQ score (treatment difference -9.57) and the percentages of improvement in function (22% versus 0%), fatigue (29% versus 7%), and global (38% versus 3%) scores on the MDHAQ. Compared with baseline, some outcomes showed a better trend for pramipexole treatment than for placebo, but failed to reach statistical significance, including improvement in the tender point score (51% versus 36%) and decreases in the MDHAQ psychiatric score (37% versus 28%), the BAI score (39% versus 27%), and the HAM-d score (29% versus 9%). No end points showed a better trend for the placebo arm. The most common adverse events associated with pramipexole were transient anxiety and weight loss. No patient withdrew from the study because of inefficacy or an adverse event related to pramipexole.

CONCLUSION: In a subset of patients with fibromyalgia, approximately 50% of whom required narcotic analgesia and/or were disabled, treatment with pramipexole improved scores on assessments of pain, fatigue, function, and global status, and was safe and well-tolerated.

Safety and efficacy of the dopamine agonist, pramipexole, on pain score for refractory fibromyalgia.

Holman AJ.

Arthritis Rheum. 2000;43 Suppl:A1599.

A retrospective chart review of pramipexole for 166 patients with FM revealed encouraging results. Patients added pramipexole to their best regimen to date and increased by 0.125-0.25 mg weekly, similar to its use for RLS. For those who continued pramipexole for more than 7 days (n = 127), the tenderness score decreased 54% at a mean dose of 1.55 mg qhs for 2-12 months (mean 4 mo). Inefficacy correlated with seeing a psychiatrist ($p < 0.05$, chi-square test), but not with age, pretreatment tenderness score, or disability. Twenty-three percent quickly discontinued for non-serious intolerances, usually nausea or anxiety. There were no serious adverse events even with doses up to 6.0 mg qhs. By ITT analysis (n = 166), 58% achieved = 50% decrease in tenderness score, even though 22 (13%) discontinued pramipexole before they could be evaluated. Other measures of FM activity were not collected. Further, for 19 patients unresponsive or intolerant to pramipexole, ITT analysis showed that 74% achieved = 50% decreased ten-

derness score after adding the other known dopamine 3-specific agonist, ropinirole, for a mean of 4 months. Thirteen of 19 discontinued for nonserious intolerances, especially nausea.

SODIUM OXYBATE

A randomized, double-blind, placebo-controlled, parallel-group, multi-center trial comparing the effects of orally administered Xyrem® (Sodium Oxybate) with placebo for the treatment of fibromyalgia.

Wood PB.

Pain Medicine. 2006;7(2):170–209.

INTRODUCTION: The purpose of this study was to evaluate the efficacy of 2 doses of sodium oxybate for the treatment of primary fibromyalgia.

METHODS: The study was an 8-week randomized, placebo-controlled, double blind trial comparing 2 doses of sodium oxybate (4.5g/day, n=58; 6.0g/day, n=66) with placebo (n=64) for the treatment of primary fibromyalgia. Primary outcome measure was a composite endpoint of visual analog scale (VAS) for pain, Fibromyalgia Impact Questionnaire (FIQ) total score, and Patient Global Assessment of Change (PGIC). Secondary measures included Tender Point Count (TPC), Tender Point Index (TPI) and as well as measures of sleep efficiency and well-being. Subject screening included polysomnogram to rule out obstructive sleep apnea or parasomnias and to establish baseline sleep parameters. Treatment group differences were evaluated using an ANOVA method and the Fisher's exact test, using an intention to treat analysis. The protocol was approved by local institutional review boards and all subjects signed informed consent prior to evaluation.

RESULTS: Both doses of sodium oxybate resulted in significantly greater improvement in pain VAS (4.5g/day, p=0.04; 6.0g/day, p=0.03), FIQ (4.5g/day, p=0.007; 6.0g/day, p=0.02), and PGIC (4.5g/day, p=0.03; 6.0g/day, p=0.11). Subjects receiving sodium oxybate also demonstrated a strong trend towards significant improvement in TPC (4.5g/day, p=0.08; 6.0g/day, p=0.05) and TPI (4.5g/day, p=0.06; 6.0g/day, p=0.09). Sodium oxybate also resulted in significantly greater improvement in nearly all secondary and health outcome measures, with significantly more subjects receiving active medication classified as responders in comparison with placebo (4.5g/day, p=0.005; 6.0g/day, p=0.05). No significant difference was demonstrated between active treatments and placebo regarding total adverse outcomes (p=0.14). Subjects receiving sodium oxybate 6.0g/day reported more nausea, vomiting, headache and dizziness as compared to placebo or sodium oxybate 4.5g/day.

