

FIBROMYALGIA: ABSTRACTS 2004 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 2004. 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, 2004, and abstracts will be added to this selection at the end of the year. Similar collections of abstracts produced annually from 1999 on can be found on the website of the National Fibromyalgia Partnership: www.fmpartnership.org.

The abstracts are arranged in alphabetical order by lead author.

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

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

OBJECTIVE: To assess the efficacy and safety of duloxetine, a serotonin and norepinephrine reuptake inhibitor, in subjects with primary fibromyalgia, with or without current major depressive disorder. **METHODS:** This study was a randomized, double-blind, placebo-controlled trial conducted in 18 outpatient research centers in the US. A total of 207 subjects meeting the American College of Rheumatology criteria for primary fibromyalgia were enrolled (89% female, 87% white, mean age 49 years, 38% with current major depressive disorder). After single-blind placebo treatment for 1 week, subjects were randomly assigned to receive duloxetine 60 mg twice a day (n = 104) or placebo (n = 103) for 12 weeks. Co-primary outcome measures were the Fibromyalgia Impact Questionnaire (FIQ) total score (score range 0–80, with 0 indicating no impact) and FIQ pain score (score range 0–10). Secondary outcome measures included mean tender point pain threshold, number of tender points, FIQ fatigue, tiredness on awakening, and stiffness scores, Clinical Global Impression of Severity (CGI-Severity) scale, Patient Global Impression of Improvement (PGI-Improvement) scale, Brief Pain Inventory (short form), Medical Outcomes Study Short Form 36, Quality of Life in Depression Scale, and Sheehan Disability Scale. **RESULTS :** Compared with placebo-treated subjects, duloxetine-treated subjects improved significantly more (P = 0.027) on the FIQ total score, with a treatment difference of -5.53 (95% confidence interval -10.43, -0.63), but not significantly more on the FIQ pain score (P = 0.130). Compared with placebo-treated subjects, duloxetine-

treated subjects had significantly greater reductions in Brief Pain Inventory average pain severity score ($P = 0.008$), Brief Pain Inventory average interference from pain score ($P = 0.004$), number of tender points ($P = 0.002$), and FIQ stiffness score ($P = 0.048$), and had significantly greater improvement in mean tender point pain threshold ($P = 0.002$), CGI-Severity ($P = 0.048$), PGI-Improvement ($P = 0.033$), and several quality-of-life measures. Duloxetine treatment improved fibromyalgia symptoms and pain severity regardless of baseline status of major depressive disorder. Compared with placebo-treated female subjects ($n = 92$), duloxetine-treated female subjects ($n = 92$) demonstrated significantly greater improvement on most efficacy measures, while duloxetine-treated male subjects ($n = 12$) failed to improve significantly on any efficacy measure. The treatment effect on significant pain reduction in female subjects was independent of the effect on mood or anxiety. Duloxetine was safely administered and well tolerated. **CONCLUSION:** In this randomized, controlled, 12-week trial (with a 1-week placebo lead-in phase), **duloxetine was an effective and safe treatment for many of the symptoms associated with fibromyalgia in subjects with or without major depressive disorder, particularly for women, who had significant improvement across most outcome measures.**

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

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

Family study of fibromyalgia

OBJECTIVE: To assess for familial aggregation of fibromyalgia (FM) and measures of tenderness and pain, and for familial coaggregation of FM and major mood disorder (major depressive disorder or bipolar disorder). **METHODS:** Proband meeting the American College of Rheumatology criteria for FM and control probands with rheumatoid arthritis (RA) and no lifetime diagnosis of FM were recruited from consecutive referrals to 2 community-based rheumatology practices. Proband were ages 40–55 years and had at least 1 first-degree relative age 18 years or older who was available for interview and examination. All probands and interviewed relatives underwent a dolorimeter tender point examination and a structured clinical interview. Interviewed relatives were asked about first-degree relatives who were not available for interview, using a structured family interview. Logistic and linear regression models, adjusting for the correlation of observation within families, were applied to study the aggregation and coaggregation effects. **RESULTS:** Information was collected for 533 relatives of 78 probands with FM and 272 relatives of 40 probands with RA. FM aggregated strongly in families: the odds ratio (OR) measuring the odds of FM in a relative of a proband with FM versus the odds of FM in a relative of a proband with RA was 8.5 (95% confidence interval [95% CI] 2.8–26, $P = 0.0002$). The number of tender points was significantly higher, and the total myalgic score was significantly lower in the relatives of probands with FM compared with the relatives of probands

with RA. FM coaggregated significantly with major mood disorder: the OR measuring the odds of major mood disorder in a relative of a proband with FM versus the odds of major mood disorder in a relative of a proband with RA was 1.8 (95% CI 1.1–2.9, P = 0.013). **CONCLUSION: FM and reduced pressure pain thresholds aggregate in families, and FM coaggregates with major mood disorder in families. These findings have important clinical and theoretical implications, including the possibility that genetic factors are involved in the etiology of FM and in pain sensitivity.** In addition, mood disorders and FM may share some of these inherited factors.

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

Axovan Ltd. [no authors listed]

Pregabalin (Pfizer)

Pregabalin is a gamma-aminobutyric acid analog that is **under development by Pfizer for the potential treatment of central nervous system disorders, including epilepsy, neuropathic pain, fibromyalgia and generalized anxiety disorder.** By April 2003, Pfizer had filed for approval of pregabalin in Europe for neuropathic pain and as an adjunctive therapy for epilepsy, and in October 2003 an NDA was filed for these indications and generalized anxiety disorder. At this time, phase III trials in fibromyalgia were ongoing.

