

FIBROMYALGIA: ABSTRACTS 2001 FROM ARTICLES IN MEDICAL JOURNALS

The abstracts in this collection are intended to provide doctors and other health professionals with a convenient overview of trends in research on fibromyalgia published in medical journals in the year 2001. The studies were selected from the extensive literature on fibromyalgia so as to cover a wide range of subjects in limited space.

The following studies were published in the period January through September, 2001, and abstracts will be added to this selection at intervals during the year. Similar collections of abstracts published in 1999 and 2000 can be found on the website of the National Fibromyalgia Partnership: www.fmpartnership.org.

The abstracts are arranged in alphabetical order by lead author.

Aaron LA, Buchwald D

A review of the evidence for overlap among unexplained clinical conditions

PURPOSE: Unexplained clinical conditions share features, including symptoms (fatigue, pain), disability out of proportion to physical examination findings, inconsistent demonstration of laboratory abnormalities, and an association with "stress" and psychosocial factors. This literature review examines the nature and extent of the overlap among these unexplained clinical conditions and the limitations of previous research. **DATA SOURCES:** English-language articles were identified by a search of the MEDLINE database from 1966 to January 2001 by using individual syndromes and their hallmark symptoms as search terms. **STUDY SELECTION:** Studies that assessed patients with at least one unexplained clinical condition and that included information on symptoms, overlap with other unexplained clinical conditions, or physiologic markers. Conditions examined were the chronic fatigue syndrome, fibromyalgia, the irritable bowel syndrome, multiple chemical sensitivity, temporomandibular disorder, tension headache, interstitial cystitis, and the postconcussion syndrome. **DATA EXTRACTION:** Information on authorship, patient and control groups, eligibility criteria, case definitions, study methods, and major findings. **DATA SYNTHESIS:** Many similarities were apparent in case definition and symptoms, and the proportion of patients with one unexplained clinical condition meeting criteria for a second unexplained condition was striking. Tender points on physical examination and decreased pain threshold and tolerance were the most frequent and consistent objective findings. A major

shortcoming of all proposed explanatory models is their inability to account for the occurrence of unexplained clinical conditions in many affected patients. CONCLUSIONS: Overlap between unexplained clinical conditions is substantial. Most studies are limited by methodologic problems, such as case definition and the selection and recruitment of case-patients and controls.

Ann Intern Med 2001 May 1; 134(9 Pt 2):868–81

Anders C, Sprott H, Scholle HC

Surface EMG of the lumbar part of the erector trunci muscle in patients with fibromyalgia

OBJECTIVE: To determine differences supposed in EMG parameters of the erector trunci region between patients with fibromyalgia and healthy subjects during defined investigation situations. METHODS: During sitting and standing in upright position surface EMG (SEMG) from 15 subjects with fibromyalgia and 10 healthy controls was performed using a 16-channel technique where the electrodes were applied in a well-defined grid pattern (gain 5000, 3 db points at 5 Hz and 700 Hz respectively). SEMG quantification was done by Fourier algorithm using 512 measurement points for calculation. RESULTS: An increased EMG amplitude could be recorded during rest in fibromyalgia patients compared with controls. Spatial amplitude differences (frequency range 100-500 Hz) in the low back region were significantly ($p < 0.01$) decreased in the patients' group during sitting. CONCLUSION: It is the first time that a decreased difference in EMG amplitude of different parts within a certain muscle could be proven in patients with fibromyalgia. As far as is known from the literature this result seems to be a unique finding in fibromyalgia patients. *Clin Exp Rheumatol* 2001 Jul-Aug; 19(4):453–5

Anthony KK, Schanberg L

Juvenile primary fibromyalgia syndrome

Juvenile primary fibromyalgia syndrome (JPFS) is a common musculoskeletal pain syndrome of unknown etiology characterized by widespread persistent pain, sleep disturbance, fatigue, and the presence of multiple discrete tender points on physical examination. Other associated symptoms include chronic anxiety or tension, chronic headaches, subjective soft tissue swelling, and pain modulated by physical activity, weather, and anxiety or stress. Research and clinical observations suggest that JPFS may have a chronic course that impacts the functional status and psychosocial development of children and adolescents. In addition, several factors have been implicated in the etiology and maintenance of JPFS including genetic and anatomic factors, disordered sleep, psychological distress, and

familial and environmental influences. A multidisciplinary approach to treatment of JPFS is advocated, including pharmacologic and nonpharmacologic interventions (e.g., psychotherapy, aerobic exercise, sleep hygiene).

Curr Rheumatol Rep 2001 Apr; 3(2):165–71

Barkhuizen A

Pharmacologic treatment of fibromyalgia

Fibromyalgia is a chronic syndrome characterized by widespread pain, unrefreshed sleep, disturbed mood, and fatigue. Until such time as we have a clearer understanding of the trigger and/or pathophysiologic mechanisms producing these symptoms, pharmacologic treatment should be aimed at individual symptoms. Such treatment should ideally be offered as part of a multidisciplinary treatment program using both pharmacologic and nonpharmacologic treatment modalities. Critical components of any successful fibromyalgia treatment program include addressing physical fitness, work and other functional activities, and mental health, in addition to symptom-specific therapies. The main symptoms that should be addressed include pain, sleep disturbances including restless leg syndrome, mood disturbances, and fatigue. Pharmacologic therapy should also be considered for syndromes commonly associated with fibromyalgia including irritable bowel syndrome, interstitial cystitis, migraine headaches, temporomandibular joint dysfunction, dysequilibrium including neurally mediated hypotension, sicca syndrome, and growth hormone deficiency. This article provides general guidelines in initiating a successful pharmacologic treatment program for fibromyalgia.

