

FIBROMYALGIA: ABSTRACTS FROM SELECTED JOURNAL ARTICLES, 2000

The abstracts in this collection are intended to provide health professionals and patients with a convenient overview of trends in research on fibromyalgia published in medical journals in the year 2000. The studies were selected from the extensive literature on fibromyalgia so as to cover a wide range of subjects in limited space. The abstracts are arranged in alphabetical order by lead author. Similar collections of abstracts published in 1999 and 2001 can be found on the website of the National Fibromyalgia Partnership: www.fmpartnership.org.

Aaron LA, Burke MM, Buchwald D

Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder

BACKGROUND: Patients with chronic fatigue syndrome (CFS), fibromyalgia (FM), and temporomandibular disorder (TMD) share many clinical illness features such as myalgia, fatigue, sleep disturbances, and impairment in ability to perform activities of daily living as a consequence of these symptoms. A growing literature suggests that a variety of co-morbid illnesses also may commonly coexist in these patients, including irritable bowel syndrome, chronic tension-type headache, and interstitial cystitis. **OBJECTIVE:** To describe the frequency of 10 clinical conditions among patients with CFS, FM, and TMD compared with healthy controls with respect to past diagnoses, degree to which they manifested symptoms for each condition as determined by expert-based criteria, and published diagnostic criteria. **METHODS:** Patients diagnosed as having CFS, FM, and TMD by their physicians were recruited from hospital-based clinics. Healthy control subjects from a dermatology clinic were enrolled as a comparison group. All subjects completed a 138-item symptom checklist and underwent a brief physical examination performed by the project physicians. **RESULTS:** With little exception, patients reported few past diagnoses of the 10 clinical conditions beyond their referring diagnosis of CFS, FM, or TMD. In contrast, patients were more likely than controls to meet lifetime symptom and diagnostic criteria for many of the conditions, including CFS, FM, irritable bowel syndrome, multiple chemical sensitivities, and headache. Lifetime rates of irritable bowel syndrome were particularly striking in the patient groups (CFS, 92%; FM, 77%; TMD, 64%) compared with controls (18%) ($p < .001$). Individual symptom analysis revealed that patients with CFS, FM, and TMD share common symptoms, including generalized pain sensitivity, sleep and concentration difficulties, bowel complaints, and headache. However, several symptoms also distinguished the patient groups. **CONCLUSIONS:** This study provides preliminary evidence that

patients with CFS, FM, and TMD share key symptoms. It also is apparent that other localized and systemic conditions may frequently co-occur with CFS, FM, and TMD. Future research that seeks to identify the temporal relationships and other pathophysiologic mechanism(s) linking CFS, FM, and TMD will likely advance our understanding and treatment of these chronic, recurrent conditions. *Arch Intern Med* 2000 Jan 24; 160(2):221-7

Anderberg UM, Marteinsdottir I, von Knorring L

Citalopram in patients with fibromyalgia--a randomized, double-blind, placebo-controlled study

The effect of the selective serotonin reuptake inhibitor citalopram was studied in a randomized, double-blind, placebo-controlled, 4-month trial in patients with the fibromyalgia syndrome (FMS) who all fulfilled the American College of Rheumatology criteria. The citalopram doses varied between 20-40 mg daily. Forty female patients, 21 patients in the citalopram and 19 in the placebo group, participated. Assessment of pain, depressive symptoms and physical functioning were made using Visual Analogue Scales (VAS), the Montgomery Asberg Depression Rating Scale (MADRS) and the Fibrositis Impact Questionnaire (FIQ). In the global judgment of improvement, no significant changes were found between the citalopram and placebo groups as concerns pain or well-being, either in the Intention to Treat (ITT) analysis or in the completer analysis. However, among the completers, it was a tendency that more patients in the citalopram group (52.9%) were improved as compared to the placebo group (22.2%) concerning well-being. Furthermore, the results indicated that treatment with citalopram had a significant effect on pain on the VAS after 2 months of treatment compared to baseline. After 4 months, however, the effect had diminished. Measured with the FIQ, significant differences in the pain ratings were seen at the end of the trial. Significant effects on the depressive symptomatology measured by means of the MADRS were seen already after 1 month of treatment and were increasing further at the end of the trial, when a significant difference between the groups was also found.

Eur J Pain 2000; 4(1): 27-35

Arnold LM, Keck PE Jr, Welge JA

Antidepressant treatment of fibromyalgia. A meta-analysis and review

Fibromyalgia is a common musculoskeletal pain disorder associated with mood disorders. Antidepressants, particularly tricyclics, are commonly recommended treatments. Randomized, controlled trials of antidepressants for treatment of fibromyalgia were reviewed by methodology, results, and potential predictors of response. Twenty-one controlled trials, 16 involving tricyclic agents, were identified; 9 of these 16 studies were suitable for meta-analysis. Effect sizes were

calculated for measurements of physician and patient overall assessment, pain, stiffness, tenderness, fatigue, and sleep quality. Compared with placebo, tricyclic agents were associated with effect sizes that were substantially larger than zero for all measurements. The largest improvement was associated with measures of sleep quality; the most modest improvement was found in measures of stiffness and tenderness. Further studies are needed utilizing randomized, double-blind, placebo-controlled, parallel designs with antidepressants administered at therapeutic dose ranges, using standardized criteria for fibromyalgia and systematically assessed for co-occurring psychiatric illness.

