FIBROMYALGIA: ABSTRACTS 2005
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 2005. The studies were selected from the extensive literature on fibromyalgia so as to cover a wide range of subjects in limited space.

Abstracts for 2006 will be posted at intervals during 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.

Adler GK, Geenen R

Hypothalamic-pituitary-adrenal and autonomic nervous system functioning in fibromyalgia

In general, there seems to be a reduction in some neuroendocrine and autonomic nervous system (ANS) responses to applied stresses in individuals who have fibromyalgia. This article presents an **overview and discussion of these findings with respect to the role of the ANS and the neuroendocrine system in the response to stress, with emphasis on the hypothalamic-pituitary-adrenal axis and the possible implication for fibromyalgia.**

Rheum Dis Clin North Am. 2005 Feb; 31(1):187–202, xi

Akkasilpa S, Goldman D, Magder LS, Petri M

Number of fibromyalgia tender points is associated with health status in patients with systemic lupus erythematosus

OBJECTIVE: To ascertain the association between fibromyalgia (FM) tender points (TP) and health status in patients with systemic lupus erythematosus (SLE). METHODS: We performed a cross-sectional study of 173 SLE patients enrolled in the Hopkins Lupus Cohort. Patients were examined for FM TP and asked to complete the Health Assessment Questionnaire (HAQ) at the same visit. RESULTS: We found 38.2% of patients had no TP, 44.5% had 1–10 TP, and 17.3% had > or = 11 TP. No significant association was found between the number of FM TP and age, sex, race, or level of education. The mean score of the HAQ was 1.3 +/- 0.4. There were significant associations between FM TP and HAQ (no TP 1.1 +/- 0.3, 1-10 TP 1.4 +/- 0.4, > or = 11 TP 1.6 +/- 0.6; p = 0.0001).

CONCLUSION: A strong association between the number of FM TP and health status was found in patients with SLE. **The number of TP, and not just the presence/absence of FM, is associated with health status in SLE.**

J Rheumatol. 2005 Jan;32(1):48–50

Anthony KK, Schanberg LE

Pediatric pain syndromes and management of pain in children and adolescents with rheumatic disease

This article introduces important issues related to pain in children with musculoskeletal pain syndromes and rheumatic disease, using juvenile primary fibromyalgia syndrome (JPFS) and juvenile idiopathic arthritis (JIA) as models. A brief summary of the prevalence of pain in healthy children is followed by a summary of existing pain-assessment techniques. The remainder of the article describes the pain experience of children with JPFS and JIA and discusses issues related to pain management.

Pediatr Clin North Am. 2005 Apr; 52(2):611–39, vii

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

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

This was a 12-week, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, in 354 female patients with primary fibromyalgia, with or without current major depressive disorder. Patients (90% Caucasian; mean age, 49.6 years; 26% with current major depressive disorder) received duloxetine 60 mg once daily (QD) (N=118), duloxetine 60 mg twice daily (BID) (N=116), or placebo (N=120). The primary outcome was the Brief Pain Inventory average pain severity score. Response to treatment was defined as >or=30% reduction in this score. Compared with placebo, both duloxetine-treated groups improved significantly more (P<0.001) on the Brief Pain Inventory average pain severity score. A significantly higher percentage of duloxetine-treated patients had a decrease of >or=30% in this score (duloxetine 60 mg QD (55%; P<0.001); duloxetine 60 mg BID (54%; P=0.002); placebo (33%)). The treatment effect of duloxetine on pain reduction was independent of the effect on mood and the presence of major depressive disorder. Compared with patients on placebo, patients treated with duloxetine 60 mg QD or duloxetine 60 mg BID had significantly greater improvement in remaining Brief Pain Inventory pain severity

and interference scores, Fibromyalgia Impact Questionnaire, Clinical Global Impression of Severity, Patient Global Impression of Improvement, and several quality-of-life measures. Both doses of duloxetine were safely administered and well tolerated. In conclusion, **both duloxetine 60 mg QD and duloxetine 60 mg BID were effective and safe in the treatment of fibromyalgia in female patients with or without major depressive disorder.**

Pain. 2005 Dec 15; 119(1–3):5–15. Epub 2005 Nov 17

Assefi NP, Sherman KJ, Jacobsen C, Goldberg J, Smith WR, Buchwald D

A randomized clinical trial of acupuncture compared with sham acupuncture in fibromyalgia

BACKGROUND: Fibromyalgia is a common chronic pain condition for which patients frequently use acupuncture. OBJECTIVE: To determine whether acupuncture relieves pain in fibromyalgia. DESIGN: Randomized, sham-controlled trial in which participants, data collection staff, and data analysts were blinded to treatment group. SETTING: Private acupuncture offices in the greater Seattle, Washington, metropolitan area. PATIENTS: 100 adults with fibromyalgia. INTERVENTION: Twice-weekly treatment for 12 weeks with an acupuncture program that was specifically designed to treat fibromyalgia, or 1 of 3 sham acupuncture treatments: acupuncture for an unrelated condition, needle insertion at nonacupoint locations, or noninsertive simulated acupuncture. MEASUREMENTS: The primary outcome was subjective pain as measured by a 10-cm visual analogue scale ranging from 0 (no pain) to 10 (worst pain ever). Measurements were obtained at baseline; 1, 4, 8, and 12 weeks of treatment; and 3 and 6 months after completion of treatment. Participant blinding and adverse effects were ascertained by self-report. The primary outcomes were evaluated by pooling the 3 sham-control groups and comparing them with the group that received acupuncture to treat fibromyalgia. RESULTS: The mean subjective pain rating among patients who received acupuncture for fibromyalgia did not differ from that in the pooled sham acupuncture group (mean between-group difference, 0.5 cm [95% CI, -0.3 cm to 1.2 cm]). Participant blinding was adequate throughout the trial, and no serious adverse effects were noted. LIMITATIONS: A prescription of acupuncture at fixed points may differ from acupuncture administered in clinical settings, in which therapy is individualized and often combined with herbal supplementation and other adjunctive measures. A usual-care comparison group was not studied. CONCLUSION: **Acupuncture was no better than sham acupuncture at relieving pain in fibromyalgia.**

Ann Intern Med. 2005 Jul 5; 143(1):10–19
Summary for patients in: *Ann Intern Med*. 2005 Jul 5; 143(1):I24

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. 2005 Apr; 25(3):188–90. Epub 2003 Dec 20

Bennett R

Fibromyalgia: present to future

There has been a dramatic increase in our understanding of fibromyalgia throughout the past 14 years since the publication of the 1990 American College of Rheumatology classification criteria. Before 1990, and for most of the 20th century, fibromyalgia was considered to be predominantly a muscle disorder; now the critical abnormality is described as "central sensitization." However, central sensitization has to have an initial genesis and nociceptive stimuli from painful foci in muscle are increasingly recognized as being relevant to the development of fibromyalgia. Clinicians also recognize an association between the initiation of fibromyalgia and chronic psychologic stressors and inflammatory disorders. It has been more difficult to understand how two such apparently diverse events could affect central pain physiology. However, some **clues are emerging from the role of diverse stimuli in activating glial cells and the role of disordered cytokine networks. Some predictions about future developments in fibromyalgia are ventured based on the current state of knowledge.**