CONCLUSIONS: Sodium oxybate is a well-tolerated and efficacious treatment for primary fibromyalgia at doses of 4.5g/day and 6.0g/day.

The effects of sodium oxybate on clinical symptoms and sleep patterns in patients with fibromyalgia.

Scharf MB, Baumann M, Berkowitz DV.

J Rheumatol. 2003 May;30(5):1070-4.

OBJECTIVE: Fibromyalgia (FM) is associated with the sleep phenomenon of alpha intrusion, and with low growth hormone secretion. Sodium oxybate has been shown to increase both slow-wave sleep and growth hormone levels. This double blind, randomized, placebo controlled crossover trial was conducted to evaluate the effects of sodium oxybate on the subjective symptoms of pain, fatigue, and sleep quality and the objective polysomnographic (PSG) sleep variables of alpha intrusion, slow-wave (stage 3/4) sleep, and sleep efficiency in patients with FM.

METHODS: Patients received either 6.0 g/day sodium oxybate or placebo for 1 month, with an intervening 2 week washout period. Efficacy measures included PSG evaluations, tender point index (TPI), and subjective measurements from daily diary entries. Safety measures included clinical laboratory values, vital signs, and adverse events.

RESULTS: Twenty-four female patients were included in the study; 18 completed the trial. TPI was decreased from baseline by 8.5, compared with an increase of 0.4 for placebo ($p = 0.0079$). Six of the 7 pain/fatigue scores (overall pain, pain at rest, pain during movement, end of day fatigue, overall fatigue, and morning fatigue) were relieved by 29% to 33% with sodium oxybate, compared with 6% to 10% relief with placebo ($p < 0.005$). Alpha intrusion, sleep latency, and rapid-eye-movement sleep were significantly decreased, while slow-wave (stage 3/4) sleep was significantly increased, compared with placebo ($p < 0.005$). Two of the 5 subjective sleep related variables were significantly different from placebo: morning alertness (improved by 18% with sodium oxybate, compared with 2% for

placebo; p = 0.0033) and quality of sleep (improved by 33% and 10%, respectively; p = 0.0003).

CONCLUSION: Sodium oxybate effectively reduced the symptoms of pain and fatigue in patients with FM, and dramatically reduced the sleep abnormalities (alpha intrusion and decreased slow-wave sleep) associated with the nonrestorative sleep characteristic of this disorder.

GABAPENTIN

Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial.

Arnold LM, Goldenberg DL, Stanford SB, Lalonde JK, Sandhu HS, Keck PE Jr, Welge JA, Bishop F, Stanford KE, Hess EV, Hudson JI.

Arthritis Rheum. 2007 Apr;56(4):1336-44.

OBJECTIVE: To assess the efficacy and safety of gabapentin in patients with fibromyalgia.

METHODS: A 12-week, randomized, double-blind study was designed to compare gabapentin (1,200-2,400 mg/day) (n=75 patients) with placebo (n=75 patients) for efficacy and safety in treating pain associated with fibromyalgia. The primary outcome measure was the Brief Pain Inventory (BPI) average pain severity score (range 0-10, where 0=no pain and 10=pain as bad as you can imagine). Response to treatment was defined as a reduction of >or=30% in this score. The primary analysis of efficacy for continuous variables was a longitudinal analysis of the intent-to-treat sample, with treatment-by-time interaction as the measure of effect.

RESULTS: Gabapentin-treated patients displayed a significantly greater improvement in the BPI average pain severity score (P=0.015; estimated difference between groups at week 12=-0.92 [95% confidence interval -1.75, -0.71]). A significantly greater proportion of gabapentin-treated patients compared with placebo-treated patients achieved response at end point (51% versus 31%; P=0.014). Gabapentin compared with placebo also significantly improved the BPI average pain interference score, the Fibromyalgia Impact Questionnaire total score, the Clinical Global Impression of Severity, the Patient Global Impression of Improvement, the Medical Outcomes Study (MOS) Sleep Problems Index, and the MOS Short Form 36 vitality score, but not the mean tender point pain threshold or the Montgomery Asberg Depression Rating Scale. Gabapentin was generally well tolerated.