Psychosomatics 2000 Mar-Apr; 41(2): 104-13

Buskila D

Fibromyalgia, chronic fatigue syndrome, and myofascial pain syndrome

Fibromyalgia and widespread pain were common in Gulf War veterans with unexplained illness referred to a rheumatology clinic. Increased tenderness was demonstrated in the postmenstrual phase of the cycle compared with the intermenstrual phase in normally cycling women but not in users of oral contraceptives. Patients with fibromyalgia had high levels of symptoms that have been used to define silicone implant-associated syndrome. Tender points were found to be a common transient finding associated with acute infectious mononucleosis, but fibromyalgia was an unusual long-term outcome. The common association of fibromyalgia with other rheumatic and systemic illnesses was further explored. A preliminary study revealed a possible linkage of fibromyalgia to the HLA region. Patients with fibromyalgia were found to have an impaired ability to activate the hypothalamic pituitary portion of the hypothalamic pituitary adrenal axis as well as the sympathoadrenal system, leading to reduced corticotropin and epinephrine response to hypoglycemia. Much interest has been expressed in the literature on the possible role of autonomic dysfunction in the development or exacerbation of fatigue and other symptoms in chronic fatigue syndrome. Mycoplasma genus and mycoplasma fermentans were detected by polymerase chain reaction in patients with chronic fatigue syndrome. It was reported that myofascial temporomandibular disorder does not run in families. No major therapeutic trials in fibromyalgia, chronic fatigue syndrome, or myofascial pain syndrome were reported over the past year. The effectiveness of cognitive behavioral therapy and behavior therapy for chronic pain in adults was emphasized. A favorable outcome of fibromyalgia and chronic fatigue syndrome in children and adolescents was reported.

Curr Opin Rheumatol 2000 Mar; 12(2): 113-23

Chang L, Mayer EA, Johnson T, FitzGerald LZ, Naliboff B

Differences in somatic perception in female patients with irritable bowel syndrome with and without fibromyalgia

BACKGROUND: Irritable bowel syndrome (IBS) and fibromyalgia (FM) are considered chronic syndromes of altered visceral and somatic perception, respectively. Because there is a significant overlap of IBS and FM, shared pathophysiological mechanisms have been suggested. Although visceral perception has been well studied in IBS, somatic perception has not. **AIMS:** To compare hypervigilance and altered sensory perception in response to somatic stimuli in patients with IBS, IBS + FM, and healthy controls. **METHODS:** Eleven IBS females (mean age 40), 11 IBS+FM females (mean age 46), and ten healthy female controls (mean age 39) rated pain perception in response to pressure stimuli administered to active somatic tender points, non-tender control points and the T-12 dermatome, delivered in a predictable ascending series, and delivered in an unpredictable randomized fashion (fixed stimulus). **RESULTS:** Although IBS patients had similar pain thresholds during the ascending series compared with controls, they were found to have somatic hypoalgesia with higher pain thresholds and lower pain frequency and severity during fixed stimulus series compared with IBS+FM patients and controls ($p < 0.05$). Patients with IBS + FM were more bothered by the somatic stimuli and had somatic hyperalgesia with lower pain thresholds and higher pain frequency and severity. **CONCLUSIONS:** Both hypervigilance and somatic hypoalgesia contribute to the altered somatic perception in IBS patients. Co-morbidity with FM results in somatic hyperalgesia in IBS patients.

Pain 2000 Feb; 84(2-3):297-307

Cohen H, Neumann L, Shore M, Amir M, Cassuto Y, Buskila D

Autonomic dysfunction in patients with fibromyalgia: application of power spectral analysis of heart rate variability

OBJECTIVES: To assess the interaction between the sympathetic and parasympathetic systems in patients with fibromyalgia syndrome (FM), using power spectrum analysis (PSA) of heart rate variability (HRV). In addition, we explored the association between HRV, measures of tenderness, FM symptoms, physical function, psychological well being and quality of life. **METHODS:** We studied 22 women with FM and 22 age-matched healthy women. Twenty-minute electrocardiogram recordings were obtained in a supine position during complete rest. Spectral analysis of R-R intervals was done by the fast-Fourier transform algorithm. **RESULTS:** Heart rate was significantly higher in FM patients compared with controls ($p < .006$). FM patients had significantly lower HRV compared with controls ($p = .001$), and higher low-frequency (LF) and lower high-frequency (HF) components of PSA than controls ($p < .001$). Quality of life, physical function, anxiety, depression, and perceived stress were moderately to highly correlated with LF, HF (in normalized units), and LF/HF. No association was observed between HRV parameters and measures of tenderness and FM symptoms. **CONCLUSIONS:** The basal autonomic state of patients with FM is characterized

by increased sympathetic and decreased parasympathetic tones. Autonomic dysregulation may have implications regarding the symptomatology, physical and psychological aspects of health status.

Semin Arthritis Rheum 2000 Feb; 29(4):217-27

Da Costa D, Dobkin PL, Fitzcharles MA, Fortin PR, Beaulieu A, Zummer M, Senecal JL, Goulet JR, Rich E, Choquette D, Clarke AE

Determinants of health status in fibromyalgia: a comparative study with systemic lupus erythematosus