Curr Rheumatol Rep. 2005 Oct; 7(5):371–6

Bennett RM, Schein J, Kosinski MR, Hewitt DJ, Jordan DM, Rosenthal NR

Impact of fibromyalgia pain on health-related quality of life before and after treatment with tramadol/acetaminophen

OBJECTIVE: To assess health-related quality of life (HRQOL) in patients with moderate-to-severe fibromyalgia pain compared with the general population, and to assess the relationship between pain severity and HRQOL before and after treatment with an analgesic. METHODS: Data were obtained from a randomized, double-blind study of patients with moderate-to-severe fibromyalgia pain. Patients received either tramadol/acetaminophen or placebo 4 times/day as needed for 91 days. HRQOL was measured with the Short Form 36 Health Survey (SF-36) and the Fibromyalgia Impact Questionnaire (FIQ). Baseline HRQOL scores were compared with a national sample of noninstitutionalized adults and a sample of patients with impaired HRQOL due to congestive heart failure. Patients with fibromyalgia were divided into tertiles by change in pain severity, and SF-36 scores were compared across the tertiles. Mean changes in SF-36 and FIQ scores were compared between treatment groups. RESULTS: Patients with fibromyalgia scored lower than the US norm on all SF-36 scales ($P<0.0001$) and lower than patients with congestive heart failure on most scales. More severe pain was associated with greater impairment of HRQOL compared with less severe pain ($P < 0.0001$). Patients in the highest tertile for improved pain severity had greater improvement in HRQOL scores than patients in the lower tertiles. **Compared with patients who received placebo (n = 157), patients treated with tramadol/ acetaminophen (n = 156) showed greater improvement on SF-36 physical functioning, role physical, bodily pain, and physical summary scales, as well as FIQ scales for ability to do job, pain, and stiffness** ($P<0.01$). CONCLUSION: Moderate-to-severe fibromyalgia pain significantly impairs HRQOL, and effective pain relief in these patients significantly increases HRQOL.

Arthritis Rheum. 2005 Aug 15; 53(4):519–27

Blanco LE, de Serres FJ, Fernandez-Bustillo E, Kassam DA, Arbesu D, Rodriguez C, Torre JC

Alpha1-Antitrypsin and fibromyalgia: new data in favour of the inflammatory hypothesis of fibromyalgia

Alpha1-Antitrypsin (AAT) circulates in high serum concentrations, and impregnates most body tissues. AAT has a broad anti-inflammatory spectrum, and modulates most inflammatory reactions occurring in human body. Recently, a possible relationship between AAT deficiency (AAT-D) and fibromyalgia (FM) has been raised, with the finding that intravenous infusions of purified human AAT efficiently controlled FM symptoms in two patients with severe hereditary AAT-D. On the other hand, functional magnetic resonance imaging has detected a significant greater activity in pain sensitive areas of the brain in patients with FM,

in response to cutaneous stimuli, providing further evidence for a physiological explanation for FM pain. In recent studies abnormal profiles of inflammation markers in serum and biopsies have been found in FM patients. Since most of these inflammation mediators can be inhibited by AAT, these observations would suggest that **at least a subset of the FM syndrome could be related to an inflammatory process, possibly due to an imbalance between inflammatory and anti-inflammatory substances, in the soft body tissues.** Future directions of research would be: (1) to develop epidemiological studies to determine the gene frequency of AAT deficiency alleles in FM patients; (2) implementation of a double-blind placebo-controlled clinical trial to determine the specific role of AAT augmentation therapy in AAT-D patients with FM; (3) identification of specific laboratory markers for diagnostic and clinical evaluation purposes in FM; (4) application of the newest medical imaging techniques for diagnosis; and (5) identification of genetic, familial, and environmental risk factors suspected to participate in the FM syndrome development.

Med Hypotheses. 2005;64(4):759–69

Boonen A, van den Heuvel R, van Tubergen A, Goossens M, Severens JL, van der Heijde D, van der Linden S

Large differences in cost of illness and wellbeing between patients with fibromyalgia, chronic low back pain, or ankylosing spondylitis

OBJECTIVE: To compare the cost of illness of three musculoskeletal conditions in relation to general wellbeing. METHODS: Patients with fibromyalgia, chronic low back pain (CLBP), and ankylosing spondylitis who were referred to a specialist and participated in three randomised trials completed a cost diary for the duration of the study, comprising direct medical and non-medical resource utilisation and inability to perform paid and unpaid work. Patients rated perceived wellbeing (0-100) at baseline. Univariate differences in costs between the groups were estimated by bootstrapping. Regression analyses assessed which variables, in addition to the condition, contributed to costs and wellbeing. RESULTS: 70 patients with fibromyalgia, 110 with chronic low back pain, and 111 with ankylosing spondylitis provided data for the cost analyses. Average annual disease-related total societal costs per patient were 7813 euro for fibromyalgia, 8533 euro for CLBP, and 3205 euro for ankylosing spondylitis. Total costs were higher for fibromyalgia and CLBP than for ankylosing spondylitis, mainly because of cost of formal and informal care, aids and adaptations, and work days lost. Wellbeing was lower in fibromyalgia (mean, 48) and low back pain (mean, 42) than in ankylosing spondylitis (mean, 67). No variables other than diagnostic group contributed to differences in costs or wellbeing. CONCLUSIONS: In patients under the care of a specialist, **there were marked differences in costs and wellbeing between those with fibromyalgia or CLBP and those with ankylosing**

spondylitis. In particular, direct non-medical costs and productivity costs were higher in fibromyalgia and CLBP.