Curr Opin Investig Drugs. 2004 Jan; 5(1):82–9

Bagis S, Tamer L, Sahin G, Bilgin R, Guler H, Ercan B, Erdogan C

Free radicals and antioxidants in primary fibromyalgia: an oxidative stress disorder?

The role of free radicals in fibromyalgia is controversial. In this study, 85 female patients with primary fibromyalgia and 80 age-, height-, and weight-matched healthy women were evaluated for oxidant/antioxidant balance. Malondialdehyde is a toxic metabolite of lipid peroxidation used as a marker of free radical damage. Superoxide dismutase is an intracellular antioxidant enzyme and shows antioxidant capacity. Pain was assessed by visual analog scale. Tender points were assessed by palpation. Age, smoking, body mass index (BMI), and duration of disease were also recorded. Malondialdehyde levels were significantly higher and superoxide dismutase levels significantly lower in fibromyalgic patients than controls. Age, BMI, smoking, and duration of disease did not affect these parameters. We found no correlation between pain and number of tender points. In conclusion, **oxidant/antioxidant balances were changed in fibromyalgia. Increased free radical levels may be responsible for the development of fibromyalgia.** These findings may support the hypothesis of fibromyalgia as an oxidative disorder.

Rheumatol Int. 2003 Dec 20

Banic B, Petersen-Felix S, Andersen OK, Radanov BP, Villiger PM, Arendt-Nielsen L, Curatolo M

Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in fibromyalgia

Patients with chronic pain after whiplash injury and fibromyalgia patients display exaggerated pain after sensory stimulation. Because evident tissue damage is usually lacking, this exaggerated pain perception could be explained by hyperexcitability of the central nervous system. The nociceptive withdrawal reflex (a spinal reflex) may be used to study the excitability state of spinal cord neurons. We tested the hypothesis that patients with chronic whiplash pain and fibromyalgia display facilitated withdrawal reflex and therefore spinal cord hypersensitivity. Three groups were studied: whiplash (n = 27), fibromyalgia (n = 22) and healthy controls (n = 29). Two types of transcutaneous electrical stimulation of the sural nerve were applied: single stimulus and five repeated stimuli at 2 Hz. Electromyography was recorded from the biceps femoris muscle. The main outcome measurement was the minimum current intensity eliciting a spinal reflex (reflex threshold). Reflex thresholds were significantly lower in the whiplash compared with the control group, after both single (P = 0.024) and repeated (P = 0.035) stimulation. The same was observed for the fibromyalgia group, after both stimulation modalities (P = 0.001 and 0.046, respectively). **We provide evidence for spinal cord hyperexcitability in patients with chronic pain after whiplash injury and in fibromyalgia patients. This can cause exaggerated pain following low intensity nociceptive or innocuous peripheral stimulation. Spinal hypersensitivity may explain, at least in part, pain in the absence of detectable tissue damage.**

Pain. 2004 Jan; 107(1-2):7-15

Bennett R

Growth hormone in musculoskeletal pain states

Growth hormone is essential for normal linear growth and the attainment of an adult mature height. It also plays an important role in cartilage growth and the attainment of normal bone mass. There is only one rheumatic disorder, namely acromegaly, in which abnormalities of growth hormone production play a major etiologic role. However, there is increasing appreciation that **suboptimal growth hormone secretion, leading to a state of adult growth hormone deficiency, may occur in the setting of chronic inflammatory disease, chronic corticosteroid use, and fibromyalgia.** Therefore, the evaluation and effective management of growth hormone oversecretion and undersecretion is relevant to practicing rheumatologists.

Curr Rheumatol Rep. 2004 Aug; 6(4):266-73

Berger A, Dukes EM, Oster G

Clinical characteristics and economic costs of patients with painful neuropathic disorders

Using a large US health insurance claims database, we identified all persons aged 18 years or older with 2 or more medical encounters in calendar year 2000 for painful neuropathic disorders (PNDs). We also identified an age- and gender-matched group of patients without PNDs (matched control subjects). We then compared the clinical characteristics and economic costs of PND patients with those of matched control subjects. There were a total of 55,686 patients with PNDs in the study database. The most frequently noted PNDs were back and neck pain with neuropathic involvement (62.3% of PND patients), causalgia (12.1%), and diabetic neuropathy (10.8%). In comparison with matched control subjects, PND patients were more likely to have other pain-related conditions, including fibromyalgia (6.0% vs 0.6% for control subjects), osteoarthritis (13.6% vs 3.6%), and other chronic comorbidities, such as coronary heart disease (13.6% vs 6.5%) and depression (6.4% vs 2.3%). Total calendar year 2000 health care charges were 3-fold higher for PND patients than matched control subjects (\$17,355 vs \$5,715, respectively). Our results suggest that patients with PNDs are generally in poorer health and have higher health care costs than their peers without these conditions. **PERSPECTIVE: Use of nonsteroidal anti-inflammatory agents and opioids was widespread in patients with PNDs, while relatively few received antiepileptic drugs and tricyclic antidepressants, both of which are often more effective against neuropathic pain.** Our study raises questions about the optimality of PND treatment in clinical practice.