OBJECTIVE: To compare perceived health status in women with fibromyalgia (FM) and systemic lupus erythematosus (SLE) using the Medical Outcomes Study (MOS) Short Form Health Survey (SF-36); and to identify determinants of physical and mental health in each patient group. **METHODS:** A cross sectional study of 46 women with FM (mean age 48.13 yrs, SD 9.40) and 59 women with SLE (mean age 42.36 yrs, SD 11.31). Patients with FM were recruited from a rheumatology clinic and a rheumatology practice, while patients with SLE were recruited from 4 rheumatology clinics. Clinical examination determined disease activity (by Systemic Lupus Activity Measure) in SLE and a tender point count was used for FM. Patients completed questionnaires assessing health status (SF-36), stress (Hassles), social support (Social Support Questionnaire 6), and coping (Coping Inventory for Stressful Situations). **RESULTS:** Patients with FM reported more impairment on the following SF-36 subscales: physical function ($p < 0.001$), role physical ($p < 0.001$), bodily pain ($p < 0.001$), and vitality ($p < 0.001$). Physical component summary scores were also significantly lower ($p < 0.001$) for the FM group. Four hierarchical regression analyses were computed to determine factors related to physical and mental health in each patient group, with the following variables in the equation: age, income, disease activity (Step 1), hassles (Step 2), emotional and task coping, and social support (Step 3). Better physical health in FM was related to higher income ($R^2 = 0.17$, $p < 0.05$). In the SLE group, better physical health was associated with younger age, less disease activity, and lower hassles ($R^2 = 0.37$, $p < 0.0001$). Worse mental health among women with FM was associated with more hassles, more emotional coping, and less satisfaction with social support ($R^2 = 0.64$, $p < 0.0001$), while lower income, higher hassles, and more emotional coping were linked to worse mental health in SLE ($R^2 = 0.46$, $p < 0.0001$). **CONCLUSION:** Health related quality of life (HRQL) is impaired among women with FM and SLE, with FM patients reporting greater impairment along several dimensions. Enhancing the HRQL of patients with FM and SLE requires targeting specific modifiable psychosocial factors.

J Rheumatol 2000 Feb; 27(2):365-72

Graven-Nielsen T, Aspegren KS, Henriksson KG, Bengtsson M, Sorensen J, Johnson A, Gerdle B, Arendt-Nielsen L

Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients

Central mechanisms related to referred muscle pain and temporal summation of muscular nociceptive activity are facilitated in fibromyalgia syndrome (FMS) patients. The present study assessed the effects of an NMDA-antagonist (ketamine) on these central mechanisms. FMS patients received either i.v. placebo or ketamine (0.3 mg/kg, Ketalar ((R)) 50% decrease in pain intensity at rest by active drug on two consecutive VAS assessments). Fifteen out of 17 ketamine responders were included in the second part of the study. Before and after ketamine or placebo, experimental local and referred pain was induced by intramuscular (i.m.) infusion of hypertonic saline (0.7 ml, 5%) into the tibialis anterior (TA) muscle. The saline-induced pain intensity was assessed on an electronic VAS, and the distribution of pain drawn by the subject. In addition, the pain threshold (PT) to i.m. electrical stimulation was determined for single stimulus and five repeated (2 Hz, temporal summation) stimuli. The pressure PT of the TA muscle was determined, and the pressure PT and pressure pain tolerance threshold were determined at three bilaterally located tender points (knee, epicondyle, and mid upper trapezius). VAS scores of pain at rest were progressively reduced during ketamine infusion compared with placebo infusion. Pain intensity (area under the VAS curve) to the post-drug infusion of hypertonic saline was reduced by ketamine (-18.4 +/- 0.3% of pre-drug VAS area) compared with placebo (29.9 +/- 18.8%, $p < 0.02$). Local and referred pain areas were reduced by ketamine (-12.0 +/- 14.6% of pre-drug pain areas) compared with placebo (126.3 +/- 83.2%, $p < 0.03$). Ketamine had no significant effect on the PT to single i.m. electrical stimulation. However, the span between the PT to single and repeated i.m. stimuli was significantly decreased by the ketamine (-42.3 +/- 15.0% of pre-drug PT) compared with placebo (50.5 +/- 49.2%, $p < 0.03$) indicating a predominant effect on temporal summation. Mean pressure pain tolerance from the three paired tender points was increased by ketamine (16.6 +/- 6.2% of pre-drug thresholds) compared with placebo (-2.3 +/- 4.9%, $p < 0.009$). The pressure PT at the TA muscle was increased after ketamine (42.4 +/- 9.2% of pre-drug PT) compared with placebo (7.0 +/- 6.6%, $p < 0.011$). The present study showed that mechanisms involved in referred pain, temporal summation, muscular hyperalgesia, and muscle pain at rest were attenuated by the NMDA-antagonist in FMS patients. It suggested a link between central hyperexcitability and the mechanisms for facilitated referred pain and temporal summation in a sub-group of the fibromyalgia syndrome patients. Whether this is specific for FMS patients or a general phenomenon in painful musculoskeletal disorders is not known.

Pain 2000 Apr; 85(3):483-91

Hakkinen A, Hakkinen K, Hannonen P, Alen M

Force production capacity and acute neuromuscular responses to fatiguing loading in women with fibromyalgia are not different from those of healthy women

OBJECTIVE: To compare the maximal and explosive strength characteristics of the leg muscles in premenopausal women with fibromyalgia (FM) with those of healthy female controls (HC) and to examine acute neuromuscular fatigue during heavy resistance loading and short-term recovery from fatigue in these 2 groups. **METHODS:** Subjects were 11 women with FM, 38.6 (5.8) years old, and 12 healthy female controls, 37.3 (6.1) years old. The following were recorded before, during, and after a fatiguing loading session: maximal bilateral concentric and isometric force, isometric force-time curves and relaxation-time curves with agonist-antagonist neural activation (by EMG) of the leg muscles, muscle pain, and blood lactate concentrations. **RESULTS:** At baseline all the measured muscle strength characteristics were comparable between the study groups. The heavy fatiguing loading led to considerable and comparable acute fatigue found in both muscle strength characteristics and agonist-antagonist electromyography in both groups. The respective changes in blood lactate concentration and subjectively perceived muscular pain in the loaded muscles during strenuous resistance loading and recovery from fatigue were similar in both groups. **CONCLUSION:** Premenopausal women with FM do not demonstrate lower dynamic or isometric muscle strength characteristics compared to matched healthy controls. Second, the similar neuromuscular responses recorded during and after the fatiguing loading strongly support the hypothesis of normal muscle structure and neuromuscular function in patients with FM.