Ann Rheum Dis. 2005 Mar;64(3):396–402. Epub 2004 Jul 22

Burckhardt CS, Jones KD

Effects of chronic widespread pain on the health status and quality of life of women after breast cancer surgery

BACKGROUND: Most research and treatment of post-breast cancer chronic pain has focused on local or regional pain problems in the operated area. The purpose of this pilot study was to compare and contrast the pain characteristics, symptom impact, health status, and quality of life of post-breast cancer surgery women with regional chronic pain versus those with widespread chronic pain. METHODS: A cross-sectional, descriptive design compared two groups of women with chronic pain that began after surgery: regional pain (n = 11) and widespread pain (n = 12). Demographics, characteristics of the surgery, as well as standardized questionnaires that measured pain (Brief Pain Inventory (BPI), Short Form McGill Pain Questionnaire (MPQ-SF)), disease impact (Fibromyalgia Impact Questionnaire (FIQ)), Functional Assessment of Cancer Therapy-Breast (FACT-B)), health status (Medical Outcomes Short Form (SF-36)) and quality of life (Quality of Life Scale (QOLS)) were gathered. RESULTS: There were no significant differences between the groups on any demographic or type of surgery variable. A majority of both groups described their pain as aching, tender, and sharp on the MPQ-SF. On the BPI, intensity of pain and pain interference were significantly higher in the widespread pain group. Differences between the two groups reached statistical significance on the FIQ total score as well as the FACT-B physical well-being, emotional well-being and breast concerns subscales. The SF-36 physical function, physical role, and body pain subscales were significantly lower in the widespread pain group. QOLS scores were lower in the widespread pain group, but did not reach statistical significance. CONCLUSION: This preliminary work suggests that **the women in this study who experienced widespread pain after breast cancer surgery had significantly more severity of pain, pain impact and lower physical health status than those with regional pain.**

Health Qual Life Outcomes. 2005 Apr 28; 3(1):30

Buskila D, Neumann L, Press J

Genetic factors in neuromuscular pain

Recent evidence suggests that fibromyalgia, a chronic widespread pain condition and related syndromes (chronic fatigue syndrome, irritable bowel syndrome, etc.) may share heritable pathophysiologic features. **We review the recent literature on genetic and familial factors found to participate in the pathogenesis of**

these syndromes, specifically fibromyalgia, including evidence suggesting that serotonin- and dopamine-related genes may play a role in the pathogenesis of these illnesses. The importance of environmental factors triggering these conditions in predisposed individuals is also discussed.

CNS Spectr. 2005 Apr; 10(4):281–4

Crofford LJ

The relationship of fibromyalgia to neuropathic pain syndromes

The appropriateness and utility of considering fibromyalgia syndrome (FM) and other syndromes without anatomically localized pathology of the nervous system as neuropathic pain syndromes is uncertain. In this afterword, **a synthesis of the information presented in these proceedings and opinion as to how FM relates to classical neuropathic pain syndromes is provided.**

J Rheumatol Suppl. 2005 Aug; 75:41–5

Crofford LJ, Rowbotham MC, Mease PJ, Russell IJ, Dworkin RH, Corbin AE, Young JP, Jr, LaMoreaux LK, Martin SA, Sharma U; Pregabalin 1008–105 Study Group

Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial

OBJECTIVE: Fibromyalgia syndrome (FMS) is characterized by widespread musculoskeletal pain and lowered pain threshold. Other prominent symptoms include disordered sleep and fatigue. FMS affects an estimated 2% of the population, predominantly women. This trial was designed to evaluate the efficacy and safety of pregabalin, a novel alpha(2)-delta ligand, for treatment of symptoms associated with FMS. METHODS: This multicenter, double-blind, 8-week, randomized clinical trial compared the effects of placebo with those of 150, 300, and 450 mg/day pregabalin on pain, sleep, fatigue, and health-related quality of life in 529 patients with FMS. The primary outcome variable was the comparison of end-point mean pain scores, derived from daily diary ratings of pain intensity, between each of the pregabalin treatment groups and the placebo group. RESULTS: Pregabalin at 450 mg/day significantly reduced the average severity of pain in the primary analysis compared with placebo (-0.93 on a 0-10 scale) (P </= 0.001), and significantly more patients in this group had >/=50% improvement in pain at the end point (29%, versus 13% in the placebo group; P = 0.003). Pregabalin at 300 and 450 mg/day was associated with significant improvements in sleep quality, fatigue, and global measures of change. Pregabalin at 450 mg/day improved several domains of health-related quality of life. Dizziness and somnolence were the most frequent adverse events. Rates of

discontinuation due to adverse events were similar across all 4 treatment groups. CONCLUSION: **Pregabalin at 450 mg/day was efficacious for the treatment of FMS, reducing symptoms of pain, disturbed sleep, and fatigue compared with placebo. Pregabalin was well tolerated and improved global measures and health-related quality of life.**

Arthritis Rheum. 2005 Apr; 52(4):1264–73

Degotardi PJ, Klass ES, Rosenberg BS, Fox DG, Gallelli KA, Gottlieb BS

Development and evaluation of a cognitive-behavioral intervention for juvenile fibromyalgia

OBJECTIVE: To describe the development and test the efficacy of a cognitive-behavioral intervention (CBT) for juvenile fibromyalgia. METHOD: Sixty-seven children with fibromyalgia and their parents were recruited to participate in an 8-week intervention that included modules of pain management, psychoeducation, sleep hygiene, and activities of daily living. Children were taught techniques of cognitive restructuring, thought stopping, distraction, relaxation, and self-reward. Additionally, they kept daily pain and sleep dairies. Children completed questionnaires of pre- and post-treatment measuring physical status and psychological functioning. RESULTS: **Following CBT, children reported significant reductions ($p < .006$) in pain, somatic symptoms, anxiety, and fatigue, as well as improvements in sleep quality.** Additionally, children reported improved functional ability and had fewer school absences. CONCLUSION: Children with fibromyalgia can be taught CBT strategies that help them effectively manage this chronic and disabling musculoskeletal pain disorder.

J Pediatr Psychol. 2005 Aug 24; [Epub ahead of print]

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

Efficacy of milnacipran in patients with fibromyalgia

OBJECTIVE: Fibromyalgia (FM) is a common musculoskeletal condition characterized by widespread pain, tenderness, and a variety of other somatic symptoms. Current treatments are modestly effective. Arguably, the best studied and most effective compounds are tricyclic antidepressants (TCA). Milnacipran, a nontricyclic compound that inhibits the reuptake of both serotonin and norepinephrine, may provide many of the beneficial effects of TCA with **a superior side effect profile**. METHODS: One hundred twenty-five patients with FM were randomly assigned in a 3:3:2 ratio to receive milnacipran twice daily, milnacipran once daily, or placebo for 3 months in a double-blind dose-escalation trial; 92% of twice-daily and 81% of once-daily participants achieved dose escalation to the

target milnacipran dose of 200 mg. RESULTS: The primary endpoint was reduction of pain. Both the once- and twice-daily groups showed statistically significant improvements in pain, as well as improvements in global well being, fatigue, and other domains. Response rates for patients receiving milnacipran were equal in patients with and without comorbid depression, but placebo response rates were considerably higher in depressed patients, leading to significantly greater overall efficacy in the nondepressed group. CONCLUSION: In this Phase II study, **milnacipran led to statistically significant improvements in pain and other symptoms of FM. The effect sizes were equal to those previously found with TCA, and the drug was generally well tolerated.**