J Pain. 2004 Apr; 5(3):143-9

Calis M, Gokce C, Ates F, Ulker S, Izgi HB, Demir H, Kirnap M, Sofuoglu S, Durak AC, Tutus A, Kelestimur F

Investigation of the hypothalamo-pituitary-adrenal axis (HPA) by 1 microg ACTH test and metyrapone test in patients with primary fibromyalgia syndrome

Primary fibromyalgia syndrome (PFS) is characterized by widespread chronic pain that affects the musculoskeletal system, fatigue, anxiety, sleep disturbance, headache and postural hypotension. The pathophysiology of PFS is unknown. The hypothalamic-pituitary-adrenal (HPA) axis seems to play an important role in PFS. Both hyperactivity and hypoactivity of the HPA axis have been reported in patients with PFS. In this study we assessed the HPA axis by 1 microg ACTH stimulation test and metyrapone test in 22 patients with PFS and in 15 age-, sex-, and body-mass-index (BMI)-matched controls. Metyrapone (30 mg/kg) was administered orally at 23:00h and blood was sampled at 08:30h the following morning for 11-deoxycortisol. ACTH stimulation test was carried out by using 1

microg (iv) ACTH as a bolus injection after an overnight fast, and blood samples were drawn at 0, 30 and 60 min. Peak cortisol level (659.4 ± 207.2 nmol/l) was lower in the patients with PFS than peak cortisol level (838.7 ± 129.6 nmol/l) in the control subjects ($p < 0.05$). Ten patients (45%) with PFS had peak cortisol responses to 1 microg ACTH test lower than the lowest peak cortisol detected in healthy controls. After metyrapone test 11-deoxycortisol level was 123.7 ± 26 nmol/l in patients with PFS and 184.2 ± 17.3 nmol/l in the controls ($p < 0.05$). Ninety five percent of the patients with PFS had lower 11-deoxycortisol level after metyrapone than the lowest 11-deoxycortisol level after metyrapone detected in healthy controls. We also compared the adrenal size of the patients with that of the healthy subjects and we found that the adrenal size between the groups was similar. **This study clearly shows that HPA axis is underactivated in PFS, rather than overactivated.**

J Endocrinol Invest. 2004 Jan; 27(1):42–6

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

Functional imaging of pain in patients with primary fibromyalgia

OBJECTIVE: To examine the function of the nociceptive system in patients with fibromyalgia (FM) using functional magnetic resonance imaging (fMRI). **METHODS:** Two groups of women, 9 with FM and 9 pain-free, volunteered to participate. In Experiment 1, we assessed psychophysical responses to painful stimuli and prepared participants for fMRI testing. For Experiment 2, subjects underwent fMRI scanning while receiving painful and nonpainful heat stimuli. Conventional and functional MR images were acquired using a 1.5 T MR scanner. Scanning occurred over 5 conditions. Condition 1 served as a practice session (no stimuli). Conditions 2 and 5 consisted of nonpainful warm stimuli. Conditions 3 and 4 consisted of an absolute thermal pain stimulus (47 degrees C) and a perceptually equivalent pain stimulus delivered in counterbalanced order. **RESULTS:** Experiment 1 indicated that subjects with FM were significantly more sensitive to experimental heat pain than controls ($p < 0.001$). In Experiment 2, fMRI data indicated that the FM group exhibited greater activity than controls over multiple brain regions in response to both nonpainful and painful stimuli ($p < 0.01$). Specifically, in response to nonpainful warm stimuli, FM subjects had significantly greater activity than controls in prefrontal, supplemental motor, insular, and anterior cingulate cortices ($p < 0.01$). In response to painful stimuli, FM subjects had greater activity in the contralateral insular cortex ($p < 0.01$). **Data from the practice session indicated brain activity in pain-relevant areas for the FM group but not for controls.** **CONCLUSION:** Our results provide further evidence for a physiological explanation for FM pain.

J Rheumatol. 2004 Feb; 31(2):364–78

Crofford LJ

Pharmaceutical treatment options for fibromyalgia

Fibromyalgia syndrome (FMS) is a chronic multisymptom illness characterized by widespread pain and associated with neuropsychological symptoms including fatigue, unrefreshing sleep, cognitive dysfunction, anxiety, and depression. A discrete cause of FMS has not been identified. It is likely that multiple mechanisms give rise to symptom expression. Understanding specific etiologic factors and pathogenic mechanisms in individual patients will allow clinicians to determine treatments that are most effective for a given patient. Available evidence implicates the central nervous system as key in maintaining pain and other core symptoms of FMS. The approach to treatment of pain will typically address these central mechanisms. Nonpain symptoms may be treated by drugs affecting similar central neurochemicals. **This paper will review the rationale for the different types of pharmaceutical treatments that may be useful for the treatment of FMS** and issues regarding new drug development for this indication.

Curr Rheumatol Rep. 2004 Aug; 6(4): 274–80

Denko CW, Malemud CJ

Serum growth hormone and insulin but not insulin-like growth factor-1 levels are elevated in patients with fibromyalgia syndrome