CONCLUSION: Gabapentin (1,200-2,400 mg/day) is safe and efficacious for the treatment of pain and other symptoms associated with fibromyalgia.

TRAMADOL

Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study.

Bennett RM, Kamin M, Karim R, Rosenthal N.

Am J Med. 2003 May;114(7):537-45.

PURPOSE: To evaluate the efficacy and safety of a combination analgesic tablet (37.5 mg tramadol/325 mg acetaminophen) for the treatment of fibromyalgia pain.

METHODS: This 91-day, multicenter, double-blind, randomized, placebo-controlled study compared tramadol/acetaminophen combination tablets with placebo. The primary outcome variable was cumulative time to discontinuation (Kaplan-Meier analysis). Secondary measures at the end of the study included pain, pain relief, total tender points, myalgia, health status, and Fibromyalgia Impact Questionnaire scores.

RESULTS: Of the 315 subjects who were enrolled in the study, 313 (294 women [94%], mean [+/- SD] age, 50 +/- 10 years) completed at least one postrandomization efficacy assessment (tramadol/acetaminophen: n = 156; placebo: n = 157). Discontinuation of treatment for any reason was less common in those treated with tramadol/acetaminophen compared with placebo (48% vs. 62%, P = 0.004). Tramadol/acetaminophen-treated subjects also had significantly less pain at the end of the study (53 +/- 32 vs. 65 +/- 29 on a visual analog scale of 0 to 100, P <0.001), and better pain relief (1.7 +/- 1.4 vs. 0.8 +/- 1.3 on a scale of -1 to 4, P <0.001) and Fibromyalgia Impact Questionnaire scores (P = 0.008). Indexes of physical functioning, role-physical, body pain, health transition, and physical component summary all improved significantly in the tramadol/acetaminophen-treated subjects. Discontinuation due to adverse events occurred in 19% (n = 29) of tramadol/acetaminophen-treated subjects and 12% (n = 18) of placebo-treated subjects (P = 0.09).

The mean dose of tramadol/acetaminophen was 4.0 +/- 1.8 tablets per day.

CONCLUSION: A tramadol/acetaminophen combination tablet was effective for the treatment of fibromyalgia pain without any serious adverse effects.

FLUOXETINE/AMITRIPTYLINE

A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia.

Goldenberg D, Mayskiy M, Mossey C, Ruthazer R, Schmid C.

Arthritis Rheum. 1996 Nov;39(11):1852-9.

OBJECTIVE: To study the effect of fluoxetine (FL) and amitriptyline (AM), alone and in combination, in patients with fibromyalgia (FM).

METHODS: Nineteen patients with FM completed a randomized, double-blind crossover study, which consisted of 4 6-week trials of FL (20 mg), AM (25 mg), a combination of FL and AM, or placebo. Patients were evaluated on the first and last day of each trial period. Outcome measures included a tender point score, the Fibromyalgia Impact Questionnaire (FIQ), the Beck Depression Inventory (BDI) scale, and visual analog scales (VAS) for global well-being (1 completed by the physician and 1 by the patient), pain, sleep trouble, fatigue, and feeling refreshed upon awakening.

RESULTS: Both FL and AM were associated with significantly improved scores on the FIQ and on the VAS for pain, global well-being, and sleep disturbances. When combined, the 2 treatments worked better than either medication alone. Similar, but nonsignificant, improvement occurred in the BDI scale, the physician global VAS, and the VAS for fatigue and feeling refreshed upon awakening. Trends were less clear for the tender point score.

CONCLUSION: Both FL and AM are effective treatments for FM, and they work better in combination than either medication alone.

CYCLOBENZAPRINE

Treatment of fibromyalgia with cyclobenzaprine: A meta-analysis.

Tofferi JK, Jackson JL, O'Malley PG.

Arthritis Rheum. 2004 Feb 15;51(1):9-13.

OBJECTIVE: To systematically review the effectiveness of cyclobenzaprine in the treatment of fibromyalgia.