Curr Pain Headache Rep 2001 Aug; 5(4):351–8

Bell IR, Baldwin CM, Stoltz E, Walsh BT, Schwartz GE

EEG beta 1 oscillation and sucrose sensitization in fibromyalgia with chemical intolerance

Patients with fibromyalgia (FM) have diffuse musculoskeletal pain; half report concomitant intolerance for low levels of environmental chemicals (CI). Previous investigators have hypothesized that the chronic pain and chemical intolerance reflect sensitization of different central nervous system limbic and/or mesolimbic reward pathways. We evaluated electroencephalographic (EEG) beta activity and blood glucose responses of FM patients with and without CI and normals during three repeated sucrose ingestion sessions and during a final, water-only session (testing for conditioning). The FM with CI exhibited oscillation (reversal in direction of change from session to session) at rest and then

sensitization (progressive amplification) of EEG beta 1 over time across the 3 sucrose sessions versus controls. FM with CI showed sensitization of blood glucose over the 3 sucrose sessions, which, like the EEG findings, reverted toward baseline in the final water-only session. The data suggest that the subset of FM patients with CI have increased susceptibility to oscillation and physiological sensitization without conditioning, perhaps contributing to fluctuations in their chronic course.

Int J Neurosci 2001 May; 108(1-2):31–42

Buskila D

Fibromyalgia, chronic fatigue syndrome, and myofascial pain syndrome

The prevalence of chronic widespread pain in the general population in Israel was comparable with reports from the USA, UK, and Canada. Comorbidity with fibromyalgia (FM) resulted in somatic hyperalgesia in patients with irritable bowel syndrome. One sixth of the subjects with chronic widespread pain in the general population were also found to have a mental disorder. Mechanisms involved in referred pain, temporal summation, muscle hyperalgesia, and muscle pain at rest were attenuated by the N-methyl-D-aspartate (NMDA) antagonist, ketamine, in FM patients. Delayed corticotropin release, after interleukin-6 administration, in FM was shown to be consistent with a defect in hypothalamic corticotropin-releasing hormone neural function. The basal autonomic state of FM patients was characterized by increased sympathetic and decreased parasympathetic systems tones. The severity of functional impairment as assessed by the Medical Outcome Survey Short Form (SF-36) discriminated between patients with widespread pain alone and FM patients. Chronic fatigue syndrome (CFS) occurred in about 0.42% of a random community-based sample of 28,673 adults in Chicago, Illinois. A significant clinical overlap between CFS and FM was reported. Cytokine dysregulation was not found to be a singular or dominant factor in the pathogenesis of CFS. A favorable outcome of CFS in children was reported; two-thirds recovered and resumed normal activities. No major therapeutic trials in FM and CFS were reported over the past year.

Curr Opin Rheumatol 2001 Mar; 13(2):117–27

Clark SR, Jones KD, Burckhardt CS, Bennett R

Exercise for patients with fibromyalgia: risks versus benefits

Although exercise in the form of stretching, strength maintenance, and aerobic conditioning is generally considered beneficial to patients with fibromyalgia (FM), there is no reliable

evidence to explain why exercise should help alleviate the primary symptom of FM, namely pain. Study results are varied and do not provide a uniform consensus that exercise is beneficial or what type, intensity, or duration of exercise is best. Patients who suffer from exercise-induced pain often do not follow through with recommendations. Evidence-based prescriptions are usually inadequate because most are based on methods designed for persons without FM and, therefore, lack individualization. A mismatch between exercise intensity and level of conditioning may trigger a classic neuroendocrine stress reaction. This review considers the adverse and beneficial effects of exercise. It also provides a patient guide to exercise that takes into account the risks and benefits of exercise for persons with FM.

Curr Rheumatol Rep 2001 Apr; 3(2):135–40

Clauw DJ

Elusive syndromes: treating the biologic basis of fibromyalgia and related syndromes

Newer theories suggest that patients with fibromyalgia have a biologic predisposition to perceiving pain with more sensitivity than people without fibromyalgia. Several biologic triggers are implicated as possibly initiating or worsening the symptoms of fibromyalgia. Treatments to manage pain, help with sleep, and, when needed, treat cognitive disturbances show some success.