Standard radioimmunoassay (RIA) was employed to quantify basal serum growth hormone (GH), insulin-like growth factor-I (IGF-1), and insulin levels in 32 normoglycemic patients with clinically active fibromyalgia and in 29 normoglycemic control subjects. The GH concentration was significantly higher ($P < 0.001$) in female fibromyalgia patients than age-matched, normal female subjects. In contrast, basal serum IGF-1 concentrations did not differ between these groups. A scatter plot generated from two-stage, least-squares analysis showed that serum GH lacked correlation with the serum IGF-1 concentrations of normal female subjects ($P = 0.73$) and female fibromyalgia patients ($P = 0.19$). In addition to the results from serum GH and IGF-1 RIA, we also found significantly higher fasting serum insulin levels ($P = 0.03$) in male fibromyalgia patients and a trend toward elevated fasting serum insulin levels in the female fibromyalgia population ($P = 0.07$), with the mean fasting level in the male fibromyalgia group (35.7 microU/ml(-1)) exceeding the upper limit of normal serum insulin levels (i.e., 27 microU/ml(-1)). **Based on these results, basal serum GH and fasting serum insulin levels appear to be valuable surrogate markers in clinically active, normoglycemic fibromyalgia patients.**

Rheumatol Int. 2004 Jul 24

DeWalt DA, Reed GW, Pincus T

Further clues to recognition of patients with fibromyalgia from a simple 2-page patient multidimensional health assessment questionnaire (MDHAQ)

OBJECTIVE: To analyze quantitative scores for pain, fatigue, functional disability, and the number of symptoms on a review of systems on a multidimensional health assessment questionnaire (MDHAQ), including the ratios of scores for pain to physical function and fatigue to physical function, and to further study how these scores can help to identify patients with fibromyalgia. METHODS: All consecutive patients seen at a rheumatology clinic completed a 2-sided, 1-page MDHAQ at each visit to assess physical function, pain, fatigue, global status, helplessness and review of systems, and had their erythrocyte sedimentation rate (ESR) measured. Scores for these variables were analyzed in 78 consecutive patients with fibromyalgia over a two-year period, and in 149 patients with rheumatoid arthritis (RA) as a "control" group. A subset analysis was conducted in patients with RA who were classified independently according to clinical criteria as having or not having coexistent fibromyalgia. Descriptive statistics, logistic regression, and receiver-operating-characteristic curves were computed for patients with fibromyalgia and compared to patients with RA. RESULTS: Patients with fibromyalgia had high ratios of pain:physical function and fatigue:physical function scores, and a high number of reported symptoms. These quantitative data differed significantly from patients with RA. Patients with fibromyalgia also had a lower ESR than patients with RA, whose scores were similar whether or not there was coexistent fibromyalgia. Patients with fibromyalgia were distinguished equally well from patients with RA by patient questionnaire data as by the ESR. CONCLUSION: **A simple 1-page, 2-sided patient questionnaire provides quantitative information which may contribute to identify patients with fibromyalgia, including patients with RA who may also have coexistent fibromyalgia.**

Clin Exp Rheumatol 2004 Jul-Aug; 22(4):453-61

Finset A, Wigers SH, Gotestam KG

Depressed mood impedes pain treatment response in patients with fibromyalgia

OBJECTIVE: To investigate prognostic factors in the course of the fibromyalgia syndrome (FM) from baseline to post-treatment. METHODS: Fifty-seven patients with FM were examined in a randomized intervention study. Pre-treatment variables were entered into linear regression analyses: gender, age, duration of disease, allocation to treatment, pain distribution (based on a patient-made drawing), fatigue, sleep disturbance, and depressed mood (based on visual analog scores), with pain distribution at treatment completion as the dependent variable.

RESULTS: Depressed mood at baseline was a significant predictor of sustained widespread pain at treatment completion. CONCLUSION: **The findings indicate a role for depressed mood as a predictive factor for treatment response.**

J Rheumatol. 2004 May; 31(5):976–80

Gold AR, Dipalo F, Gold MS, Broderick J

Inspiratory airflow dynamics during sleep in women with fibromyalgia

STUDY OBJECTIVES: To determine whether women with fibromyalgia have inspiratory airflow dynamics during sleep similar to those of women with upper-airway resistance syndrome (UARS). DESIGN: A descriptive study of consecutive female patients with fibromyalgia. SETTING: An academic sleep disorders center. PATIENTS OR PARTICIPANTS: Twenty-eight women with fibromyalgia diagnosed by rheumatologists using established criteria. Fourteen of the women gave a history of snoring, while 4 claimed to snore 'occasionally' and 10 denied snoring. The comparison group comprised 11 women with UARS matched for age and obesity. INTERVENTIONS: Eighteen of the 28 women with fibromyalgia and all of the women with UARS had a full-night polysomnogram. All participants had a nasal continuous positive airway pressure (CPAP) study with quantitative monitoring of inspiratory airflow and effort between atmospheric pressure and therapeutic CPAP. Fourteen patients with fibromyalgia and all patients with UARS had a successful determination of pharyngeal critical pressure. MEASUREMENTS AND RESULTS: Twenty-seven of 28 women with fibromyalgia had sleep-disordered breathing. One of the 27 had obstructive sleep apnea hypopnea while 26 had milder inspiratory airflow limitation with arousals. One patient had no apnea or hypopnea or inspiratory airflow limitation during sleep. While the patients were sleeping at atmospheric pressure, apnea-hypopnea index, arousal index, the prevalence of flow-limited breaths, and maximal inspiratory flow were similar between groups. The pharyngeal critical pressure of the patients with fibromyalgia was -6.5 ± 3.5 cmH₂O (mean \pm SD) compared to -5.8 ± 3.5 cmH₂O for patients with UARS ($P = .62$). Treatment of 14 consecutive patients with nasal CPAP resulted in an improvement in functional symptoms ranging from 23% to 47%, assessed by a validated questionnaire. CONCLUSION: **Inspiratory airflow limitation is a common inspiratory airflow pattern during sleep in women with fibromyalgia.** Our findings are compatible with the hypothesis that inspiratory flow limitation during sleep plays a role in the development of the functional somatic syndromes.