METHODS: Articles describing randomized, placebo-controlled trials of cyclobenzaprine in people with fibromyalgia were obtained from Medline, EMBase, Psyclit, the Cochrane Library, and Federal Research in Progress Database. Unpublished literature and bibliographies were also reviewed. Outcomes, including global improvement, treatment effects on pain, fatigue, sleep, and tender points over time, were abstracted.

RESULTS: Five randomized, placebo-controlled trials were identified. The odds ratio for global improvement with therapy was 3.0 (95% confidence interval [95% CI] 1.6-5.6) with a pooled risk difference of 0.21 (95% CI 0.09-0.34), which calculates to 4.8 (95% CI 3.0-11) individuals needing treatment for 1 patient to experience symptom improvement. Pain improved early on, but there was no improvement in fatigue or tender points at any time.

CONCLUSION: Cyclobenzaprine-treated patients were 3 times as likely to report overall improvement and to report moderate reductions in individual symptoms, particularly sleep.

GROWTH HORMONE/PYRIDOSTIGMINE

A combination of 6 months of treatment with pyridostigmine and tri-weekly exercise fails to improve insulin-like growth factor-I levels in fibromyalgia, despite improvement in the acute growth hormone response to exercise.

Jones KD, Deodhar AA, Burckhardt CS, Perrin NA, Hanson GC, Bennett RM.

J Rheumatol. 2007 May;34(5):1103-11.

OBJECTIVE: People with fibromyalgia (FM) often have low insulin-like growth factor-I (IGF-I) levels and a suboptimal growth hormone (GH) response to acute exercise. As previous work had demonstrated a normalization of the acute GH response to exercise with the use of pyridostigmine (PYD), we tested the hypothesis that 6 months of PYD therapy plus supervised exercise would increase IGF-I levels.

METHODS: Subjects with primary FM were randomized into 4 groups: (1) PYD/exercise; (2) PYD/diet recall; (3) placebo/exercise; and (4) placebo/diet recall. The dosing of PYD was 60 mg tid for 6 months. Resting IGF-I levels were measured at baseline and after 6 months of treatment. In addition the acute GH response to exercise at VO2 max was measured at baseline and after treatment.

RESULTS: A total of 165 FM subjects (mean age 49.5 yrs, 5 male) were entered and 154 (93.3%) completed the study. Six months of therapy (PYD plus exercise or exercise alone) failed to improve the IGF-I levels. The use of PYD 1 hour prior to exercise improved the acute GH response (4.54 ng/dl) compared to placebo (1.74 ng/dl) ($p = 0.001$) at the end of the 6-month trial. The acute GH response to exercise at baseline did not correlate with IGF-I, age, depression, medications, estrogen status, or obesity.

CONCLUSION: A combination of triweekly supervised exercise plus the daily use of PYD for 6 months failed to increase IGF-I levels in patients with FM, despite the confirmation that PYD normalizes the acute GH response to strenuous aerobic exercise.

A randomized, double-blind, placebo-controlled study of growth hormone in the treatment of fibromyalgia.

Bennett RM, Clark SC, Walczyk J.

Am J Med. 1998 Mar;104(3):227-31.

PURPOSE: The cause of fibromyalgia (FM) is not known. Low levels of insulin-like growth factor 1 (IGF-1), a surrogate marker for low growth hormone (GH) secretion, occur in about one third of patients who have many clinical features of growth hormone deficiency, such as diminished energy, dysphoria, impaired cognition, poor general health, reduced exercise capacity, muscle weakness, and cold intolerance. To determine whether suboptimal growth hormone production could be relevant to the symptomatology of fibromyalgia, we assessed the clinical effects of treatment with growth hormone.

METHODS: Fifty women with fibromyalgia and low IGF-1 levels were enrolled in a randomized, placebo-controlled, double-blind study of 9 months' duration. They gave themselves daily subcutaneous injections of growth hormone or placebo. Two outcome measures--the Fibromyalgia Impact Questionnaire and the number of fibromyalgia tender points-were evaluated at 3-monthly intervals by a blinded investigator. An unblinded investigator reviewed the IGF-1 results monthly and adjusted the growth hormone dose to achieve an IGF-1 level of about 250 ng/mL.