Cleve Clin J Med 2001 Oct; 68(10):830, 832–4

Crofford LJ, Appleton BE

Complementary and alternative therapies for fibromyalgia

Fibromyalgia (FM) is a syndrome of chronic widespread musculoskeletal pain that is accompanied by sleep disturbance and fatigue. Clinical treatment usually includes lifestyle modifications and pharmacologic interventions meant to relieve pain, improve sleep quality, and treat mood disorders. These therapies are often ineffective or have been shown in clinical studies to have only short-term effectiveness. Pharmacologic treatments have considerable side effects. Patients may have difficulty complying with exercise-based treatments. Thus, patients seek alternative therapeutic approaches and physicians are routinely asked for advice about these treatments. This article reviews nontraditional treatment alternatives, from use of nutritional and herbal supplements to acupuncture and mind-body therapy. Little is known about efficacy and tolerance of complementary and

alternative therapies in FM and other chronic musculoskeletal pain syndromes. Most studies on these treatments have been performed for osteoarthritis, rheumatoid arthritis, or focal musculoskeletal conditions. Clinical trials are scarce; the quality of these trials is often criticized because of small study population size, lack of appropriate control interventions, poor compliance, or short duration of follow-up. However, because of widespread and growing use of alternative medicine, especially by persons with chronic illnesses, it is essential to review efficacy and adverse effects of complementary and alternative therapies. *Curr Rheumatol Rep* 2001 Apr; 3(2):147–56

Elert J, Kendall SA, Larsson B, Mansson B, Gerdle B

Chronic pain and difficulty in relaxing postural muscles in patients with fibromyalgia and chronic whiplash associated disorders

OBJECTIVE: To investigate if muscle tension according to the surface electromyogram (EMG) of the shoulder flexors is increased in consecutive patients with fibromyalgia (FM) or chronic whiplash associated disorders (WAD). METHODS: A total of 59 consecutive patients with FM ($N = 36$) or chronic WAD ($N = 23$) performed 100 maximal isokinetic contractions combined with surface electromyography of the trapezius and infraspinatus. A randomized group of pain-free female ($N = 27$) subjects served as control group. Peak torque initially (PTi) and absolute and relative peak torque at endurance level (PTE, PTER) were registered as output variables, together with the EMG level of unnecessary muscle tension, i.e., the signal amplitude ratio (SAR). RESULTS: The patient groups had a higher level of unnecessary tension initially and at the endurance level. The patients had lower absolute output (PTi and PTE), but the relative levels (PTer) did not differ comparing all 3 groups. Subjects with FM had significantly higher body mass index (BMI) than the other groups. BMI did not influence the SAR but correlated positively with PT. CONCLUSION: The results confirmed earlier findings that groups of patients with chronic pain have increased muscle tension and decreased output during dynamic activity compared to pain-free controls. However, the results indicated there is heterogeneity within groups of patients with the same chronic pain disorder and that not all patients with chronic pain have increased muscle tension.

J Rheumatol 2001 Jun; 28(6):1361–8

Gantz NM, Coldsmith EE

Chronic fatigue syndrome and fibromyalgia resources on the world wide web: a descriptive journey

A wealth of information on chronic fatigue syndrome (CFS) and fibromyalgia is available on the World Wide Web for health care providers and patients. These illnesses have overlapping features, and their etiologies remain unknown. Multiple Web sites were reviewed, and selected sites providing useful information were identified. Sites were classified according to their content and target audience and were judged according to suggested standards of Internet publishing. Fifty-eight sites were classified into groups as follows: comprehensive and research Web sites for CFS and fibromyalgia, meetings, clinical trials, literature search services, bibliographies, journal, and CFS and fibromyalgia Web sites for the patient.

Clin Infect Dis 2001 Mar 15; 32(6):938–48

Glass JM, Park DC

Cognitive dysfunction in fibromyalgia

Fibromyalgia is a puzzling syndrome of widespread musculoskeletal pain. In addition to pain, patients with fibromyalgia frequently report that cognitive function, memory, and mental alertness have declined. A small body of literature suggests that there is cognitive dysfunction in fibromyalgia. This article addresses several questions that physicians may have regarding cognitive function in their patients. These questions concern the types of cognitive tasks that are problematic for patients with fibromyalgia, the role of psychological factors such as depression and anxiety, the role of physical factors such as pain and fatigue, the nature of patients' perceptions of their cognitive abilities, and whether patients can be tested for cognitive dysfunction. Critical areas for further investigation are highlighted.

Curr Rheumatol Rep 2001 Apr; 3(2):123–7

Goulding C, O'Connell P, Murray FE

Prevalence of fibromyalgia, anxiety and depression in chronic hepatitis C virus infection: relationship to RT-PCR status and mode of acquisition

BACKGROUND: Musculoskeletal complaints, dry eyes, fatigue and anxiety are common symptoms in patients with hepatitis C virus (HCV) infection, but there are few controlled