Sleep. 2004 May 1; 27(3):459–6

Gowans SE, deHueck A

Effectiveness of exercise in management of fibromyalgia

PURPOSE OF REVIEW: Exercise was established as an integral part of the nonpharmacological treatment of fibromyalgia approximately 20 years ago. Since then many studies have investigated the effects of exercise—either alone or in combination with other interventions. This review will discuss the benefits of exercise alone and provide practical suggestions on how patients can exercise without causing a long-term exacerbation of their pain. **RECENT FINDINGS: Short-term exercise programs for individuals with fibromyalgia have consistently improved physical function, especially physical fitness, and reduced tenderpoint pain. Exercise has also produced improvements in self-efficacy.** These effects can persist for periods of up to 2 years but may require participants to continue to exercise. Most exercise studies have examined the effects of moderately intense aerobic exercise. Only in the past 2 years have muscle-strengthening programs, in isolation, been evaluated. **To be well tolerated, exercise programs must start at a level just below the capacity of the participants and then progress slowly.** Even with these precautions, exercise may still produce tolerable, short-term increases in pain and fatigue that should abate within the first few weeks of exercising. **SUMMARY:** Future studies should investigate the possible benefits of low-intensity exercise and test strategies that may enhance long-term compliance with exercise. Individuals with fibromyalgia also need to be able to access community exercise programs that are appropriate for them. This may require community instructors to receive instruction on exercise prescription and progression for individuals with fibromyalgia.

Curr Opin Rheumatol. 2004 Mar;16(2):138–42

Gronemann ST, Ribel-Madsen S, Bartels EM,
Danneskiold-Samsøe B, Bliddal H

Collagen and muscle pathology in fibromyalgia patients

OBJECTIVE: To measure collagen concentration and search for muscle pathology in muscle non-tender-point areas from fibromyalgia (FM) patients. **METHODS:** Muscle biopsies were obtained from m. vastus lateralis of 27 carefully selected, female fibromyalgia patients, and from eight age-matched female control subjects. Amino acids were determined by HPLC and electron microscopy was performed. **RESULTS:** The FM patients had lower hydroxyproline and lower total concentration of the major amino acids of collagen than the controls. No significant difference was seen in the concentration of the major amino acids of myosin or of total protein. Electron microscopy showed no significant differences between FM patients and controls although atrophied muscle fibrils occurred in FM patients only, but frequencies were not significantly different. **CONCLUSION:**

Fibromyalgia patients had a significantly lower amount of intramuscular collagen. This may lower the threshold for muscle micro-injury and thereby result in non-specific signs of muscle pathology.

Rheumatology (Oxford). 2004 Jan; 43(1):27–31. Epub 2003 Jul 16

Grothe DR, Scheckner B, Albano D

Treatment of pain syndromes with venlafaxine

Major depressive disorder (MDD) and anxiety disorders such as generalized anxiety disorder (GAD) are often accompanied by chronic painful symptoms. Examples of such symptoms are backache, headache, gastrointestinal pain, and joint pain. In addition, pain generally not associated with major depression or an anxiety disorder, such as peripheral neuropathic pain (e.g., diabetic neuropathy and postherpetic neuralgia), cancer pain, and fibromyalgia, can be challenging for primary care providers to treat. Antidepressants that block reuptake of both serotonin and norepinephrine, such as the tricyclic antidepressants (e.g., amitriptyline), have been used to treat pain syndromes in patients with or without comorbid MDD or GAD. Venlafaxine, a serotonin and norepinephrine reuptake inhibitor, has been safe and effective in animal models, healthy human volunteers, and patients for treatment of various pain syndromes. **The use of venlafaxine for treatment of pain associated with MDD or GAD, neuropathic pain, headache, fibromyalgia, and postmastectomy pain syndrome is reviewed. Currently, no antidepressants, including venlafaxine, are approved for the treatment of chronic pain syndromes.** Additional randomized, controlled trials are necessary to fully elucidate the role of venlafaxine in the treatment of chronic pain.

Pharmacotherapy. 2004 May; 24(5):621–9

Kendall SA, Schaadt ML, Graff LB, Wittrup I, Malmskov H, Krogsgaard K, Bartels EM, Bliddal H, Danneskiold-Samsøe B

No effect of antiviral (valacyclovir) treatment in fibromyalgia: a double blind, randomized study

OBJECTIVE: To investigate the effect of an antiviral compound, valacyclovir, on pain and tenderness in patients with the fibromyalgia (FM) syndrome. **METHODS:** Sixty patients were randomized into a double blind, placebo controlled 6 week trial. Primary outcome was pain intensity change (on visual analog scale). Secondary outcome measures were tender points (myalgic score) and Fibromyalgia Impact Questionnaire (FIQ). **RESULTS:** Fifty-two patients completed the study. The numbers of dropouts due to adverse events were equal in valacyclovir (2) and placebo (2) groups. **The effect of valacyclovir on pain and tenderness and FIQ did not differ from placebo.** **CONCLUSION:** Valacyclovir cannot be recommended as a therapy for FM at this point.