J Rheumatol. 2005 Oct; 32(10):1975–85

Giesecke T, Gracely RH, Williams DA, Geisser ME, Petzke FW, Clauw DJ

The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort

OBJECTIVE: Individuals with chronic pain frequently display comorbid depression, but the impact of symptoms of depression on pain processing is not completely understood. This study evaluated the effect of symptoms of depression and/or clinically diagnosed major depressive disorder (MDD) on pain processing in patients with fibromyalgia (FM). METHODS: Results of quantitative sensory testing and neural responses to equally painful pressure stimuli (measured by functional magnetic resonance imaging [fMRI]) were compared with the levels of symptoms of depression and comorbid MDD among patients with FM. RESULTS: Neither the level of symptoms of depression nor the presence of comorbid MDD was associated with the results of sensory testing or the magnitude of neuronal activation in brain areas associated with the **sensory dimension of pain (primary and secondary somatosensory cortices)**. However, symptoms of depression and the presence of MDD were associated with the magnitude of pain-evoked neuronal activations in brain regions associated with **affective pain processing (the amygdalae and contralateral anterior insula)**. Clinical pain intensity was associated with measures of both the sensory dimension of pain (results of sensory testing) and the affective dimension of pain (activations in the insula bilaterally, contralateral anterior cingulate cortex, and prefrontal cortex). CONCLUSION: In patients with FM, neither the extent of depression nor the presence of comorbid major depression modulates the sensory-discriminative aspects of pain processing (i.e., localizing pain and reporting its level of intensity), as measured by sensory testing or fMRI. However, depression is associated with the magnitude of neuronal activation in brain regions that process the affective-motivational dimension of pain. **These data suggest that there are parallel, somewhat independent neural pain-processing networks for sensory and affective pain elements. The implication for treatment is that addressing an individual's depression (e.g., by prescribing an antidepressant medication**

that has no analgesic properties) will not necessarily have an impact on the sensory dimension of pain.

Arthritis Rheum. 2005 May; 52(5):1577–84

Glass JM, Park DC, Minear M, Crofford LJ

Memory beliefs and function in fibromyalgia patients

OBJECTIVE: The aim of this study was to investigate memory beliefs and their relationship to actual memory function in fibromyalgia (FM) patients. METHODS: Twenty-three FM patients, 23 age- and education-matched controls, and 22 older controls completed the Metamemory in Adulthood (MIA) questionnaire, which assessed beliefs about seven aspects of memory function. Group differences on the seven scales were assessed, and scores on the capacity scale were correlated with objective memory performance. RESULTS: FM patients reported lower memory capacity and more memory deterioration than did either control group. Patients reported lower control or self-efficacy over memory, higher achievement motivation, higher strategy use, and higher anxiety about memory than age-matched controls did. Among the patients, perceived capacity, achievement motivation, and self-efficacy were significantly correlated with objective memory performance on a recall task. CONCLUSION: **FM patients' complaints about memory function have some accuracy.**

J Psychosom Res. 2005 Mar; 58(3):263–9

Holman AJ, Myers RR

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

OBJECTIVE: To assess the efficacy and safety of pramipexole, a dopamine 3 receptor agonist, in patients with fibromyalgia. METHODS: In this 14-week, single-center, double-blind, placebo-controlled, parallel-group, escalating-dose trial, 60 patients with fibromyalgia were randomized 2:1 (pramipexole:placebo) to receive 4.5 mg of pramipexole or placebo orally every evening. The primary outcome was improvement in the pain score (10-cm visual analog scale [VAS]) at 14 weeks. Secondary outcome measures were the Fibromyalgia Impact Questionnaire (FIQ), the Multidimensional Health Assessment Questionnaire (MDHAQ), the pain improvement scale, the tender point score, the 17-question Hamilton Depression Inventory (HAM-d), and the Beck Anxiety Index (BAI). Patients with comorbidities and disability were not excluded. Stable dosages of concomitant medications, including analgesics, were allowed. RESULTS: Compared with the placebo group, patients receiving pramipexole experienced gradual and more significant improvement in measures of pain, fatigue, function,

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

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

Julien N, Goffaux P, Arsenault P, Marchand S

Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition

A deficit of endogenous pain inhibitory systems has been suggested to contribute to some chronic pain conditions, one of them being fibromyalgia. The aim of the investigation was to test whether endogenous pain inhibitory systems were activated by a spatial summation procedure in 30 fibromyalgia, 30 chronic low back pain, and 30 healthy volunteers who participated in a cross-over trial (two sessions). Each session consisted of visual analog scale ratings of pain during the immersion of different surfaces of the arm in circulating noxious cold (12 degrees C) water. The arm was arbitrarily divided into eight segments from the fingertips to the shoulder. One session was ascending (from the fingertips to the shoulder) and the other was descending (from the shoulder to the fingertips); they included eight consecutive 2-min immersions separated by 5-min resting periods. For healthy and low back pain subjects, pain was perceived differently during the ascending and descending sessions (P=0.0001). The descending session resulted in lower pain intensity and unpleasantness. This lowering of the perception curve seems to be due to a full recruitment of inhibitory systems at the beginning of the descending session as opposed to a gradual recruitment during the ascending session. For fibromyalgia subjects, no significant differences were found between the increasing and decreasing sessions (P>0.05). **These data support a deficit of**

endogenous pain inhibitory systems in fibromyalgia but not in chronic low back pain. The treatments proposed for fibromyalgia patients should aim at stimulating the activity of those endogenous systems.

Pain. 2005 Mar;114(1–2):295–302

Krell HV, Leuchter AF, Cook IA, Abrams M

Evaluation of reboxetine, a noradrenergic antidepressant, for the treatment of fibromyalgia and chronic low back pain

Clinical experience supports the use of antidepressant medications to treat chronic pain syndromes, such as low back pain and fibromyalgia. Although this use of antidepressants is common in clinical practice, the literature supporting this off-label use has some limitations. In this report, the authors review the body of clinical data on the use of antidepressants in treating pain and present a case series of depressed patients with these syndromes who experienced relief of pain symptoms while being treated with the noradrenergic antidepressant reboxetine. **These subjects experienced significant relief of pain before any significant improvement in actual mood symptoms**. **Our experience with reboxetine suggests that this noradrenergic antidepressant may have efficacy in the treatment of chronic pain in patients with depression.**

Psychosomatics. 2005 Sep-Oct; 46(5):379–84

Le Goff P

Is fibromyalgia a muscle disorder?

The presence of abnormalities in fibromyalgia muscle using current methodological approaches is well established. The **more serious abnormalities** are demonstrated by histologic studies particularly on electron microscopy: **disorganisation of Z bands and abnormalities in the number and shape of mitochondria. Biochemical studies and P 31 magnetic resonance spectroscopy show inconstant abnormalities of ATP and phosphocreatine levels.** Mitochondrial abnormalities, reduced capillary circulation and thickened capillary endothelium may result in decreased availability of oxygen and impaired oxidative phosphorylation as well as ATP synthesis. These abnormalities do not seem to be the consequences of the much-discussed deconditioning of muscles although these consequences are not well known. Further studies of energy metabolism of the muscle during exercise are needed.