RESULTS: Daily growth hormone injections resulted in a prompt and sustained increase in IGF-1 levels. The treatment (n=22) group showed a significant improvement over the placebo group (n=23) at 9 months in both the Fibromyalgia Impact Questionnaire score ($P < 0.04$) and the tender point score ($P < 0.03$). Fifteen subjects in the growth hormone group and 6 subjects in the control group experienced a global improvement ($P < 0.02$). There was a delayed response to therapy, with most patients experiencing improvement at the 6-month mark. After discontinuing growth hormone, patients experienced a worsening of symptoms. Carpal tunnel symptoms were more prevalent in the growth hormone group (7 versus 1); no other adverse events were more common in this group.

CONCLUSIONS: Women with fibromyalgia and low IGF-1 levels experienced an improvement in their overall symptomatology and number of tender points after 9 months of daily growth hormone therapy. This suggests that a secondary growth hormone deficiency may be responsible for some of the symptoms of fibromyalgia.

SYNTHETIC CANNABOIDS

Nabilone for the treatment of pain in fibromyalgia.

Skrabek RQ, Galimova L, Ethans K, Perry D.

J Pain. 2008 Feb;9(2):164-73.

A randomized, double-blind, placebo-controlled trial was conducted to determine the benefit of nabilone in pain management and quality of life improvement in 40 patients with fibromyalgia. After a baseline assessment, subjects were titrated up on nabilone, from 0.5 mg PO at bedtime to 1 mg BID over 4 weeks or received a corresponding placebo. At the 2- and 4-week visits, the primary outcome measure, visual analog scale (VAS) for pain, and the secondary outcome measures, number of tender points, the average tender point pain threshold, and the Fibromyalgia Impact Questionnaire (FIQ), were evaluated.

After a 4-week washout period, subjects returned for reassessment of the outcome measures. There were no significant differences in population demographics between groups at baseline. There were significant decreases in the VAS (-2.04, $P < .02$), FIQ (-12.07, $P < .02$), and anxiety (-1.67, $P < .02$) in the nabilone treated group at 4 weeks. There were no significant improvements in the placebo group. The treatment group experienced more side effects per person at 2 and 4 weeks (1.58, $P < .02$ and 1.54, $P < .05$), respectively. Nabilone appears to be a beneficial, well-tolerated treatment option for fibromyalgia patients, with significant benefits in pain relief and functional improvement.

PERSPECTIVE: To our knowledge, this is the first randomized, controlled trial to assess the benefit of nabilone, a synthetic cannabinoid, on pain reduction and quality of life improvement in patients with fibromyalgia. As nabilone improved symptoms and was well-tolerated, it may be a useful adjunct for pain management in fibromyalgia.

RX, UNCONTROLLED DATA

PINDOLOL

Open trial of pindolol in the treatment of fibromyalgia.

Wood PB, Kablinger AS, Caldito GS.

Ann Pharmacother. 2005 Nov;39(11):1812-6.

BACKGROUND: Evidence suggests that fibromyalgia is related to both chronic sympathetic hyperactivity and decreased levels of serotonin.

OBJECTIVE: To examine the efficacy of pindolol, a mixed serotonin (5-HT)(1A) presynaptic autoreceptor/beta-adrenergic receptor antagonist, in the treatment of fibromyalgia.

METHODS: An open trial was conducted using 20 female patients who met the American College of Rheumatology criteria for fibromyalgia. Treatment was initiated with pindolol 7.5 mg/day and titrated to a maximum dose of 15 mg/day for a total of 90 days. Primary outcome measures were tender point analysis and the Fibromyalgia Impact Questionnaire (FIQ). Anxiety and depression were measured with the Hamilton Depression and Anxiety Scales and Beck Depression Inventory.

RESULTS: There was significant improvement in primary outcome measures, including Tender Point Count (mean +/- SD, 16.3 +/- 2.2 vs 12.3 +/- 5.0; $F = 8.9$; $p < 0.001$), Tender Point Score (24.4 +/- 5.7 vs 17.5 +/- 9.4; $F = 7.8$; $p < 0.001$), and FIQ (45.3 +/- 10.8 vs 35.0 +/- 15.0; $F = 5.6$; $p < 0.005$). The depression and anxiety scores did not change significantly among women who completed the study, while the impact on cardiovascular parameters was clinically insignificant.

CONCLUSIONS: While the current results are encouraging, further studies are needed to determine whether pindolol might be effective in the treatment of fibromyalgia. Limitations of this study include small group size and lack of placebo control.