Decreased sleep spindles and spindle activity in midlife women with fibromyalgia and pain

OBJECTIVES: To compare sleep-spindle incidence (number of spindles per minute of non-rapid eye movement [NREM] stage 2 sleep) and duration, spindle wave time (seconds per epoch in NREM stage 2 sleep), spindle frequency activity, and pain measures (pressure pain threshold, number of tender points, skinfold tenderness) between midlife women with fibromyalgia (FM) and moderate to high pain to a control group of sedentary women without pain. A second goal was to explore the extent to which pain pressure thresholds, age, and depression explain the variance in spindle incidence. **DESIGN:** A cross-sectional descriptive study. **SETTING:** A university-based sleep research laboratory and a referral clinic for chronic fatigue and pain. **PARTICIPANTS:** Thirty-seven medication-free women with FM (mean age, 44.9 +/- 8 years) and 30 women with self-reported good sleep and no pain (mean age, 44.1 +/- 7.7 years) completed a psychiatric interview and the Beck Depression Inventory prior to 2 consecutive nights of polysomnography, with pain measures obtained in the morning. Time domain analysis of spindle incidence and spectral analysis of spindle frequency activity were conducted on night 2 of polysomnography recordings. **Interventions:** NA. **RESULTS:** Women with FM had fewer mean spindles per minute of NREM stage 2 sleep and lower mean spindle time per epoch of NREM stage 2 sleep (both P values < .02), but mean spindle duration, although slightly shorter, was not statistically significantly different (P < .06) compared to control women. Women with FM had a lower mean pressure pain threshold, a higher average number of positive tender points, and higher skinfold tenderness compared to control women (all P values < .001). Group differences in spindle frequency activity were found after controlling for age, depression, and psychiatric diagnosis in a general linear model (P < .02). One-way analysis of variance revealed significantly lower spindle activity in the 3 frequency bins (12-12.5 Hz, 13-13.5 Hz, 14-14.5 Hz) at C3 (all P values < .04), Fz (all P values < .02), and Cz (all P values < .02). Finally, after controlling for age and depression, pain pressure threshold significantly predicted spindles per minute and spindle time per epoch of NREM stage 2 sleep ($r^2 = .26$; P < .001). **CONCLUSIONS:** Women with FM and pain have fewer sleep spindles and reduced electroencephalogram power in spindle frequency activity compared to control women of similar age. **These data imply that some aspect of thalamocortical mechanisms of spindle generation might be impaired in FM.**

Sleep. 2004 Jun 15; 27(4):741–50

Nielson WR, Jensen MP

Relationship between changes in coping and treatment outcome in patients with Fibromyalgia Syndrome

The present study utilized a sample of 198 individuals with Fibromyalgia Syndrome (FMS) to examine the association between treatment process variables (beliefs, coping strategies) and treatment outcomes (pain severity, activity level, emotional distress and life interference) related to a 4-week multidisciplinary fibromyalgia treatment program. Multiple regression analyses were utilized to evaluate these relationships pretreatment to posttreatment as well as from pretreatment to 3- and 6-month follow-ups. The results indicated that outcomes were most closely related to: (1) an increased sense of control over pain, (2) a belief that one is not necessarily disabled by FM, (3) a belief that pain is not necessarily a sign of damage, (4) decreased guarding, (5) increased use of exercise, (6) seeking support from others, (7) activity pacing and (8) use of coping self-statements. **These findings are consistent with a cognitive-behavioural model of fibromyalgia, and suggest targets for therapeutic change.**

Pain. 2004 Jun; 109(3):233–41

Rizzi M, Sarzi-Puttini P, Atzeni F, Capsoni F, Andreoli A, Pecis M, Colombo S, Carrabba M, Sergi M

Cyclic alternating pattern: a new marker of sleep alteration in patients with fibromyalgia?

OBJECTIVE: In the dynamic organization of sleep, cyclic alternating pattern (CAP) expresses a condition of instability of the level of vigilance that manifests the brain's fatigue in preserving and regulating the macrostructure of sleep. We evaluated the presence of CAP in patients with fibromyalgia (FM) compared to healthy controls. **METHODS:** Forty-five patients with FM (42 women) were studied and compared with 38 healthy subjects (36 women) matched for age, sex, and body mass index. Entry criteria were diagnosis of FM according to 1990 American College of Rheumatology criteria; willingness to participate in the study; and having no other diagnosis of autoimmune, neoplastic, or other possible causes of secondary diffuse musculoskeletal pain. Patients in the study underwent polysomnography recordings and a sleep questionnaire. Hypersomnolence was evaluated according to the Epworth Sleepiness Scale. **RESULTS:** FM patients had less sleep efficiency (sleep time/time in bed) than controls (79 +/- 10 vs 89 +/- 6; $p < 0.01$), a higher proportion of stage 1 non-rapid eye movement (non-REM) sleep (20 +/- 5 vs 12 +/- 5; $p < 0.001$), and twice as many arousals per hour of sleep (9.7 +/- 3.3 vs 4.1 +/- 1.9; $p < 0.01$). The CAP rate (total CAP time/non-REM sleep time) was significantly increased in FM patients compared to controls (68

+/- 6% vs 45 +/- 11%; $p < 0.001$). CAP rate seemed to correlate with the severity of clinical symptoms in FM patients (tender points index; $p < 0.01$) and with less efficiency of sleep ($p < 0.01$). **CONCLUSION: The increase of CAP rate indicates a worse quality of sleep in patients with FM. These data are strongly correlated to the severity of symptoms.**