J Rheumatol 2000 May; 27(5): 1277-82

Henriksson C, Liedberg G

Factors of importance for work disability in women with fibromyalgia

OBJECTIVE: To identify factors of importance for women with fibromyalgia (FM) to continue working despite the limitations imposed by the symptoms. **METHODS:** A mail questionnaire with questions regarding social background, symptoms, sickness benefits, work situation, work conditions and adjustments, opinions regarding own work ability, and satisfaction with the situation was sent to 218 consecutive women seen at a university pain or rheumatology clinic. Answers were obtained from 176 women. **RESULTS:** Pain, poor quality sleep, abnormal tiredness, muscle stiffness, and increased pain after muscle exertion were frequently reported symptoms. Fifty percent of the women were employed, 15% full-time. Twenty-three percent reported FM as the reason for not working. The work situation had been changed for 58% of the working women, and 80% counted on being able to continue working. **CONCLUSION:** Work disability is a

serious concern in FM, and the majority of women with FM have limitations in their ability to work. Our results indicate that individual adjustments in the work situation need to be made and that women who have found a level matching their ability may continue to work and find it satisfactory. Early intervention in the work situation is recommended.

J Rheumatol 2000 May; 27(5):1271-6

Jeschonneck M, Grohmann G, Hein G, Sprott H

Abnormal microcirculation and temperature in skin above tender points in patients with fibromyalgia

OBJECTIVE: Skin temperature and skin blood flow were studied above different tender points in 20 patients with fibromyalgia (FM) and 20 healthy controls.

METHODS: Blood flow was measured by laser Doppler flowmetry and skin temperature was measured with an infrared thermometer. **RESULTS:** In the skin above the five tender points examined in each subject, we found an increased concentration of erythrocytes, decreased erythrocyte velocity and a consequent decrease in the flux of erythrocytes. A decrease in temperature was recorded above four of the five tender points. **CONCLUSION:** Vasoconstriction occurs in the skin above tender points in FM patients, supporting the hypothesis that FM is related to local hypoxia in the skin above tender points.

Rheumatology (Oxford) 2000 Aug; 39(8): 917-21

Kaplan RM, Schmidt SM, Cronan TA

Quality of well being in patients with fibromyalgia

OBJECTIVE: The Quality of Well-being Scale (QWB) is a generic measure of health related quality of life that can be used for population monitoring, measurement of clinical outcomes, or cost effectiveness analysis. We report data on the validity of the QWB for patients with fibromyalgia (FM) and compare the effect of FM to that of other chronic diseases. **METHODS:** The participants were 594 people recruited from a private health maintenance organization with a confirmed diagnosis of FM. The QWB was administered, along with measures of self-rated health status, physical functioning, pain, stiffness, anxiety, sleep, and depression. The QWB places levels of wellness on a continuum ranging from 0.0 (for death or the equivalent of being dead) to 1.0 (for optimum functioning without symptoms). **RESULTS:** Patients with FM had mean QWB scores of 0.559 (SD 0.074), which is lower than scores reported for patients in most other chronic disease categories. QWB was significantly correlated with measures of physical functioning, stiffness, anxiety, depression, pain, and sleep quality. **CONCLUSION:** Evidence supports the validity of the QWB for patients with FM. Patients with FM obtain lower scores on the QWB than patients with diagnoses of chronic obstructive pulmonary disease, rheumatoid arthritis, atrial fibrillation,

advanced cancer, and several other chronic diseases. Although FM is generally considered a syndrome rather than a disease, substantial disability is experienced by people with this diagnosis.

J Rheumatol 2000 Mar; 27(3): 785-9

Karjalainen K, Malmivaara A, van Tulder M, Roine R, Jauhiainen M, Hurri H, Koes B

Multidisciplinary rehabilitation for fibromyalgia and musculoskeletal pain in working age adults

BACKGROUND: Non-malignant musculoskeletal pain is an increasing problem in western countries. Fibromyalgia syndrome is an increasingly recognized chronic musculoskeletal disorder. **OBJECTIVES:** The objective of this systematic review was to determine the effectiveness of multidisciplinary rehabilitation for fibromyalgia and widespread musculoskeletal pain among working age adults. **SEARCH STRATEGY:** An electronic search was conducted and included Medline from 1966, PsycLIT from 1967 and EMBASE from 1980 to April 1998. The Cochrane Musculoskeletal Group Trials Register was searched as well as, the Cochrane Controlled Trials Register (CCTR). The references of identified articles and reviews were checked, studies published in the Finnish medical database Medic from 1978 to 1998 screened and the Science Citation Index searched. Content experts were also contacted for additional or unpublished studies. **SELECTION CRITERIA:** From all references found in our original search, we selected all randomized controlled trials (RCTs) and clinical controlled trials (CCTs). Trials had to assess the effectiveness of multidisciplinary rehabilitation for patients suffering from fibromyalgia and widespread musculoskeletal pain among working age adults. The rehabilitation program was required to be multidisciplinary; that is, it had to consist of a physician's consultation, plus a psychological, social or vocational intervention, or a combination of both. **DATA COLLECTION AND ANALYSIS:** Four reviewers independently selected the RCTs and CCTs that met the specified inclusion criteria. Two experts in the field of rehabilitation evaluated the relevance and applicability of the findings of the selected studies to actual clinical use. Two other reviewers extracted the data and assessed the main results and the methodological quality of the studies using standardized forms. Finally, a qualitative analysis was performed to evaluate the level of scientific evidence for the effectiveness of multidisciplinary rehabilitation. **MAIN RESULTS:** After screening 1808 abstracts, and the references of 65 reviews, we found only seven relevant studies (1050 patients) that met our inclusion criteria. None of these were considered, methodologically, a high quality randomized controlled trial. Four of the included RCTs on fibromyalgia were graded low quality and suggest no quantifiable benefits. The three which included RCTs on widespread musculoskeletal pain showed that based on limited evidence, overall, no evidence of efficacy was observed.