VENLAFAXINE

Venlafaxine treatment of fibromyalgia.

Sayar K, Aksu G, Ak I, Tosun M.

Ann Pharmacother. 2003 Nov;37(11):1561-5.

BACKGROUND: Although the pathophysiology of fibromyalgia is unknown, central monoaminergic transmission may play a role. Antidepressants have proved to be successful in alleviating symptoms of fibromyalgia. Medications that act on multiple neurotransmitters may be more effective in symptom management.

OBJECTIVE: To assess the efficacy of venlafaxine, a potent inhibitor of both norepinephrine and serotonin reuptake, in the treatment of patients with fibromyalgia.

METHODS: Fifteen patients with fibromyalgia were assessed prior to and after treatment with fixed-dose venlafaxine 75 mg/d. Before initiation of pharmacotherapy, patients were interviewed with the Structured Clinical Interview for Axis I disorders in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. The study lasted for 12 weeks, and patients were evaluated in weeks 6 and 12. The primary outcome measures were the Fibromyalgia Impact Questionnaire (FIQ) total score and pain score. The anxiety and depression levels of the patients were measured with the Beck Depression, the Beck Anxiety, the Hamilton Anxiety, and the Hamilton Depression scales.

RESULTS: There was a significant improvement in the mean intensity of pain ($F = 14.3$; $p = 0.0001$) and in the disability caused by fibromyalgia ($F = 42.7$; $p = 0.0001$) from baseline to week 12 of treatment. The depression and anxiety scores also decreased significantly from baseline to week 12. The improvement in the FIQ scores did not correlate with the decrease of scores in both patient- and physician-rated depression and anxiety inventories. Change in pain scores also was not correlated with the change in depression and anxiety scores.

CONCLUSIONS: Venlafaxine was quite promising in alleviating the pain and disability associated with fibromyalgia. This effect seems to be independent of its anxiolytic and antidepressant properties. Blockade of both norepinephrine and serotonin reuptake might be more effective than blockade of either neurotransmitter alone in the treatment of fibromyalgia.

OVER-THE-COUNTER MEDICATIONS

ACETYL L-CARNITINE

Double-blind, multicenter trial comparing acetyl l-carnitine with placebo in the treatment of fibromyalgia patients.

Rossini M, Di Munno O, Valentini G, Bianchi G, Biasi G, Cacace E, Malesci D, La Montagna G, Viapiana O, Adami S.

Clin Exp Rheumatol. 2007 Mar-Apr;25(2):182-8.

OBJECTIVE: Fibromyalgia (FMS) is a chronic syndrome characterized by widespread pain, troubled sleep, disturbed mood, and fatigue. Several analgesic strategies have been evaluated but the results are moderate and inconsistent. Antidepressant agents are now considered the treatment of choice in most patients. It has been recently suggested that FMS may be associated with metabolic alterations including a deficit of carnitine. In this multicenter randomized clinical trial we evaluated the efficacy of acetyl L-carnitine (LAC) in patients with overt FMS.

METHODS: One hundred and two patients meeting the American College of Rheumatology criteria for FMS were randomized into the study. The treatment consisted of 2 capsules/day of 500 mg LAC or placebo plus one intramuscular (i.m.) injection of either 500 mg LAC or placebo for 2 weeks. During the following 8 weeks the patients took 3 capsules daily containing either 500 mg LAC or placebo. The patients were seen during treatment after 2 (visit 3), 6 (visit 4) and 10 weeks (visit 5). The patients were also visited 4 weeks after treatment discontinuation (follow-up visit). Outcome measures included the number of positive tender points, the sum of pain threshold (kg/cm2 or "total myalgic score"), the Short Form 36 (SF36), a 100 mm visual analog scale (VAS) for self-perceived stiffness, fatigue, tiredness on awakening, sleep, work status, depression, and muscular-skeletal pain, and the Hamilton depression scale.

RESULTS: The "total myalgic score" and the number of positive tender points declined significantly and equally in both groups until the 6th week of treatment. At the 10th week both parameters remained unchanged in the placebo group but they continued to improve in the LAC group with a sta-

tistically significant between-group difference. Most VAS scores significantly improved in both groups. A statistically significant between-group difference was observed for depression and musculo-skeletal pain. Significantly larger improvements in SF36 questionnaire were observed in LAC than in placebo group for most parameters. Treatment was well-tolerated.