J Rheumatol. 2004 Jun; 31(6):1193–9

Schaefer KM

Caring for the patient with fibromyalgia: the rehabilitation nurse's role

Fibromyalgia (FM) is a chronic, potentially disabling, cluster of symptoms that manifests as pain for 3 months or more and pain with pressure on 11 of 18 tender points throughout the body. Because there is no known cause, and therefore, no cure, treatment focuses on the control or relief of symptoms. Many patients are referred to rehabilitation settings for physical or exercise therapy. While exercise is helpful in the control of the pain, stiffness, fatigue, sleep disorders, and mood changes, a holistic approach to treatment is more effective. Rehabilitation nurses provide major support for patients with FM. Validation of the patients' experiences is essential for achieving quality of life. Many patients have a history of being undertreated because of a lack of credibility and invisibility of the illness. **This article provides background information about FM, summarizes the FM trajectory, reviews approaches to management, and discusses the role of rehabilitation nurses in a holistic approach to care of clients with FM.**

Rehabil Nurs. 2004 Mar–Apr; 29(2):49–55

Sprott H, Salemi S, Gay RE, Bradley LA, Alarcon GS,
Oh SJ, Michel BA, Gay S

Increased DNA fragmentation and ultrastructural changes in fibromyalgic muscle fibres

OBJECTIVE: To determine whether there is evidence of increased DNA fragmentation and ultrastructural changes in muscle tissue of patients with fibromyalgia (FM) compared with healthy controls. **METHODS:** Muscle tissues from 10 community residents with FM and 10 age and sex matched healthy controls were examined “blindly” for the presence of DNA fragmentation by two different methods: terminal deoxynucleotidyl transferase (TdT) staining (TUNEL) and the FragEL-Klenow DNA fragmentation detection kit. Ultrastructural analysis of tissue was performed by electron microscopy. **RESULTS:** DNA fragmentation was detected by both methods in 55.4 (SEM 2.5)% of the nuclei in muscle tissue of patients with FM compared with 16.1 (4.1)% ($p < 0.001$) of the nuclei in

healthy controls. Contrary to expectation, no typical features of apoptosis could be detected by electron microscopy. The myofibres and actin filaments were disorganised and lipofuscin bodies were seen; glycogen and lipid accumulation were also found. The number of mitochondria was significantly lower in patients with FM than in controls and seemed to be morphologically altered. **CONCLUSION: The ultrastructural changes described suggest that patients with FM are characterised by abnormalities in muscle tissue that include increased DNA fragmentation and changes in the number and size of mitochondria. These cellular changes are not signs of apoptosis. Persistent focal contractions in muscle may contribute to ultrastructural tissue abnormalities as well as to the induction and/or chronicity of nociceptive transmission from muscle to the central nervous system.**

Ann Rheum Dis. 2004 Mar; 63(3):245–51

Staud R

Fibromyalgia pain: do we know the source?

PURPOSE OF REVIEW: Fibromyalgia Syndrome (FMS) is a chronic pain condition of unknown origin. Multiple abnormalities have been described, including peripheral tissue and central nervous system changes. The relation of these mechanisms, however, is likely bidirectional. FMS pain clearly depends on peripheral nociceptive input as well as abnormal central pain processing. This review will focus on the role of peripheral nociceptive input for pain in FMS. **RECENT FINDINGS:** There is strong evidence for abnormal central pain processing in FMS. Sensitized spinal cord neurons in the dorsal horn are responsible for augmented pain processing of nociceptive signals from the periphery. In addition, glial activation, possibly by cytokines and excitatory amino acids may play a role in the initiation and perpetuation of this sensitized state. **SUMMARY: Nociceptive input clearly plays an important role in FMS. Acute or repetitive tissue injury has been associated with FMS pain. Cytokines related to such injuries may be responsible for long-term activation of spinal cord glia and dorsal horn neurons, thus resulting in central sensitization.** A better understanding of these important neuro-immune interactions may provide relevant insights into future effective therapies.

Curr Opin Rheumatol. 2004 Mar; 16(2):157–63

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

Body pain area and pain-related negative affect predict clinical pain intensity in patients with fibromyalgia

Patients with fibromyalgia (FM) report widespread chronic musculoskeletal pain. Palpation of 9 paired tender points (TPs) is commonly used for the diagnosis of

FM according to criteria specified by the American College of Rheumatology. Although TP palpation can be used to assess deep tissue hypersensitivity, it has failed as a reliable indicator of clinical pain intensity in FM. The sum of local areas of pain (SLAP) obtained from a body pain diagram represents a relevant measure of the spatial extent of clinical pain, a feature most likely important for FM pain. Because spatial summation of pain can be an important determinant of clinical pain intensity, we hypothesized that this measure would predict clinical pain intensity in FM patients. Because pain is strongly associated with negative emotions, we evaluated the relationship of pain-related negative affect (PRNZ) with clinical pain intensity in FM. The independent contributions of SLAP, PRNZ, and TP count to the variance of clinical pain intensity were assessed in 280 FM patients. Clinical pain intensity of 280 FM patients was measured by using a visual analogue scale. FM patients shaded all painful body areas on body pain diagrams. Dolorimetry was used for TP evaluations. PRNZ was assessed with the Medical College of Virginia Pain Questionnaire. Hierarchical linear regression was used to test the association of SLAP, TPs, and PRNZ with clinical pain intensity. FM patients' mean visual analogue scale rating (0 to 100) of usual clinical pain was 50.1. Mean SLAP, TP count, and PRNZ were 11.4, 16.0, and 44.3, respectively. Hierarchical linear regression analysis identified SLAP, TP count, and PRNZ as independent predictors of clinical pain that accounted for 45% of the variance in clinical pain intensity ratings in FM patients. Consistent with the literature, TP count predicted only a small part (4%) of this variance. Our statistical model of body pain areas and negative affect predicts a large portion of the variance of pain intensity in FM. This result suggests that the extent of pain areas and negative emotions are uniquely associated with clinical pain intensity in FM. **PERSPECTIVE: The number of painful body areas obtained by body pain diagrams is a better predictor of clinical pain intensity than TPs in FM patients. The combination of painful body areas, TP counts, and PRNZ predicts 45% of the clinical pain intensity of FM patients. This finding might be useful for clinical evaluations of FM patients.**