However, behavioral treatment and stress management appear to be important components. Education combined with physical training showed some positive effects in long term follow up. REVIEWER'S CONCLUSIONS: We conclude that there appears to be little scientific evidence for the effectiveness of multi-disciplinary rehabilitation for these musculoskeletal disorders. However, multi-disciplinary rehabilitation is a commonly used intervention for chronic musculoskeletal disorders, which cause much personal suffering and substantial economic loss to the society. There is a need for high quality trials in this field.
Cochrane Database Syst Rev 2000; (2):CD001984

Korszun A, Young EA, Engleberg NC, Masterson L, Dawson EC, Spindler K, McClure LA, Brown MB, Crofford LJ

Follicular phase hypothalamic-pituitary-gonadal axis function in women with fibromyalgia and chronic fatigue syndrome

OBJECTIVE: Fibromyalgia (FM) and chronic fatigue syndrome (CFS) are clinically overlapping stress-associated disorders. Neuroendocrine perturbations have been noted in both syndromes, and they are more common in women, suggesting abnormalities of gonadal steroid hormones. We tested the hypothesis that women with FM and CFS manifest abnormalities of the hypothalamic-pituitary-gonadal (HPG) hormonal axis. **METHODS:** We examined the secretory characteristics of estradiol, progesterone, follicle stimulating hormone (FSH), and luteinizing hormone (LH), including a detailed analysis of LH in premenopausal women with FM (N = 9) or CFS (N = 8) during the follicular phase of the menstrual cycle compared to matched healthy controls. Blood was collected from an indwelling intravenous catheter every 10 min. over a 12 h period. LH was assayed from every sample; pulses of LH were identified by a pulse-detection program. FSH and progesterone were assayed from a pool of hourly samples for the 12 h period and estradiol from samples pooled over four 3 h time periods. **RESULTS:** There were no significant differences in FSH, progesterone, or estradiol levels in patients versus controls. There were no significant differences in pulsatile secretion of LH. **CONCLUSION:** There is no indication of abnormal gonadotropin secretion or gonadal steroid levels in this small, but systematic, study of HPG axis function in patients with FM and CFS.

J Rheumatol 2000 Jun; 27(6): 1526-30

Kwiatek R, Barnden L, Tedman R, Chew J, Rowe C, Pile K, Tedman R
Regional Cerebral Blood Flow in Fibromyalgia: Single-Photon-Emission Computed Tomography Evidence of Reduction in the Pontine Tegmentum and Thalami

BACKGROUND: Prior to this study, the most direct evidence of alteration in central pain pathway function in fibromyalgia was demonstrated in research

conducted at the University of Alabama at Birmingham by Mountz et al. (1995). In this new investigation, the goal was to replicate the findings of the Birmingham study and, if possible, make new observations. **METHODS:** A resting single-photon-emission computed tomography (SPECT) brain scan was used to evaluate rCBF, and a T1-weighted magnetic resonance imaging (MRI) scan was used to enable precise anatomic location in 17 women who met the ACR criteria for fibromyalgia and 22 age and education-matched, healthy, female controls. Using state-of-the-art statistical parametric mapping (SPM), SPECT scans were analyzed for differences in rCBF between groups. In addition, regions of interest (ROI) were manually drawn on coregistered MRI. Compared to healthy controls, fibromyalgia patients had significantly reduced rCBF in the right thalamus ($p=0.006$), but not in the left thalamus or the head of either caudate nucleus. SPM analysis also demonstrated a significant reduction in rCBF in the inferior pontine tegmentum with consistent findings from ROI analysis. SPM also identified a reduction in rCBF on the perimeter of the right lentiform nucleus. **CONCLUSION:** The finding of reduction in thalamic rCBF is consistent with the results of studies on other chronic clinical pain syndromes. However, the finding of reduced pontine tegmental rCBF is new. Additional replication of these SPECT findings is warranted, preferably using PET technology and paying special attention to the lower brainstem.
Arthritis & Rheumatism 2000 Dec; 43(12): 2823-2833

Larson AA, Giovengo SL, Russell IJ, Michalek JE

Changes in the concentrations of amino acids in the cerebrospinal fluid that correlate with pain in patients with fibromyalgia: implications for nitric oxide pathways

Substance P (SP), a putative nociceptive transmitter, is increased in the CSF of patients with fibromyalgia syndrome (FMS). Because excitatory amino acids (EAAs) also appear to transmit pain, we hypothesized that CSF EAAs may be similarly involved in this syndrome. We found that the mean concentrations of most amino acids in the CSF did not differ amongst groups of subjects with primary FMS (PFMS), fibromyalgia associated with other conditions (SFMS), other painful conditions not exhibiting fibromyalgia (OTHER) or age-matched, healthy normal controls (HNC). However, in SFMS patients, individual measures of pain intensity, determined using an examination-based measure of pain intensity, the tender point index (TPI), covaried with their respective concentrations of glutamine and asparagine, metabolites of glutamate and aspartate, respectively. This suggests that re-uptake and biotransformation mask pain-related increases in EAAs. Individual concentrations of glycine and taurine also correlated with their respective TPI values in patients with PMS. While taurine is affected by a variety of excitatory manipulations, glycine is an inhibitory transmitter as well as a positive modulator of the N-methyl-D-aspartate (NMDA) receptor. In both PFMS and SFMS patients, TPI covaried with arginine,

the precursor to nitric oxide (NO), whose concentrations, in turn, correlated with those of citrulline, a byproduct of NO synthesis. These events predict involvement of NO, a potent signaling molecule thought to be involved in pain processing. Together these metabolic changes that covary with the intensity of pain in patients with FMS may reflect increased EAA release and a positive modulation of NMDA receptors by glycine, perhaps resulting in enhanced synthesis of NO.
Pain 2000 Aug; 87(2):201-11