Joint Bone Spine. 2005 Nov 9; [Epub ahead of print]

Maizels M, McCarberg B

Antidepressants and antiepileptic drugs for chronic non-cancer pain

The development of newer classes of antidepressants and second-generation antiepileptic drugs has created unprecedented opportunities for the treatment of chronic pain. These drugs modulate pain transmission by interacting with specific neurotransmitters and ion channels. The actions of antidepressants and antiepileptic drugs differ in neuropathic and non-neuropathic pain, and agents within each medication class have varying degrees of efficacy. Tricyclic antidepressants (e.g., amitriptyline, nortriptyline, desipramine) and certain novel antidepressants (i.e., bupropion, venlafaxine, duloxetine) are effective in the treatment of neuropathic pain. **The analgesic effect of these drugs is independent of their antidepressant effect and appears strongest in agents with mixed-receptor or predominantly noradrenergic activity, rather than serotoninergic activity.** First-generation antiepileptic drugs (i.e., carbamazepine, phenytoin) and second-generation antiepileptic drugs (e.g., gabapentin, pregabalin) are effective in the treatment of neuropathic pain. The efficacy of antidepressants and antiepileptic drugs in the treatment of neuropathic pain is comparable; tolerability also is comparable, but safety and side effect profiles differ. Tricyclic antidepressants are the most cost-effective agents, but second-generation antiepileptic drugs are associated with fewer safety concerns in elderly patients. Tricyclic antidepressants have documented (although limited) efficacy in the treatment of fibromyalgia and chronic low back pain. **Recent evidence suggests that duloxetine and pregabalin have modest efficacy in patients with fibromyalgia.**

Am Fam Physician. 2005 Feb 1; 71(3):483–90

Mannerkorpi K

Exercise in fibromyalgia

PURPOSE OF REVIEW: Several studies have indicated that physical exercise is beneficial for patients with fibromyalgia. The aim of this article is to review the recent literature relating to exercise in fibromyalgia, specifically articles published between September 2003 and September 2004, to highlight developments in the field. RECENT FINDINGS: Previous studies indicate that aerobic exercise performed at adequate intensity for an individual can improve function, symptoms, and well-being. A recent study of aerobic exercise showed that training in sedentary women with fibromyalgia using short bouts of exercise produces improvements in health outcomes. A study of aerobic walking resulted in improvements in physical function, symptoms, and distress. Two studies of low-intensity pool exercise reported a positive impact on fibromyalgia symptoms and distress. Two studies of qigong movement therapy were reported, one indicating improvements in symptoms and the other in movement harmony, indicating that

this mode of exercise needs to be evaluated further. SUMMARY: The recent studies support existing literature on the benefits of exercise for patients with fibromyalgia. The outcomes appear to be related to the program design and the characteristics of the populations studied. **As the patients with fibromyalgia form a heterogeneous population, more research is required to identify the characteristics of patients who benefit from specific modes of exercise. Moreover, long-term planning is needed to motivate the patients to continue regular exercise**. Informing patients about the benefits of exercise and adjusting the exercise intensity to individual limitations enhances adherence. The social support gained by exercising in groups also enhances adherence to exercise.

Curr Opin Rheumatol. 2005 Mar; 17(2):190–4

Marcus DA, Bernstein C, Rudy TE

Fibromyalgia and headache: an epidemiological study supporting migraine as part of the fibromyalgia syndrome

Fibromyalgia is defined by widespread body pain, tenderness to palpation of tender point areas, and constitutional symptoms. The literature reports headache in about half of fibromyalgia patients. The current epidemiological study was designed to determine the prevalence and characteristics of headache in fibromyalgia patients. Treatment-seeking fibromyalgia patients were evaluated with measures for fibromyalgia, chronic headache, quality of life, and psychological distress. Multivariate analysis of variance (MANOVA) and t-tests were used to identify significant differences, as appropriate. A total of 100 fibromyalgia patients were screened (24 fibromyalgia without headache and 76 fibromyalgia with headache). International Headache Society diagnoses included: migraine alone (n=15 with aura, n=17 without aura), tension-type alone (n=18), combined migraine and tension-type (n=16), post-traumatic (n=4), and probable analgesic overuse headache (n=6). Fibromyalgia tender point scores and counts and most measures of pain severity, sleep disruption, or psychological distress were not significantly different between fibromyalgia patients with and without headache. As expected, the fibromyalgia patients with headache scored higher on the Headache Impact Test (HIT-6) (62.1+/-0.9 vs 48.3+/-1.6, $p < 0.001$). HIT-6 scores were >60 in 80% of fibromyalgia plus headache patients, representing severe impact from headache, and 56–58 in 4%, representing substantial impact. In summary, chronic headache was endorsed by 76% of treatment-seeking fibromyalgia patients, with 84% reporting substantial or severe impact from their headaches. Migraine was diagnosed in 63% of fibromyalgia plus headache patients, with probable analgesic overuse headache in only 8%. General measures of pain, pain-related disability, sleep quality, and psychological distress were similar in fibromyalgia patients with and without headache. Therefore, fibromyalgia patients with headache do not appear to represent a significantly different subgroup compared to fibromyalgia patients without headache. **The high prev-**

alence and significant impact associated with chronic headache in fibromyalgia patients, however, warrants inclusion of a headache assessment as part of the routine evaluation of fibromyalgia patients.

Clin Rheumatol. 2005 May 18; [Epub ahead of print]

McIver KL, Evans C, Kraus RM, Ispas L, Sciotti VM, Hickner RC

NO-mediated alterations in skeletal muscle nutritive blood flow and lactate metabolism in fibromyalgia

The purpose of these investigations was to determine if differences exist in skeletal muscle nutritive blood flow and lactate metabolism in women with fibromyalgia (FM) compared to healthy women (HC); furthermore, to determine if differences in nitric oxide-mediated systems account for any detected alterations in blood flow and lactate metabolism and contribute to exertional fatigue in FM. FM (n=8) and HC (n=8) underwent a cycle ergometry test of aerobic capacity, a muscle biopsy for determination of nitric oxide synthase (eNOS, nNOS, iNOS) content, and microdialysis for investigation of muscle nutritive blood flow and lactate metabolism. During prolonged (3h) resting conditions, the ethanol outflow/inflow ratio (inversely related to blood flow) increased in FM over time compared to HC ($P<0.05$). FM also exhibited a reduced nutritive blood flow response to aerobic exercise ($P<0.05$). There was an increase in dialysate lactate in response to acetylcholine in FM, and to sodium nitroprusside in both groups, with a greater rise in dialysate lactate in FM ($P<0.05$). The iNOS protein content was higher in FM and was negatively correlated with total exercise time ($r(2)=0.462$, $P<0.05$). In conclusion: (1) **There is reduced nutritive flow response to aerobic exercise and reduced maximal exercise time in FM that might relate to higher iNOS protein content and contribute to exertional fatigue in FM;** (2) The increased dialysate lactate in FM in response to stimulation of NOS or a nitric oxide donor suggest that **FM may be more sensitive than HC to the suppressive effect of nitric oxide on oxidative phosphorylation.**