CONCLUSION: Although this experience deserves further studies, these results indicate that LAC may be of benefit in patients with FMS, providing improvement in pain as well as the general and mental health of these patients.

MELATONIN

The effect of melatonin in patients with fibromyalgia: a pilot study.

Citera G, Arias MA, Maldonado-Cocco JA, Lázaro MA, Rosemffet MG, Brusco LI, Scheines EJ, Cardinalli DP.

Clin Rheumatol. 2000;19(1):9-13.

The aim of the study was to determine the possible effect of melatonin treatment on disturbed sleep, fatigue and pain symptoms observed in fibromyalgia (FM) patients.

Twenty-one consecutive patients with FM were included in an open 4-week-duration pilot study. Before and after treatment with melatonin 3 mg at bedtime, patients were evaluated using tender point count by palpation of 18 classic anatomical regions, pain score in four predesignated areas, pain severity on a 10 cm visual analogue scale (VAS), sleep disturbances, fatigue, depression, anxiety, and patient and physician global assessments, also by a VAS. Urine 6-sulphatoxymelatonin levels (aMT-6S) were measured in the patients and 20 age- and sex-matched controls.

Nineteen patients completed the study. One patient withdrew because of migraine and another was lost to follow-up. At day 30, median values for the tender point count and severity of pain at selected points, patient and physician global assessments and VAS for sleep significantly improved with melatonin treatment. Other variables improved but did not reach statistical significance. Adverse events were mild and transient. Lower levels of aMT-6S were found in FM patients compared with normal median controls (+/-SD, 9.16 +/- 7.9 microg/24 h vs 16.8 +/- 12.8 microg/24 h) ($p = 0.06$).

Although this is an open study, our preliminary results suggest that melatonin can be an alternative and safe treatment for patients with FM. Double-blind placebo controlled studies are needed.

COMPLEMENTARY AND ALTERNATIVE MEDICINE THERAPIES

CRANIAL ELECTROTHERAPY

The effect of cranial electrotherapy stimulation (CES) on pain associated with fibromyalgia.

Cork RC, Wood PB, Ming N, Shepherd C, Eddy J, Price L.

The Internet Journal of Anesthesiology. 2004;8(2).

Subjective pain intensity was the primary measured variable in a double-blind crossover study examining the effect of cranial electrotherapy stimulation (CES) on the pain associated with fibromyalgia. Initially, 39 patients were randomly allocated to CES and 35 patients were allocated to a sham group. Measurements taken at baseline and after three weeks included pain intensity, McGill Pain Score, tenderpoint score, profile of mood states, and Oswestry Score.

Three weeks after crossover, measurements were repeated. Significant CES effects were identified, revealing an improvement in pain intensity, McGill Score, tenderpoint score, and profile of mood states ($p<0.05$). However, no significant effect was observed on Oswestry Score, which is a score identifying functional effects of pain.

This study reveals that CES could play a significant role in the treatment of pain associated with fibromyalgia; however, the long-term effects on disability remain to be studied.

The treatment of fibromyalgia with cranial electrotherapy stimulation.

Lichtbroun AS, Raicer MM, Smith RB.

J Clin Rheumatol. 2001 Apr;7(2):72-8.

In cranial electrotherapy stimulation (CES), microcurrent levels of electrical stimulation are passed across the head via electrodes clipped to the ear lobes. After successful clinical use of CES with fibromyalgia patients in our clinic, it was decided to test these results with a double-blind, placebo-controlled study in which 60 randomly assigned patients were given 3 weeks of 1-hour-daily CES treatments, sham CES treatments, or were held as wait-in-line controls for any placebo effect in the sham-treated patients.

Treated patients showed a 28% improvement in tender point scores, and a 27% improvement in self-rated scores of general pain level. The number of subjects rating their quality of sleep as poor dropped from 60% at the beginning of the study to 5%. In addition, there were significant gains in the self-rated feelings of well-being and quality of life, plus gains in six stress-related psychological test measures. No placebo effect was found among the sham-treated controls. A theoretical role of CES in affecting the brain's pain message mechanisms and/or neurohormonal control systems is discussed.