data evaluating this. AIM: To assess the prevalence of rheumatological disease, fatigue and anxiety in different groups of patients with chronic HCV infection. PATIENTS AND METHODS: Seventy-seven patients with HCV were evaluated. Of these, 49 (64%) had been infected via contaminated anti-D immunoglobulin, 25 (33%) were intravenous drug users (IVDUs), and three were transfusion related; 78% were female. Twenty-five age- and sex-matched controls were also evaluated. Assessment was performed by history, physical examination, the Fibromyalgia Impact Questionnaire (FIQ) and the Hospital Anxiety and Depression Score (HADS). RESULTS: Four (5%) patients fulfilled the criteria for fibromyalgia. All were infected via anti-D immunoglobulin, and three were PCR positive. The mean number of tender points in anti-D patients was 5.0 (+/- 4.07) compared with 2.8 (+/- 2.7) in controls ($p = 0.028$) and 2.5 (+/- 2.2) in IVDUs ($p < 0.004$). There was no significant difference in the number of tender points between PCR-positive and PCR-negative patients ($p = 0.23$). Anxiety and depression scores were significantly higher in anti-D patients ($p = 0.0001$) and IVDUs ($p = 0.005$) compared with controls. Forty per cent of the HCV patients had a positive Schirmer test. Forty-two per cent of PCR-positive patients had a positive rheumatoid factor (RF > 1/80). CONCLUSION: This study reveals a moderate increase in prevalence of fibromyalgia in HCV patients. The number of tender points was related to mode of acquisition but not to PCR status. Anxiety and depression levels are also increased in HCV patients compared with controls. Prevalence of RF was higher in PCR-positive patients compared with controls and those who had cleared the virus.

Eur J Gastroenterol Hepatol 2001 May; 13(5):507–11

Granot M, Buskila D, Granovsky Y, Sprecher E,
Neumann L, Yarnitsky D

Simultaneous recording of late and ultra-late pain evoked potentials in fibromyalgia

OBJECTIVE: To characterize laser evoked potentials (LEP), pain psychophysics and local tissue response in fibromyalgia patients. METHODS: LEP were recorded in 14 women with fibromyalgia in response to bilateral stimulation of tender and control points in upper limbs by 4 blocks of 20 stimuli at each point. Subsequently, heat pain thresholds were measured and supra-threshold magnitude estimations of heat pain stimuli were obtained on a visual analogue scale. Finally, the extent of the local tissue response induced by the previous stimuli was evaluated. RESULTS: Laser stimuli elicited two long latency waves: A late wave (mean latency 368.9+/-66.9 ms) in most patients (13/14) from stimuli at all points, and an ultra-late wave (mean latency 917.3+/-91.8 ms) in 78.5% of the patients at the control points and in 71.4% at the tender points. Amplitude of ultra-late waves was higher at the tender points (20.67+/-11.1 &mgr;V) than at the control points (10.47+/-4.1 &mgr;V) ($p = 0.016$). Pain thresholds were lower in the tender (41.2+/-2.7 degrees C) than the control points (43.9+/-3.2 degrees C) ($p = 0.008$). Local tissue response was significantly

more intense at tender than control points ($p = 0.004$). CONCLUSIONS: Ultra-late laser evoked potentials can be recorded simultaneously with late potentials. Our findings are compatible with presence of peripheral C-fiber sensitization, mostly at tender points, probably combined with generalized central sensitization of pain pathways in fibromyalgia. *Clin Neurophysiol* 2001 Oct; 112(10):1881–7

Jentoft ES, Kvalvik AG, Mengshoel AM

Effects of pool-based and land-based aerobic exercise on women with fibromyalgia/chronic widespread muscle pain

OBJECTIVE: To examine the effects of pool-based (PE) and land-based (LE) exercise programs on patients with fibromyalgia. METHODS: The outcomes were assessed by the Fibromyalgia Impact Questionnaire, the Arthritis Self-Efficacy Scale, and tests of physical capacity. RESULTS: Eighteen subjects in the PE group and 16 in the LE group performed a structured exercise program. After 20 weeks, greater improvement in grip strength was seen in the LE group compared with the PE group ($p < 0.05$). Statistically significant improvements were seen in both groups in cardiovascular capacity, walking time, and daytime fatigue. In the PE group improvements were also found in number of days of feeling good, self-reported physical impairment, pain, anxiety, and depression. The results were mainly unchanged at 6 months follow-up. CONCLUSION: Physical capacity can be increased by exercise, even when the exercise is performed in a warm-water pool. PE programs may have some additional effects on symptoms.

Arthritis Rheum 2001 Feb; 45(1):42–7

Klerman EB, Goldenberg DL, Brown EN, Maliszewski AM, Adler GK

Circadian rhythms of women with fibromyalgia

Fibromyalgia syndrome is a chronic and debilitating disorder characterized by widespread nonarticular musculoskeletal pain whose etiology is unknown. Many of the symptoms of this syndrome, including difficulty sleeping, fatigue, malaise, myalgias, gastrointestinal complaints, and decreased cognitive function, are similar to those observed in individuals whose circadian pacemaker is abnormally aligned with their sleep-wake schedule or with local environmental time. Abnormalities in melatonin and cortisol, two hormones whose secretion is strongly influenced by the circadian pacemaker, have been reported in women with fibromyalgia. We studied the circadian rhythms of 10 women with fibromyalgia and 12 control healthy women. The protocol controlled factors known to affect markers of the

circadian system, including light levels, posture, sleep-wake state, meals, and activity. The timing of the events in the protocol were calculated relative to the habitual sleep-wake schedule of each individual subject. Under these conditions, we found no significant difference between the women with fibromyalgia and control women in the circadian amplitude or phase of rhythms of melatonin, cortisol, and core body temperature. The average circadian phases expressed in hours posthabitual bedtime for women with and without fibromyalgia were 3:43 +/- 0:19 and 3:46 +/- 0:13, respectively, for melatonin; 10:13 +/- 0:23 and 10:32 +/- 0:20, respectively for cortisol; and 5:19 +/- 0:19 and 4:57 +/- 0:33, respectively, for core body temperature phases. Both groups of women had similar circadian rhythms in self-reported alertness. Although pain and stiffness were significantly increased in women with fibromyalgia compared with healthy women, there were no circadian rhythms in either parameter. We suggest that abnormalities in circadian rhythmicity are not a primary cause of fibromyalgia or its symptoms.