Pain. 2006 Jan;120(1–2):161–9. Epub 2005 Dec 22

McLean SA, Williams DA, Harris RE, Kop WJ, Groner KH, Ambrose K, Lyden AK, Gracely RH, Crofford LJ, Geisser ME, Sen A, Biswas P, Clauw DJ

Momentary relationship between cortisol secretion and symptoms in patients with fibromyalgia

OBJECTIVE: To compare the momentary association between salivary cortisol levels and pain, fatigue, and stress symptoms in patients with fibromyalgia (FM),

and to compare diurnal cycles of cortisol secretion in patients with FM and healthy control subjects in a naturalistic environment. METHODS: Twenty-eight patients with FM and 27 healthy control subjects completed assessments on salivary cortisol levels and pain, fatigue, and stress symptoms, 5 times a day for 2 consecutive days, while engaging in usual daily activities. Only those participants who adhered to the protocol (assessed via activity monitor) were included in the final analyses. RESULTS: Twenty FM patients and 16 healthy control subjects adhered to the protocol. There were no significant differences in cortisol levels or diurnal cortisol variation between FM patients and healthy controls. Among women with FM, a strong relationship between cortisol level and current pain symptoms was observed at the waking time point ($t = 3.35$, $P = 0.008$) and 1 hour after waking ($t = 2.97$, $P = 0.011$), but not at the later 3 time points. This association was not due to differences in age, number of symptoms of depression, or self-reported history of physical or sexual abuse. Cortisol levels alone explained 38% and 14% of the variation in pain at the waking and 1 hour time points, respectively. No relationship was observed between cortisol level and fatigue or stress symptoms at any of the 5 time points. CONCLUSION: Among women with FM, **pain symptoms early in the day are associated with variations in function of the hypothalamic-pituitary-adrenal axis.**

Arthritis Rheum. 2005 Nov; 52(11):3660–9

Mease PJ, Clauw DJ, Arnold LM, Goldenberg DL, Witter J, Williams DA, Simon LS, Strand CV, Bramson C, Martin S, Wright TM, Littman B, Wernicke JF, Gendreau RM, Crofford LJ

Fibromyalgia syndrome

The objectives of the first OMERACT Fibromyalgia Syndrome (FM) Workshop were to identify and prioritize symptom domains that should be consistently evaluated in FM clinical trials, and to identify aspects of domains and outcome measures that should be part of a concerted research agenda of FM researchers. Such an effort will help standardize and improve the quality of outcomes research in FM. A principal assumption in this workshop has been that there exists a clinical syndrome, generally known as FM, characterized by chronic widespread pain typically associated with fatigue, sleep disturbance, mood disturbance, and other symptoms and signs, and considered to be related to central neuromodulatory dysregulation. FM can be diagnosed using 1990 American College of Rheumatology criteria. In preparation for the workshop a Delphi exercise involving 23 FM researchers was conducted to establish a preliminary prioritization of domains of inquiry. At the OMERACT meeting, the workshop included presentation of the Delphi results; a review of placebo-controlled trials of FM treatment, with a focus on the outcome measures used and their performance; a panel discussion of the key issues in FM trials, from both an investigator and regulatory agency perspective; and a voting process by the workshop attendees.

The results of the workshop were presented in the plenary session on the final day of the meeting. **A prioritized list of domains of FM to be investigated was thus developed, key issues and controversies in the field were debated, and consensus on a research agenda on outcome measure development was reached.**

J Rheumatol. 2005 Nov; 32(11):2270–7

Mease P

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

Fibromyalgia syndrome (FM) is a common chronic pain condition that affects at least 2% of the adult population in the USA and other regions in the world where FM is studied. Prevalence rates in some regions have not been ascertained and may be influenced by differences in cultural norms regarding the definition and attribution of chronic pain states. Chronic, widespread pain is the defining feature of FM, but patients may also exhibit a range of other symptoms, including sleep disturbance, fatigue, irritable bowel syndrome, headache, and mood disorders. Although the etiology of FM is not completely understood, the syndrome is thought to arise from influencing factors such as stress, medical illness, and a variety of pain conditions in some, but not all patients, in conjunction with a variety of neurotransmitter and neuroendocrine disturbances. These include reduced levels of biogenic amines, increased concentrations of excitatory neurotransmitters, including substance P, and dysregulation of the hypothalamic-pituitary-adrenal axis. **A unifying hypothesis is that FM results from sensitization of the central nervous system.** Establishing diagnosis and evaluating effects of therapy in patients with FM may be difficult because of the multifaceted nature of the syndrome and overlap with other chronically painful conditions. Diagnostic criteria, originally developed for research purposes, have aided our understanding of this patient population in both research and clinical settings, but need further refinement as our knowledge about chronic widespread pain evolves. Outcome measures, borrowed from clinical research in pain, rheumatology, neurology, and psychiatry, are able to distinguish treatment response in specific symptom domains. Further work is necessary to validate these measures in FM. In addition, work is under way to develop composite response criteria, intended to address the multidimensional nature of this syndrome. A range of medical treatments, including antidepressants, opioids, nonsteroidal antiinflammatory drugs, sedatives, muscle relaxants, and antiepileptics, have been used to treat FM. Nonpharmaceutical treatment modalities, including exercise, physical therapy, massage, acupuncture, and cognitive behavioral therapy, can be helpful. Few of these approaches have been demonstrated to have clear-cut benefits in randomized controlled trials. However, there is now increased interest as more effective treatments are developed and our ability to accurately measure the effects of treatment has improved. **The multifaceted nature of FM suggests that multi-**

modal individualized treatment programs may be necessary to achieve optimal outcomes in patients with this syndrome.

J Rheumatol Suppl. 2005 Aug; 75:6–21

Morf S, Amann-Vesti B, Forster A, Franzeck UK, Koppensteiner R, Uebelhart D, Sprott H

Microcirculation abnormalities in patients with fibromyalgia—measured by capillary microscopy and laser fluxmetry

This unblinded preliminary case-control study was done to demonstrate functional and structural changes in the microcirculation of patients with primary fibromyalgia (FM). We studied 10 women (54.0 +/- 3.7 years of age) with FM diagnosed in accordance with the classification criteria of the American College of Rheumatology, and controls in three groups (n = 10 in each group)—age-matched women who were healthy or who had rheumatoid arthritis or systemic scleroderma (SSc). All 40 subjects were tested within a 5-week period by the same investigators, using two noninvasive methods, laser fluxmetry and capillary microscopy. The FM patients were compared with the healthy controls (negative controls) and with rheumatoid arthritis patients and SSc patients (positive controls). FM patients had fewer capillaries in the nail fold ($P < 0.001$) and significantly more capillary dilatations ($P < 0.05$) and irregular formations ($P < 0.01$) than the healthy controls. Interestingly, the peripheral blood flow in FM patients was much less ($P < 0.001$) than in healthy controls but did not differ from that of SSc patients ($P = 0.73$). **The data suggest that functional disturbances of microcirculation are present in FM patients and that morphological abnormalities may also influence their microcirculation.**

Arthritis Res Ther. 2005; 7(2):R209–16. Epub 2004 Dec 10

Offenbaecher M, Ackenheil M

Current trends in neuropathic pain treatments with special reference to fibromyalgia.