It is concluded that CES is as effective as the drug therapies in several trials, with no negative side effects, and deserves further consideration as an additional agent for the treatment of fibromyalgia.

HEART RATE VARIABILITY BIOFEEDBACK

A pilot study of the efficacy of heart rate variability (HRV) biofeedback in patients with fibromyalgia.

Hassett AL, Radvanski DC, Vaschillo EG, Vaschillo B, Sigal LH, Karavidas MK, Buyske S, Lehrer PM.

Appl Psychophysiol Biofeedback. 2007 Mar; 32(1):1-10.

Fibromyalgia (FM) is a non-inflammatory rheumatologic disorder characterized by musculoskeletal pain, fatigue, depression, cognitive dysfunction and sleep disturbance. Research suggests that autonomic dysfunction may account for some of the symptomatology of FM. An open label trial of biofeedback training was conducted to manipulate suboptimal heart rate variability (HRV), a key marker of autonomic dysfunction.

METHODS: Twelve women ages 18-60 with FM completed 10 weekly sessions of HRV biofeedback. They were taught to breathe at their resonant frequency (RF) and asked to practice twice daily. At sessions 1, 10 and 3-month follow-up, physiological and questionnaire data were collected.

RESULTS: There were clinically significant decreases in depression and pain and improvement in functioning from Session 1 to a 3-month follow-up. For depression, the improvement occurred by Session 10. HRV and blood pressure variability (BPV) increased during biofeedback tasks. HRV increased from Sessions 1-10, while BPV decreased from Session 1 to the 3 month follow-up.

CONCLUSIONS: These data suggest that HRV biofeedback may be a useful treatment for FM, perhaps mediated by autonomic changes. While HRV effects were immediate, blood pressure, baroreflex, and therapeutic effects were delayed. This is consistent with data on the relationship among stress, HPA axis activity, and brain function.

EXERCISE

Exercise-based motivational interviewing for female patients with fibromyalgia: a case series.

Ang D, Kesavalu R, Lydon JR, Lane KA, Bigatti S.

Clin Rheumatol. 2007 Nov;26(11):1843-9.

The objective of the study is to determine the effects of motivational interviewing (MI), a novel technique of behavioral counseling to promote exercise, on pain and physical function in patients with fibromyalgia (FMS).

Patients who met the American College of Rheumatology criteria for FMS and had a visual analog pain score of > or =6 were enrolled in a single group intervention pilot study. Participants received two supervised exercise sessions and an exercise prescription. Thereafter, six exercise-based MI phone calls were made over a 10-week period. Assessments were done at baseline, week 12 (immediate post-intervention) and week 30 (follow-up). The primary endpoints were changes from baseline in the fibromyalgia impact questionnaire (FIQ)-pain

and physical impairment at week 30. Secondary measures were brief pain inventory (BPI)-pain severity and BPI-pain interference, the number of exercise minutes (NEM) per week, and the arthritis impact measurement scale (AIMS)-depression.

The 19 enrolled female participants had a mean age of 52.2 +/- 9.1 years, mean disease duration of 7.5 +/- 5.0 years, and a mean FIQ-pain score of 7.7 +/- 1.4. By week 30, there was significant improvement in both FIQ-pain (-2.6 +/- 2.6, $p < 0.001$) and FIQ-physical impairment (-1.3 +/- 2.1, $p = 0.01$). Likewise, BPI-pain severity and pain interference were reduced by -2.4 +/- 2.1 ($p < 0.001$) and -2.4 +/- 2.0 ($p < 0.001$), respectively. While the median NEM per week increased from 0 to 32 min ($p = 0.001$) at week 30, AIMS-depression score was unchanged.

In this pilot study, we conclude that telephone-delivered MI to promote exercise was associated with an improvement in patient's level of pain and physical impairment.

This publication contains abstracts assembled by the National Fibromyalgia Association in October 2008 for educational and research purposes. The information contained herein is intended for healthcare professionals and researchers, and is part of the National Fibromyalgia Association's endeavor to increase awareness and aid in the development of effective treatment options for patients with fibromyalgia.

www.FibromyalgiaHCP.org

The National Fibromyalgia Association is a nonprofit 501(c)(3) organization whose mission is to develop and execute programs dedicated to improving the quality of life for people affected by fibromyalgia.

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