Lekander M, Fredrikson M, Wik G

Neuroimmune relations in patients with fibromyalgia: a positron emission tomography study

To study relations between neural and immune activity in patients with chronic pain, we correlated regional cerebral blood flow measured with [(15)O] butanol positron emission tomography to immune function in five patients with fibromyalgia. Partly replicating previous data in healthy volunteers, natural killer cell activity correlated negatively with right hemisphere activity in the secondary somatosensory and motor cortices as well as the thalamus. Moreover, natural killer cell activity was negatively and bilaterally related to activity in the posterior cingulate cortex. Thus, immune parameters were related to activity in brain areas involved in pain perception, emotion, and attention. Implicated from a small study population, these strong neuro-immune associations are discussed in view of recent findings concerning mechanisms and adaptive values in immuno-cortical communication and regulation.

Neurosci Lett 2000 Mar 24; 282(3): 193-6

Liu Z, Welin M, Bragee B, Nyberg F

A high-recovery extraction procedure for quantitative analysis of substance P and opioid peptides in human cerebrospinal fluid

This study reports an improved approach for the determination of neuropeptide levels in human cerebrospinal fluid (CSF). The method is based on sample acidification followed by liquid-liquid extraction (LLE) combined with radioimmunoassay. It was applied to study the recovery and level of some opioid peptides (Met-enkephalin-Arg(6)-Phe(7) and Leu-enkephalin-Arg(6)), substance P and the substance P (1-7) fragment, which are all compounds known to be present in human CSF. The results indicated that the use of LLE highly improved the recovery of these peptides compared to current liquid-solid-phase extraction methods by using silica gel cartridges or mini-columns for ion-exchange chromatography. Peptides added to CSF in concentrations down to 10 fmol/ml were recovered in yields exceeding 80%. The mean recovery of synthetic peptides as recorded by radioimmunoassay in the LLE procedure was significantly

improved when HCl was added to the sample. In contrast, when the (125)I-labeled analogues of the peptides were added to CSF samples, the mean recovery of the four labeled peptides using the LLE procedure was markedly reduced in acidified samples. We also found that the inclusion of HCl effectively improved the removal of proteins present in the samples. As an application the levels of substance P and Met-enkephalin-Arg(6)-Phe(7) in CSF samples from patients with chronic pain (fibromyalgia syndrome) were measured using the new procedure. It was possible to confirm a significant difference in the CSF levels of both peptides when comparing patients and controls.
Peptides 2000 Jun; 21 (6):853-60

Okifuji A, Turk DC, Sherman JJ

Evaluation of the relationship between depression and fibromyalgia syndrome: why aren't all patients depressed?

OBJECTIVE: To examine the relationship between fibromyalgia syndrome (FM) and depression by determining the set of factors that differentiate FM patients with and without depressive disorders. **METHODS:** A sample of 69 patients with FM underwent a standardized tender point examination and a semistructured psychological interview and completed a set of self-report inventories.

RESULTS: Of the sample, 39 met criteria for depressive disorder and 30 did not. Depressed patients with FM were significantly more likely to live alone, report elevated functional limitations, and display maladaptive thoughts than non-depressed patients. Non-depressed patients were significantly more likely to have received prior physical therapy than depressed patients. Pain severity, numbers of positive tender points, and pain intensity of tender points and control points did not differentiate the depressed and non-depressed patients. Discriminant analysis revealed that living status, the perception of functional limitations, maladaptive thoughts, and physical therapy treatment together identified diagnoses of depressive disorders for 78% of the patients. **CONCLUSION:** Concurrent depressive disorders are prevalent in FM and may be independent of the cardinal features of FM, namely, pain severity and hypersensitivity to pressure pain, but are related to the cognitive appraisals of the effects of symptoms on daily life and functional activities.

J Rheumatol 2000 Jan; 27(1):212-9

Peters ML, Vlaeyen JW, van Drunen C

Do fibromyalgia patients display hypervigilance for innocuous somatosensory stimuli? Application of a body-scanning reaction-time paradigm

This study tested the hypothesis that fibromyalgia patients display hypervigilance for somatosensory signals. Hypervigilance was operationalized as the detection of

weak electrocutaneous stimuli. Innocuous electrical stimuli gradually increasing in strength were administered to one of four different body locations. A reaction-time paradigm was used in which subjects had to respond as fast as possible to stimulus detection by pressing a button corresponding to the correct body location. The detection task was presented first under single task conditions and subsequently under dual task conditions, in combination with a second (visual) reaction time task. It was predicted that hypervigilance would be most prominent under dual task conditions, where subjects can choose to allocate attention selectively to one of the tasks. Questionnaires on general body vigilance, pain vigilance, pain related-fear and pain catastrophizing were also administered. Thirty female fibromyalgia patients were compared to 30 healthy controls matched on age, sex and educational level. No evidence for hypervigilance for innocuous signals was found: patients did not show superior detection of electrical stimuli either under single or dual task conditions. Also, no differences were found between patients and controls on the body vigilance questionnaire. Detection of electrical stimuli was, however, predicted by pain-related fear and pain vigilance. *Pain* 2000 Jun; 86(3):283-92

Ramsay C, Moreland J, Ho M, Joyce S, Walker S, Pullar T

An observer-blinded comparison of supervised and unsupervised aerobic exercise regimens in fibromyalgia