J Clin Endocrinol Metab 2001 Mar; 86(3):1034–9

Landis CA, Lentz MJ, Rothermel J, Riffle SC, Chapman D, Buchwald D, Shaver JL

Decreased nocturnal levels of prolactin and growth hormone in women with fibromyalgia

Fibromyalgia (FM) is a complex syndrome, primarily of women, characterized by chronic pain, fatigue, and sleep disturbance. Altered function of the somatotrophic axis has been documented in patients with FM, but little is known about nocturnal levels of prolactin (PRL). As part of a laboratory study of sleep patterns in FM, we measured the serum concentrations of GH and PRL hourly from 2000–0700 h in a sample of 25 women with FM (mean, 46.9 +/- 7.6 yr) and in 21 control women (mean, 42.6 +/- 8.1 yr). The mean (+/-SEM) serum concentrations (micrograms per L) of GH and of PRL during the early sleep period were higher in control women than in patients with FM [GH, 1.6 +/- 0.4 vs. 0.6 +/- 0.2 ($p < 0.05$); PRL, 23.2 +/- 2.2 vs. 16.9 +/- 2.0 ($p < 0.025$)]. The mean serum concentrations of GH and PRL increased more after sleep onset in control women than in patients with FM [GH, 1.3 +/- 0.4 vs. 0.3 +/- 0.2 ($p < 0.05$); PRL, 16.2 +/- 2.4 vs. 9.7 +/- 1.5 ($p < 0.025$)]. Sleep efficiency and amounts of sleep or wake stages on the blood draw night were not different between groups. There was a modest inverse relationship between sleep latency and PRL and a direct relationship between sleep efficiency and PRL in FM. There was an inverse relationship between age and GH most evident in control women.

J Clin Endocrinol Metab 2001 Apr; 86(4):1672–8

Legangneux E, Mora JJ, Spreux-Varoquaux O, Thorin I, Herrou M, Alvado G, Gomeni C

Cerebrospinal fluid biogenic amine metabolites, plasma-rich platelet serotonin and [(3)H]imipramine reuptake in the primary fibromyalgia syndrome

BACKGROUND: Primary fibromyalgia syndrome (PFS) is a chronic disorder commonly seen in rheumatological practice. The pathophysiological disturbances of this syndrome, which was defined by the American College of Rheumatology in 1990, are poorly understood. This study evaluated, in 30 patients, the hypothesis that PFS is a pain modulation disorder induced by deregulation of serotonin metabolism. **OBJECTIVES:** To compare platelet [(3)H]imipramine binding sites and serotonin (5-HT) levels in plasma-rich platelets (PRP) of PFS patients with those of matched healthy controls and to compare the levels of biogenic amine metabolites in the cerebrospinal fluid (CSF) of PFS patients with those of matched controls. **METHODS:** Platelet [(3)H]imipramine binding sites were defined by two criteria, B(max) for their density and K(d) for their affinity. PRP 5-HT and CSF metabolites of 5-HT (5-hydroxyindoleacetic acid, 5-HIAA), norepinephrine (3-methoxy, 4-hydroxy phenylglycol, MHPG) and dopamine (homovanillic acid, HVA) were assayed by reversed-phase high-performance liquid chromatography with coulometric detection. **RESULTS:** [(3)H]imipramine platelet binding was similar ($p = 0.43$ for B(max) and $p = 0.30$ for K(d)) in PFS patients (B(max)=901+/-83 fmol/mg protein, K(d)=0.682+/-0.046) and in matched controls (B(max)=1017+/-119 fmol/mg protein, K(d)=0.606+/-0.056). PRP 5-HT was significantly higher ($p = 0.0009$) in PFS patients (955+/-101 ng/10(9) platelets) than in controls (633+/-50 ng/10(9) platelets). When adjusted for age, the levels of all CSF metabolites were lower in PFS patients. The CSF metabolite of norepinephrine (MHPG) was lower ($p = 0.003$) in PFS patients (8.33+/-0.33 ng/ml) than in matched controls (9.89+/-0.31 ng/ml) and 5-HIAA was lower ($p = 0.042$) in PFS female patients (22.34+/-1.78 ng/ml) than in matched controls (25.75+/-1.75 ng/ml). For HVA in females, the difference between PFS patients (36.32+/-3.20 ng/ml) and matched controls (38.32+/-2.90 ng/ml) approached statistical significance ($p = 0.054$). **CONCLUSION:** Changes in metabolites of CSF biogenic amines appear to be partially correlated to age but remained diagnosis- dependent. High levels of PRP 5-HT in PFS patients were associated with low CSF 5-HIAA levels in female patients but were not accompanied by any change in serotonergic uptake as assessed by platelet [(3)H]imipramine binding sites. These findings do not allow us to confirm that serotonin metabolism is deregulated in PFS patients. *Rheumatology* (Oxford) 2001 Mar; 40(3):290-6