Neuropathic pain and fibromyalgia are prevalent diseases which have major consequences on healthcare resources and the individual. From the clinical point of view, neuropathic pains represent a heterogeneous group of aetiologically different diseases ranging from cancer to diabetes. **Patients with fibromyalgia also display clinical features common in neuropathic pain suggesting that there might be some overlap.** The mechanisms responsible for symptoms and signs in both diseases are still unknown. Recently, there have been numerous reports of various pharmacological treatments of neuropathic pain and fibromyalgia with often disappointing results. Most of the studies were of short

duration, had high attrition rates, and displayed other methodological problems. Some compounds had high rates of adverse effects which makes it often difficult for the patients to tolerate the treatment, especially in the long-term. At present, the best options for medication treatment are tricyclic antidepressants in lower dosage than usual in psychiatric disorders and a wide range of anticonvulsants. Opioids are sometimes recommended but have been found to have minor efficacy. Recently, there have been more controlled trials, which are reported here if they had been published between 2002 and 2004. Various compounds have been tested in different studies. Treatment of fibromyalgia, which has many features in common with depressive symptoms, became the focus of interest. **New promising studies with dual serotonin-norepinephrine reuptake inhibitors (duloxetine and milnacipran) and a newer antiepileptic drug (pregabalin) are in progress. Future research will have to apply new approaches (e.g., using a mechanism-based classification of neuropathic pain and carrying out studies in populations with the same symptom but not necessarily the same disease) in order to find effective treatments for these common and often debilitating diseases.**

CNS Spectr. 2005 Apr;10(4):285–97

Price DD, Staud R

Neurobiology of fibromyalgia syndrome

Accumulating evidence suggests that fibromyalgia syndrome (FM) pain is maintained by tonic impulse input from deep tissues, such as muscle and joints, in combination with central sensitization mechanisms. This nociceptive input may originate in peripheral tissues (trauma and infection) resulting in hyperalgesia/ allodynia and/or central sensitization. Evidence for abnormal sensitization mechanisms in FM includes enhanced temporal summation of delayed pain in response to repeated heat taps and repeated muscle taps, as well as prolonged and enhanced painful after-sensations in FM patients but not control subjects. Moreover, magnitudes of enhanced after-sensations are predictive of FM patients' ongoing clinical pain. Such **alterations of relevant pain mechanisms may lead to longterm neuroplastic changes that exceed the antinociceptive capabilities of affected individuals, resulting in ever-increasing pain sensitivity and dysfunction.** Future research needs to address the important role of abnormal nociception and/or antinociception for chronic pain in FM.

J Rheumatol Suppl. 2005 Aug; 75:22–8

Ruster M, Franke S, Spath M, Pongratz DE, Stein G, Hein GE

Detection of elevated N epsilon-carboxymethyllysine levels in muscular tissue and in serum of patients with fibromyalgia

OBJECTIVES: To compare levels of the advanced glycation end product (AGE) N(epsilon)-carboxymethyllysine (CML) present in the muscle tissue and in the serum of patients with fibromyalgia (FM) vs. healthy controls. METHODS: The serum levels of CML were measured in 41 patients with FM and 81 healthy controls. The presence of CML, nuclear factor kappa B (NF-kappaB), the AGE receptor (RAGE), collagen types I, II, VI, and CD68-positive monocytes/ macrophages in muscle tissue of 14 patients with FM was investigated by immunohistochemistry. RESULTS: Patients with FM showed significantly increased serum levels of CML in comparison to healthy controls. The immunohistochemical investigation revealed a stronger staining for CML and NF-kappaB and more CD68-positive monocytes/macrophages in the muscle of FM patients. The collagens and CML were co-localized, suggesting that the AGE modifications were related to collagen. RAGE was absent in controls but a faint and patchy staining was seen in FM. CONCLUSIONS**: In the interstitial connective tissue of fibromyalgic muscles we found a more intensive staining of the AGE CML, activated NF-kappaB, and also higher CML levels in the serum of these patients compared to the controls. RAGE was only present in FM muscle.** AGE modification of proteins causes reduced solubility and high resistance to proteolytic digestion of the altered proteins (e.g. AGE-modified collagens). AGEs can stimulate different types of cells by activation of the transcription factor NF-kappaB, mediated by specific receptors of AGEs (e.g. RAGE) on the cell surface. Both mechanisms may contribute to the development, perpetuation, and spreading of pain characteristic in FM patients.

Scand J Rheumatol. 2005 Nov–Dec; 34(6):460–3

Staud R, Robinson ME, Price DD

Isometric exercise has opposite effects on central pain mechanisms in fibromyalgia patients compared to normal controls

Aerobic exercise has been shown to activate endogenous opioid and adrenergic systems and attenuate experimental pain in normal control subjects (NC). In contrast, **fibromyalgia (FM) subjects' experimental pain ratings increase after aerobic exercise, suggestive of abnormal pain modulation.** In order to determine whether central or peripheral mechanisms are predominantly involved in the abnormal pain modulation of FM patients, the effects of handgrip exercise on thermal (cutaneous) and mechanical (somatic) experimental pain was tested in local as well as remote body areas of FM and NC subjects. Supra-threshold thermal pain ratings and pressure pain thresholds over both forearms were obtained before and during 90 s of sustained 30% maximal voluntary contraction (MVC). This isometric exercise resulted in substantially decreased thermal pain ratings and increased mechanical thresholds in local as well as remote body areas in NC. Opposite effects were detected in FM patients. Thus, sustained local muscular contraction induced widespread pain inhibitory effects in NC. In contrast,

the **widespread hyperalgesic effects of exercise on FM patients clearly indicate altered central pain mechanisms**. However, whether these exercise effects of FM patients result from abnormal descending inhibition or excessive activation of muscle nociceptive afferents needs to be addressed in future studies.