OBJECTIVE: To compare a supervised 12-week aerobic exercise class with unsupervised home aerobic exercises in the treatment of patients with fibromyalgia. **METHODS:** This was a 48-week randomized single (observer) blind study in a teaching hospital rheumatology and physiotherapy department. The subjects were 74 patients who fulfilled the American College of Rheumatology criteria for fibromyalgia. **RESULTS AND CONCLUSIONS:** A 12-week exercise class program with home exercises demonstrated no benefit over a single physiotherapy session with home exercises in the treatment of pain in patients with fibromyalgia. Neither group (nor the groups combined) showed an improvement in pain compared with baseline. There was some significant benefit in psychological well-being in the exercise class group and perhaps a slowing of functional deterioration in this group. *Rheumatology* (Oxford) 2000 May; 39(5):501-5

Raymond MC, Brown JB

Experience of fibromyalgia. Qualitative study

OBJECTIVE: To explore illness experiences of patients diagnosed with fibromyalgia. **DESIGN:** Qualitative method of in-depth interviews. **SETTING:** Mid-size city in Ontario. **PARTICIPANTS:** Seven patients diagnosed with

fibromyalgia. **METHOD:** Seven in-depth interviews were conducted to explore the illness experience of patients diagnosed with fibromyalgia. All interviews were audiotaped and transcribed verbatim. All interview transcriptions were read independently by the researchers, who then compared and combined their analysis. Final analysis involved examining all interviews collectively, thus permitting relationships between and among central themes to emerge. The analysis strategy used a phenomenologic approach and occurred concurrently rather than sequentially. **MAIN FINDINGS:** Themes that emerged from the interpretive analysis depict patients' journeys along a continuum from experiencing symptoms, through seeking a diagnosis, to coping with the illness. Experiencing symptoms was composed of four subcategories: pain, a precipitating event, associated symptoms, and modulating factors. Seeking a diagnosis entailed frustration and social isolation. Confirmation of diagnosis brought relief as well as anxiety about the future. After diagnosis, several steps led to creation of adaptive coping strategies, which were influenced by several factors. **CONCLUSION:** Findings suggest that the conventional medical model fails to address the complex experience of fibromyalgia. Adopting a patient-centered approach is important for helping patients cope with this disease.
Can Fam Physician 2000 May; 46:1100-6

Salerno A, Thomas E, Olive P, Blotman F, Picot MC, Georgesco M
Motor cortical dysfunction disclosed by single and double magnetic stimulation in patients with fibromyalgia

OBJECTIVE: To investigate the motor cortex by single and double magnetic stimulation, in patients with fibromyalgia. **METHODS:** Thirteen patients with fibromyalgia and 13 age-matched healthy subjects were examined. We evaluated, in both limbs, motor evoked potential (MEP) latency and amplitude and the MCA/MPA ratio, i.e., MEP cortical amplitude (MCA) /maximal peripheral amplitude of the M response (MPA), the central conduction time (TCC) and the length of the silent period (SP). With double magnetic stimulation, different time intervals between shocks were used: with delays between shocks of 4, 25, 55 and 85 ms, the intensities of the conditioning shock were 80% the relaxed threshold. With delays between shocks of 55, 85, 100, 155, 200, 255 and 355 ms, the intensities of the conditioning shocks were set at 150% the relaxed threshold. In all cases, the intensity of the test shock was 150% the relaxed threshold. The results were also compared with those obtained in 5 women affected by rheumatoid arthritis (RA). **RESULTS:** As compared to control, the cortical relaxed threshold was enhanced on both sides and limbs ($p < 0.05$). The cortical silent period recorded with single magnetic stimulation was reduced in the upper limbs ($p=2.7 \times 10^{-11}$) and lower limbs (both sides $p= 3.6 \times 10^{-5}$). The other parameters investigated were normal. With double magnetic stimulation, facilitatory phenomena were absent in fibromyalgic patients and the inhibitory responses recorded with a delay of 155 ms were reduced ($p = 0.0052$). No

significant differences were noted between FM and RA patients. **CONCLUSION:** This study demonstrated motor cortical dysfunction in patients with fibromyalgia involving excitatory and inhibitory mechanisms. This indicates motor cortical involvement and supports the hypothesis of aberrant central pain mechanisms. The absence of differences between FM and RA suggest that the lesions were not specific and could be related to chronic pain disorders within the central nervous system.

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Schikler KN

Is it juvenile rheumatoid arthritis or fibromyalgia?

For the clinician evaluating adolescents with chronic musculoskeletal pain and fatigue, the distinctions between JRA and FS are clear based on physical examination findings. The two conditions can coexist. For the patient with an initial diagnosis of either JRA or FS whose clinical response to therapy is not in keeping with expectations or physical examination findings or whose clinical course worsens without explanation, reevaluation to determine if FS in the JRA patient has developed or JRA in the FS patient has emerged is warranted. Until clinicians have a better understanding of the intricacies of the neurohormonal and immunologic systems and how they affect somatic symptoms, they can continue to provide patients with a treatment plan based on current knowledge that should minimize patients' discomfort and allow them to have appropriately functional lives.