Mueller HH, Donaldson CC, Nelson DV, Layman M

Treatment of fibromyalgia incorporating EEG-driven stimulation: A clinical outcomes study

Thirty patients from a private clinical practice who met the 1990 American College of Rheumatology criteria for fibromyalgia syndrome (FS) were followed prospectively through a brainwave-based intervention known as electroencephalograph (EEG)-driven stimulation or EDS. Patients were initially treated with EDS until they reported noticeable improvements in mental clarity, mood, and sleep. Self-reported pain, then, having changed from vaguely diffuse to more specifically localized, was treated with very modest amounts of physically oriented therapies. Pre- to post-treatment and extended follow-up comparisons of psychological and physical functioning indices, specific FS symptom ratings, and EEG activity revealed statistically significant improvements. EDS appeared to be the prime initiator of therapeutic efficacy. Future research is justified for controlled clinical trials and to better understand disease mechanisms.

J Clin Psychol 2001 Jul; 57(7):933–52

Naschitz JE, Rozenbaum M, Rosner I, Sabo E, Priselac RM, Shaviv N, Ahdoot A, Ahdoot M, Gaitini L, Eldar S, Yeshurun D

Cardiovascular response to upright tilt in fibromyalgia differs from that in chronic fatigue syndrome

OBJECTIVE: To compare the cardiovascular response during postural challenge of patients with fibromyalgia (FM) to those with chronic fatigue syndrome (CFS). Age and sex matched patients were studied, 38 with FM, 30 with CFS, and 37 healthy subjects. Blood pressure (BP) and heart rate (HR) were recorded during 10 min of recumbence and 30 min of head-up tilt. Differences between successive BP values and the last recumbent BP, their average, and standard deviation (SD) were calculated. Time curves of BP differences were analyzed by computer and their outline ratios (OR) and fractal dimensions (FD) were measured. HR differences were determined similarly. Based on the latter measurements, each subject's discriminant score (DS) was computed. **RESULTS:** For patients and controls average DS values were: FM: -3.68 (SD 2.7), CFS: 3.72 (SD 5.02), and healthy controls: -4.62 (SD 2.24). DS values differed significantly between FM and CFS ($p < 0.0001$). Subgroups of FM patients with and without fatigue had comparable DS values. **CONCLUSION:** The DS confers numerical expression to the cardiovascular response during postural challenge. DS values in FM were significantly different from DS in CFS, suggesting that homeostatic responses in FM and CFS are dissimilar. This observation challenges the hypothesis that FM and CFS share a common derangement of the stress-response system.

J Rheumatol 2001 Jun; 28(6):1356–60

Pall ML

Common etiology of posttraumatic stress disorder, fibromyalgia, chronic fatigue syndrome and multiple chemical sensitivity via elevated nitric oxide/peroxynitrite

Three types of overlap occur among the disease states chronic fatigue syndrome (CFS), fibromyalgia (FM), multiple chemical sensitivity (MCS) and posttraumatic stress disorder (PTSD). They share common symptoms. Many patients meet the criteria for diagnosis for two or more of these disorders and each disorder appears to be often induced by a relatively short-term stress which is followed by a chronic pathology, suggesting that the stress may act by inducing a self-perpetuating vicious cycle. Such a vicious cycle mechanism has been proposed to explain the etiology of CFS and MCS, based on elevated levels of nitric oxide and its potent oxidant product, peroxynitrite. Six positive feedback loops were proposed to act such that when peroxynitrite levels are elevated, they may remain elevated. The biochemistry involved is not highly tissue-specific, so that variation in symptoms may be explained by a variation in nitric oxide/peroxynitrite tissue distribution. The evidence for the same biochemical mechanism in the etiology of PTSD and FM is discussed here, and while less extensive than in the case of CFS and MCS, it is nevertheless suggestive. Evidence supporting the role of elevated nitric oxide/peroxynitrite in these four disease states is summarized, including induction of nitric oxide by common apparent inducers of these disease states, markers of elevated nitric oxide/ peroxynitrite in patients and evidence for an inductive role of elevated nitric oxide in animal models. This theory appears to be the first to provide a mechanistic explanation for the multiple overlaps of these disease states and it also explains the origin of many of their common symptoms and similarity to both Gulf War syndrome and chronic sequelae of carbon monoxide toxicity. This theory suggests multiple studies that should be performed to further test this proposed mechanism. If this mechanism proves central to the etiology of these four conditions, it may also be involved in other conditions of currently obscure etiology and criteria are suggested for identifying such conditions.