J Pain. 2004 Aug; 5(6):338–43

Vitton O, Gendreau M, Gendreau J, Kranzler J, Rao SG

A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia

Fibromyalgia syndrome is a systemic disorder of widespread pain which is thought to result from abnormal pain processing within the central nervous system. There are no currently approved treatments for this indication. Anti-depressants appear, however, to be effective, especially those with an action on noradrenergic neurotransmission. The objective of the present study was to test the efficacy of the dual action noradrenaline and serotonin reuptake inhibitor antidepressant, milnacipran, in the treatment of fibromyalgia. The 125 patients,

who were enrolled in a double-blind, placebo-controlled, flexible dose escalation trial, were randomized to receive placebo or milnacipran for 4 weeks of dose escalation (up to 200 mg/day), followed by 8 weeks at a constant dose. The study evaluated the efficacy and safety of milnacipran for the treatment of pain and associated symptoms such as fatigue, depressed mood and sleep. 75% of milnacipran-treated patients reported overall improvement, compared with 38% in the placebo group ($p < 0.01$). Furthermore, 37% of twice daily milnacipran-treated patients reported at least 50% reduction in pain intensity, compared with 14% of placebo-treated patients ($p < 0.05$). 84% of all milnacipran patients escalated to the highest dose (200 mg/day) with no tolerability issues. Most adverse events were mild to moderate in intensity, and transient in duration. These results suggest that **milnacipran may have the potential to relieve not only pain but several of the other symptoms associated with fibromyalgia.**

Hum Psychopharmacol. 2004 Sep 20; 19(S1):S27

Wood PB

Stress and dopamine: implications for the pathophysiology of chronic widespread pain

Fibromyalgia has been called a “stress-related disorder” due to the onset and exacerbation of symptoms in the context of stressful events. Evidence suggests that inhibition of tonic pain is mediated by activation of mesolimbic dopamine neurons, arising from the cell bodies of the ventral tegmental area and projecting to the nucleus accumbens. This pain-suppression system is activated by acute stress, via the release of endogenous opioids and substance P within the ventral tegmental area. However, prolonged exposure to unavoidable stress produces both reduction of dopamine output in the nucleus accumbens and development of persistent hyperalgesia. **It is proposed that a stress-related reduction of dopaminergic tone within the nucleus accumbens contributes to the development of hyperalgesia in the context of chronic stress and thus plays a role in the pathogenesis of fibromyalgia. A stress-related dysfunction of mesolimbic dopaminergic activity might serve as the basis for other fibromyalgia-associated phenomena as well.**

Med Hypotheses. 2004 Mar; 62(3):420–4

Yildiz S, Kiralp MZ, Akin A, Keskin I, Ay H, Dursun H, Cimsit M

A new treatment modality for fibromyalgia syndrome: hyperbaric oxygen therapy

Fibromyalgia syndrome (FMS) is characterized by longstanding multifocal pain with generalized allodynia/hyperalgesia. There are several treatment methods but

none has been specifically approved for this application. We conducted a randomized controlled study to evaluate the effect of hyperbaric oxygen (HBO) therapy in FMS (HBO group: n = 26; control group: n = 24). Tender points and pain threshold were assessed before, and after the first and fifteenth sessions of therapy. Pain was also scored on a visual analogue scale (VAS). **There was a significant reduction in tender points and VAS scores and a significant increase in pain threshold of the HBO group after the first and fifteenth therapy sessions.** There was also a significant difference between the HBO and control groups for all parameters except the VAS scores after the first session. We conclude that HBO therapy has an important role in managing FMS.

J Int Med Res. 2004 May–Jun; 32(3):263–7

Yunus MB, Young CS, Saeed SA, Mountz JM, Aldag JC

Positron emission tomography in patients with fibromyalgia syndrome and healthy controls

OBJECTIVE: Abnormal brain findings have previously been described in fibromyalgia syndrome (FMS) by single-photon-emission computed tomography. Our goal was **to investigate change in regional cerebral glucose metabolism in people with FMS by positron emission tomography (PET)** using 18F-fluorodeoxyglucose (FDG). **METHODS:** Twelve patients with FMS and no comorbid psychiatric diagnosis and 7 healthy pain-free controls were studied with FDG-PET in a blinded manner. Those with a psychiatric diagnosis were excluded. Brain scans were obtained using a PET scanner. Semiquantitative analysis of regional 18F-FDG uptake was performed in both cortical and subcortical brain structures. **RESULTS :** In the resting state, there were no significant differences in 18F-FDG uptake between patients and controls for all brain structures measured. **CONCLUSION: FDG-PET scan findings in FMS were not significantly different from healthy controls. Normal results in our study may be explained by discordance between regional cerebral blood flow and regional cerebral glucose metabolism.**

Arthritis Rheum. 2004 Aug 15; 51(4): 513–8