Med Clin North Am 2000 Jul; 84(4):967-82

Smith TC, Gray GC, Knoke JD

Is systemic lupus erythematosus, amyotrophic lateral sclerosis, or fibromyalgia associated with Persian Gulf War service? An examination of Department of Defense hospitalization data

Since the Persian Gulf War ended in 1991, veterans have reported diverse, unexplained symptoms. Some have wondered if their development of systemic lupus erythematosus, amyotrophic lateral sclerosis, or fibromyalgia might be related to Gulf War service. The authors used Cox proportional hazard modeling to determine whether regular, active-duty service personnel deployed to the Persian Gulf War (N=551,841) were at increased risk of postwar hospitalization with the three conditions compared with nondeployed Gulf War era service personnel (N = 1,478,704). All hospitalizations in Department of Defense facilities from October 1, 1988, through July 31, 1997, were examined. With removal of personnel diagnosed with any of the three diseases before August 1, 1991, and adjustment for multiple covariates, Gulf War veterans were not at increased risk of postwar

hospitalization due to systemic lupus erythematosus (risk ratio (RR) = 0.94, 95% confidence interval (CI): 0.65, 1.35). Because of the small number of cases and wide confidence limits, the data regarding amyotrophic lateral sclerosis were inconclusive. Gulf War veterans were slightly at risk of postwar hospitalization for fibromyalgia (RR = 1.23, 95% CI: 1.05, 1.43); however, this risk difference was probably due to the Gulf War veteran clinical evaluation program beginning in 1994. These data do not support Gulf War service and disease associations.
Am J Epidemiol 2000 Jun 1; 151(11):1053-9

Sperber AD, Carmel S, Atzmon Y, Weisberg I, Shalit Y, Neumann L, Fich A, Friger M, Buskila D

Use of the Functional Bowel Disorder Severity Index (FBDSI) in a study of patients with the irritable bowel syndrome and fibromyalgia

OBJECTIVE: The purpose of this study was to evaluate the utility of the Functional Bowel Disorder Severity Index (FBDSI) as a measure of severity of disease among patients with the irritable bowel syndrome (IBS) and matched controls. **METHODS:** A total of 75 IBS patients and 69 matched controls completed questionnaires on bowel symptoms, health status, quality of life, psychological distress, concerns, anxiety, and sense of coherence. All participants also were tested for fibromyalgia (FS), a functional disorder of the musculoskeletal system. All participants were administered a questionnaire that included the FBDSI. On the basis of their responses to the questionnaire, the controls were subdivided as healthy controls (n= 48) or IBS nonpatients (N= 21). On the basis of the FS classification, 75 IBS patients were subdivided as IBS only (n = 50) or IBS and FS combined (n = 25). **RESULTS:** The mean FBDSI score was higher for the IBS patients than the controls (100.5+/-12.7 and 23.5 +/- 3.9, respectively; p <0.001). IBS nonpatients had an intermediate score of 42.3+/-18.0. Patients with both IBS and fibromyalgia had the highest mean FBDSI score: 138.8+/-31.5. There was no association between FBDSI and age or gender, but FBDSI was significantly associated with other measures of health status. **CONCLUSIONS:** An association was found between the FBDSI and IBS patient status: IBS nonpatients, patients with IBS only, and patients with both IBS and fibromyalgia had increasingly severe scores. The results provide support for the validity of FBDSI as a measure of illness severity in functional gastrointestinal disorders.

Am J Gastroenterol 2000 Apr; 95(4):995-8

White KP, Speechley M, Harth M, Ostbye T

Co-existence of chronic fatigue syndrome with fibromyalgia syndrome in the general population. A controlled study

OBJECTIVE: To determine the proportion of adults with fibromyalgia syndrome (FMS) in the general population who also meet the 1988 Center for Disease Control (CDC) criteria for chronic fatigue syndrome (CFS). **METHODS:** Seventy-four FMS cases were compared with 32 non-FMS controls with widespread pain and 23 with localized pain, all recruited in a general population survey. **RESULTS:** Among females, 58.0% of fibromyalgia cases met the full criteria for CFS, compared to 26.1% and 12.5% of controls with widespread and localized pain, respectively ($p = 0.0006$). Male percentages were 80.0, 22.2, and zero, respectively ($p = 0.003$). Compared to those with FMS alone, those meeting the case definitions for both FMS and CFS reported a worse course, worse overall health, more dissatisfaction with health, more non-CFS symptoms, and greater disease impact. The number of total symptoms and non-CFS symptoms were the best predictors of co-morbid CFS. **CONCLUSIONS:** There is significant clinical overlap between CFS and FMS.
Scand J Rheumatol 2000; 29(1):44-51

Yunus MB, Inanici F, Aldag JC, Mangold RF

Fibromyalgia in men: comparison of clinical features with women

OBJECTIVE: To describe possible differences between male and female patients with fibromyalgia syndrome (FM) in their clinical manifestations. **METHODS:** Five hundred thirty-six consecutive patients with FM (469 women, 67 men) seen in a university rheumatology clinic and 36 healthy men without significant pain seen in the same clinic were included in the study. Data on demographic and clinical features were gathered by a standard protocol. Tender point examination was performed by the same physician. Level of significance was set at $p < \text{or} = 0.01$. **RESULTS:** Several features were significantly ($p < \text{or} = 0.01$) milder or less common among men than women, including number of tender points (TP), TP score, "hurt all over," fatigue, morning fatigue, and irritable bowel syndrome (IBS). The total number of symptoms was also fewer among men and approached significance ($p = 0.02$) by parametric test, but reached significance ($p = 0.001$) by nonparametric analysis. All clinical and psychological symptoms as well as TP were significantly ($p < 0.01$) more common or greater in male patients with FM than healthy male controls, with the exception of IBS ($p = 0.03$). Patient assessed global severity of illness, Health Assessment Questionnaire disability score, and pain severity were similar in both sexes. **CONCLUSION:** Male patients with FM had fewer symptoms and fewer TP, and less common "hurt all over", fatigue, morning fatigue, and IBS, compared with female patients. Stepwise logistic regression showed significant differences between men and women in number of TP ($p < 0.001$).
J Rheumatol 2000 Feb; 27(2):485-9