Med Hypotheses 2001 Jul; 57(2):139–45

Staud R, Vierck CJ, Cannon RL, Mauderli AP, Price DD

Abnormal sensitization and temporal summation of pain (wind-up) in patients with fibromyalgia syndrome

Although individuals with fibromyalgia syndrome (FMS) consistently report widespread pain, clear evidence of structural abnormalities or other sources of chronic stimulation of pain afferents in the involved body areas is lacking. Without convincing evidence for

peripheral tissue abnormalities in FMS patients, it seems likely that a central pathophysiological process is at least partly responsible for FMS, as is the case for many chronic pain conditions. Therefore, the present study sought to obtain psychophysical evidence for the possibility that input to central nociceptive pathways is abnormally processed in individuals with longstanding FMS. In particular, temporal summation of pain (wind-up) was assessed, using series of repetitive thermal stimulation of the glabrous skin of the hands. Although wind-up was evoked both in control and FMS subjects, clear differences were observed. The perceived magnitude of the sensory response to the first stimulus within a series was greater for FMS subjects compared to controls, as was the amount of temporal summation within a series. Within series of stimuli, FMS subjects reported increases in sensory magnitude to painful levels for interstimulus intervals of 2–5 s, but pain was evoked infrequently at intervals greater than 2 s for control subjects. Following the last stimulus in a series, after-sensations were greater in magnitude, lasted longer and were more frequently painful in FMS subjects. These results have multiple implications for the general characterization of pain in FMS and for an understanding of the underlying pathophysiological basis.

Pain 2001 Mar; 91(1-2):165–75

Thomas AW, White KP, Drost DJ, Cook CM, Prato FS

A comparison of rheumatoid arthritis and fibromyalgia patients and healthy controls exposed to a pulsed (200 microT) magnetic field: effects on normal standing balance

Specific weak time-varying pulsed magnetic fields (MF) have been shown to alter animal and human behaviors, including pain perception and postural sway. Here we demonstrate an objective assessment of exposure to pulsed MF's on Rheumatoid Arthritis (RA) and Fibromyalgia (FM) patients and healthy controls using standing balance. 15 RA and 15 FM patients were recruited from a university hospital outpatient Rheumatology Clinic and 15 healthy controls from university students and personnel. Each subject stood on the center of a 3-D forceplate to record postural sway within three square orthogonal coil pairs (2 m, 1.75 m, 1.5 m) which generated a spatially uniform MF centered at head level. Four 2-min exposure conditions (eyes open/eyes closed, sham/MF) were applied in a random order. With eyes open and during sham exposure, FM patients and controls appeared to have similar standing balance, with RA patients worse. With eyes closed, postural sway worsened for all three groups, but more for RA and FM patients than controls. The Romberg Quotient (eyes closed/eyes open) was highest among FM patients. Mixed design analysis of variance on the center of pressure (COP) movements showed a significant interaction of eyes open/closed and sham/MF conditions [$F = 8.78 (1,42), p < 0.006$]. Romberg Quotients of COP movements improved significantly with MF exposure [$F = 9.5$

(1,42), $p < 0.005$] and COP path length showed an interaction approaching significance with clinical diagnosis [$F = 3.2$ (1,28), $p < 0.09$]. Therefore RA and FM patients, and healthy controls, have significantly different postural sway in response to a specific pulsed MF.

Neurosci Lett 2001 Aug 17; 309(1):17–20

Wallace DJ, Hallegua DS

Quality-of-life, legal-financial, and disability issues in fibromyalgia

Patients with fibromyalgia have an altered quality of life that is hard to quantitate using existing indices. The principal legal issues associated with the syndrome are: Does fibromyalgia exist? Can it be caused by or flared by stress or trauma? Does disability apply to fibromyalgia and if so, how? These issues are critically reviewed.

Curr Pain Headache Rep 2001 Aug; 5(4):313–9

Wallace DJ, Linker-Israeli M, Hallegua D, Silverman S, Silver D, Weisman MH

Cytokines play an aetiopathogenetic role in fibromyalgia: a hypothesis and pilot study

OBJECTIVE: To measure soluble factors having a possible role in fibromyalgia (FM) and compare the profiles of patients with recent onset of the syndrome with patients with chronic FM. **METHODS:** The production of cytokines, cytokine-related molecules, and a CXC chemokine, interleukin (IL-8), was examined. Fifty-six patients with FM (23 with < 2 yr and 33 with > 2 yr of symptoms) were compared with age- and sex-matched healthy controls. Cytokines and cytokine-related molecules were measured in sera and in supernatants of peripheral blood mononuclear cells (PBMC) that were incubated with and without lectins and phorbol myristate acetate (PMA). **RESULTS:** No differences between FMS and controls were found by measuring IL-1beta, IL-2, IL-10, serum IL-2 receptor (sIL-2R), interferon gamma (IFN-gamma), and tumour necrosis factor alpha (TNF-alpha). Levels of IL-1R antibody (IL-1Ra) and IL-8 were significantly higher in sera, and IL-1Ra and IL-6 were significantly higher in stimulated and unstimulated FM PBMC compared with controls. Serum IL-6 levels were comparable to those in controls, but were elevated in supernatants of in vitro-activated PBMC derived from patients with > 2 yr of symptoms. In the presence of PMA, there were additional increases in IL-1Ra, IL-8 and IL-6 over control values. **CONCLUSIONS:** In patients with FM we found increases over time in serum levels

and/or PBMC-stimulated activity of soluble factors whose release is stimulated by substance P. Because IL-8 promotes sympathetic pain and IL-6 induces hyperalgesia, fatigue and depression, it is hypothesized that they may play a role in modulating FM symptoms. *Rheumatology* (Oxford) 2001 Jul; 40(7):743–9