Pain. 2005 Sep 8; [Epub ahead of print]

Staud R, Vierck CJ, Robinson ME, Price DD

Effects of the N-methyl-D-aspartate receptor antagonist dextromethorphan on temporal summation of pain are similar in fibromyalgia patients and normal control subjects

Temporal summation of second pain at least partly reflects temporal summation of dorsal horn neuronal responses, and both have been termed windup (WU), a form of nociception-dependent central sensitization. Animal and human experiments have shown that both forms of WU depend on N-methyl-D-aspartate (NMDA) and substance P receptor systems. WU of second pain (WU(SP)) in patients with fibromyalgia (FM) is enhanced compared with normal control (NC) subjects and is followed by exaggerated WU(SP) aftersensations and prolonged WU(SP) maintenance at low stimulus frequencies. Because the enhanced WU(SP) of FM patients could be related to abnormal endogenous modulation of NDMA receptors, we tested the effects of the NMDA receptor antagonist dextromethorphan (DEX) on WU(SP) in FM and NC subjects in a double-blind, placebo-controlled, crossover study. WU(SP) was elicited by trains of 0.7-second duration thermal pulses applied to the glabrous surface of the hands or by 1-second mechanical stimuli to the adductor pollicis muscle of the hands at a frequency of 0.33 Hz. In comparison to baseline and placebo conditions, single oral doses of DEX 60 and 90 mg reduced thermal and mechanical WU(SP) in NC and FM subjects, with DEX 90 mg being most effective. These effects did not differ for male and female NC subjects. FM subjects required less thermal and mechanical stimulus intensity than NC to achieve maximal WU(SP), but the extent of WU(SP) reduction by DEX did not statistically differ between NC and FM subjects for all study conditions. Thus, central pain processing of FM subjects is not different from NC in at least one important aspect, namely their NMDA receptor system responsiveness to pharmacologic inhibition by DEX. PERSPECTIVE: Results of this study demonstrate that FM patients show abnormal WU(SP) during thermal and mechanical stimulation compared with NC. **Because oral doses of the NMDA receptor antagonist DEX attenuated thermal and mechanical WU(SP) similarly in FM patients and NC, other mechanisms than WU(SP) need to be considered for the widespread pain of FM patients.** These mechanisms might include tonic nociceptive input from peripheral tissues and/or enhanced descending facilitation.

J Pain. 2005 May; 6(5):323–32

Turk DC

The potential of treatment matching for subgroups of patients with chronic pain: lumping versus splitting

A large and diverse number of treatments have been shown to be effective in reducing pain and other symptoms for a minority but statistically significant number of patients in different chronic pain syndromes. The means by which such different treatments achieve similar outcomes is not well understood. In this paper, the importance of considering patient heterogeneity for those who may be diagnosed with the same medical syndrome is discussed. The author suggests that **the lack of satisfactory treatment outcomes for the treatments of chronic pain syndromes may be accounted for by the patient homogeneity myth**—the assumption that all patients with the same medical diagnosis are similar on all important variables. The importance of subdividing (splitting) patients into meaningful groups is described. Studies presenting data on the identification of patient subgroups based on psychosocial and behavioral characteristics and the reliability and validity of this approach are presented. **Some initial attempts to demonstrate the potential for matching treatments to patient subgroups are described.**

Clin J Pain. 2005 Jan-Feb; 21(1):44–55; discussion 69–72

Valkeinen H, Hakkinen K, Pakarinen A, Hannonen P, Hakkinen A, Airaksinen O, Niemitukia L, Kraemer WJ, Alen M

Muscle hypertrophy, strength development, and serum hormones during strength training in elderly women with fibromyalgia

OBJECTIVE: To examine the effects of strength training on maximal force, cross-sectional area (CSA), and electromyographic (EMG) activity of muscles and serum hormone concentrations in elderly females with fibromyalgia (FM). METHODS: Twenty-six patients with FM were randomly assigned to a training (FMT; n = 13; mean age 60 years) or a control (FMC; n = 13; 59 years) group. FMT performed progressive strength training twice a week for 21 weeks. The measurements included maximal isometric and concentric leg extension forces, EMG activity of the vastus lateralis and medialis, CSA of the quadriceps femoris, and serum concentrations of testosterone (T), free testosterone (FT), growth hormone (GH), insulin-like growth factor-1 (IGF-1), dehydroepiandrosterone sulfate (DHEAS), and cortisol. Subjectively perceived symptoms of FM were also assessed. RESULTS: All patients were able to complete the training. In FMT strength training led to increases of 36% ($p<0.001$) and 33% ($p<0.001$) in maximal isometric and concentric forces, respectively. The CSA increased by 5% ($p<0.001$) and the EMG activity in isometric action by 47% ($p<0.001$) and in concentric action by 57% ($p<0.001$). Basal serum hormone concentrations remained unaltered during strength training. The subjective perceived symptoms showed a

minor decreasing tendency (ns). No statistically significant changes occurred in any of these parameters in FMC. CONCLUSION: Progressive strength training increases strength, CSA, and voluntary activation of the trained muscles in elderly women with FM, while the measured basal serum hormone concentrations remain unaltered. **Strength training benefits the overall physical fitness of the patients without adverse effects or any exacerbation of symptoms and should be included in the rehabilitation programmes of elderly patients with FM**.

Scand J Rheumatol. 2005 Jul-Aug; 34(4):309–14

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

Serum hyaluronic acid levels are elevated in arthritis patients, but normal and not associated with clinical data in patients with fibromyalgia syndrome

BACKGROUND: Fibromyalgia syndrome (FM) is a disease with widespread chronic pain and many nonspecific symptoms. Hyaluronic acid (HA) is a disputed marker for the diagnosis of FM. The aim of the study is to clarify the discrepant results reported so far. METHODS: Serum concentrations of HA were measured with a radiometric assay (Pharmacia & Upjohn, Sweden) in 41 patients with FM (38 females), 48 with arthritis (35 females) and 31 control subjects (28 females). Correlations of HA levels with clinical parameters (duration of disease, age, gender, medication) and scores of disease severity (e.g. depression and pain) were calculated. If appropriate, partial correlations and analysis of covariance adjusted for confounding variables (e.g. age) were used. RESULTS: **HA levels were confirmed to be age-related in the whole study group** ($r(s) = 0.54$; $P < 0.001$) and each subgroup. Association between HA levels and gender, drug therapy, clinical or psychometric data could not be demonstrated in patients suffering from FM. Analyzing all study participants, HA levels were correlated with the pain disability index (PDI) ($r(tau) = 0.27$; $P < 0.02$) and, in arthritis patients only, with duration of disease ($r(tau) = 0.82$; $P < 0.001$). Moreover, analysis of covariance revealed that patients with FM had normal HA values as compared with control subjects and only patients with arthritis had significantly higher levels than both other groups. CONCLUSIONS: The present study with a quite large cohort including patients with arthritis and FM demonstrates that **serum levels of HA in FM are neither elevated nor associated with any relevant clinical data of this disease and, therefore, have no diagnostic or prognostic value**.

Clin Lab. 2005; 51(1–2):11–9