Werle E, Fischer HP, Muller A, Fiehn W, Eich W

Antibodies against serotonin have no diagnostic relevance in patients with fibromyalgia syndrome

OBJECTIVE: To determine the prevalence and potential diagnostic relevance of autoantibodies against serotonin, thromboplastin, and ganglioside Gm1 in patients with fibromyalgia syndrome (FM). METHODS: Sera from 203 patients with FM and 64 pain-free control subjects were analyzed with enzyme immunoassays. Clinical and psychometric data of the patients were analyzed for the presence or absence of autoantibodies. RESULTS: Compared with control subjects patients with FM had a significantly higher prevalence of autoantibodies against serotonin (20% vs 5%; $p = 0.003$) and thromboplastin (43% vs 9%; $p < 0.001$), but not against ganglioside Gm1 (15% vs 9%; $p = 0.301$). Differences in autoantibody prevalence between controls and FM patients were not related to age or sex. No association was found between autoantibody pattern and clinical or psychometric data, e.g., pain, depression, pain related anxiety, and activities of daily living. CONCLUSION: There is an elevated prevalence of antibodies against serotonin and thromboplastin in patients with FM. The pathophysiological significance of this finding is unknown. Calculation of positive predictive values of antiserotonin antibodies shows that measurement of these antibodies has no diagnostic relevance.

J Rheumatol 2001 Mar; 8(3):595–600

Wittrup IH, Jensen B, Bliddal H, Danneskiold-Samsøe B, Wiik A

Comparison of viral antibodies in 2 groups of patients with fibromyalgia

OBJECTIVE: The etiologies of fibromyalgia (FM) are unknown. In some cases an acute onset following a flu-like episode is described; in other cases patients report slowly developing disease. We previously found increased prevalence of enterovirus IgM antibodies in patients with acute onset of FM compared to healthy controls. We looked for differences in antimicrobial IgM antibodies in acute versus nonacute onset FM. METHODS: Two well defined, comparable groups of patients with FM (acute 19, nonacute 20) were studied for antibodies in serum to an array of viruses including IgM antibodies. RESULTS:

In most viruses no IgM antibodies were found. However, about 50% of the patients with acute FM onset had IgM antibodies against enterovirus compared to only 15% of the slow onset patients. CONCLUSION: The higher prevalence of IgM antibodies against enterovirus in patients with acute onset of FM may indicate a difference in the etiology or the immune response in these patients.

J Rheumatol 2001 Mar; 8(3):601–3

Worrel LM, Krahn LE, Sletten CD, Pond GR

Treating fibromyalgia with a brief interdisciplinary program: initial outcomes and predictors of response

OBJECTIVES: To evaluate the efficacy of a brief, intense treatment program for fibromyalgia and to determine which patient characteristics are associated with a better treatment response. PATIENTS AND METHODS: Two self-report measures, the Fibromyalgia Impact Questionnaire (FIQ) and the Multidimensional Pain Inventory (MPI), were administered before patients completed treatment and 1 month after participating in the program. The main outcome measure was the difference in FIQ score and MPI scale before and after program participation. RESULTS: Of 139 patients who met the American College of Rheumatology criteria for fibromyalgia, 100 chose to participate in the 1 1/2-day Fibromyalgia Treatment Program at the Mayo Clinic, Rochester, Minn. Of these 100 patients, 74 completed the follow-up surveys. Patients were less affected by fibromyalgia after participation in the treatment program. This was demonstrated by a post-treatment improvement in the total FIQ score ($p < .001$), the MPI pain severity score ($p < .001$), and the MPI interference score ($p = .01$). The 1 patient characteristic found to be significantly associated ($p < .001$) with a better response to treatment was a high pretreatment level of impairment from fibromyalgia, as measured by the pretreatment FIQ score. CONCLUSIONS: A brief interdisciplinary program for treating fibromyalgia reduced some associated symptoms. Patients more severely affected by fibromyalgia may benefit most from this approach. Clinicians may apply these findings to develop beneficial and convenient treatment programs for patients with fibromyalgia.

Mayo Clin Proc 2001 Apr; 76(4):384–90

Yunus MB

The role of gender in fibromyalgia syndrome

Fibromyalgia syndrome (FMS), characterized by widespread pain and tenderness on palpation (tender points), is much more common in women than in men in a proportion of

9:1. Two recent studies have shown important gender differences in various clinical characteristics of FMS. In a community and a clinic sample, women experienced significantly more common fatigue, morning fatigue, hurt all over, total number of symptoms, and irritable bowel syndrome. Women had significantly more tender points. Pain severity, global severity and physical functioning were not significantly different between the sexes, nor were psychological factors, e.g., anxiety, stress, and depression. Gender differences have also been observed in other related syndromes, e.g., chronic fatigue syndrome, irritable bowel syndrome, and headaches. The mechanisms of gender differences in these illnesses are not fully understood, but are likely to involve an interaction between biology, psychology, and sociocultural factors.

Curr Rheumatol Rep 2001 Apr; 3(2):128–34