

FIBROMYALGIA: ABSTRACTS 2007 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 2007. The studies were selected from the extensive literature on fibromyalgia so as to cover a wide range of subjects in limited space.

Abstracts for 2008 will be posted at intervals during the year. Similar collections of abstracts produced annually from 1999 on can be found on the main website of the National Fibromyalgia Partnership: www.fmpartnership.org (click Learn about Fibromyalgia, then Research).

The abstracts are arranged in alphabetical order by lead author.

Armstrong DJ, Meenagh GK, Bickle I, Lee AS, Curran ES, Finch MB

Vitamin D deficiency is associated with anxiety and depression in fibromyalgia

Fibromyalgia is a complex problem in which symptoms of anxiety and depression feature prominently. Low levels of vitamin D have been frequently reported in fibromyalgia, but no relationship was demonstrated with anxiety and depression. Seventy-five Caucasian patients who fulfilled the ACR criteria for fibromyalgia had serum vitamin D levels measured and completed the Fibromyalgia Impact Questionnaire (FIQ) and Hospital Anxiety and Depression Score (HADS). Deficient levels of vitamin D was found in 13.3% of the patients, while 56.0% had insufficient levels and 30.7% had normal levels. Patients with vitamin D deficiency (< 25 nmol/l) had higher HADS [median, IQR, 31.0 (23.8–36.8)] than patients with insufficient levels [25–50 nmol/l; HADS 22.5 (17.0–26.0)] or than patients with normal levels [50 nmol/l or greater; HADS 23.5 (19.0–27.5); Kruskal-Wallis ANOVA on ranks $p < 0.05$]. There was no relationship with global measures of disease impact or musculoskeletal symptoms. **Vitamin D deficiency is common in fibromyalgia and occurs more frequently in patients with anxiety and depression.** The nature and direction of the causal relationship remains unclear, but there are definite implications for long-term bone health.

Clin Rheumatol. 2007 Apr; 26(4):551–4. Epub 2006 Jul 19

Arnold LM, Crofford LJ, Martin SA, Young JP, Sharma U

The effect of anxiety and depression on improvements in pain in a randomized, controlled trial of pregabalin for treatment of fibromyalgia

OBJECTIVE. To assess symptoms of anxiety and depression in a large cohort of fibromyalgia patients and to determine the impact of these symptoms on response of pain to pregabalin treatment. **DESIGN.** Patients completed the Hospital Anxiety and Depression Scale at the baseline visit in a randomized, controlled trial of pregabalin for treatment of fibromyalgia. Mean anxiety and depression subscale scores were calculated, and proportions of patients by symptom severity were determined. The difference between the proportion of patients reporting anxiety and depression at baseline was tested using McNemar's test. Baseline anxiety and depression were evaluated as covariates by including them as interaction terms with treatment in an ancova model. A path analysis evaluated the association between improvements in anxiety and depression and pain relief. **RESULTS.** In total, 529 patients were enrolled. Significantly more patients reported anxiety symptoms (71%) than depressive symptoms (56%) ($p < 0.0001$). Improvement in pain symptoms with pregabalin compared with placebo did not depend linearly on baseline anxiety or depression scores. By path analysis, 75% of the pain reduction was not explained by improvements in anxiety and depressive symptoms. **CONCLUSIONS.** Anxiety symptoms were more common than depressive symptoms in this cohort. Our results suggest patients with fibromyalgia should be routinely assessed for the presence of both anxiety and depression. **The pain treatment effect of pregabalin did not depend on baseline anxiety or depressive symptoms**, suggesting pregabalin improves pain in patients with or without these symptoms. Much of the pain reduction appears to be independent of improvements in anxiety or mood symptoms.

Pain Med. 2007 Nov; 8(8):633–638

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

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

OBJECTIVE: To assess the efficacy and safety of gabapentin in patients with fibromyalgia. **METHODS:** A 12-week, randomized, double-blind study was designed to compare gabapentin (1,200–2,400 mg/day) ($n = 75$ patients) with placebo ($n = 75$ patients) for efficacy and safety in treating pain associated with fibromyalgia. The primary outcome measure was the Brief Pain Inventory (BPI) average pain severity score (range 0–10, where 0 = no pain and 10 = pain as bad as you can imagine). Response to treatment was defined as a reduction of $\geq 30\%$ in this score. The primary analysis of efficacy for continuous variables was a longitudinal analysis of the intent-to-treat sample, with treatment-by-time interaction as the measure of effect. **RESULTS:** Gabapentin-treated patients displayed a significantly greater improvement in the BPI average pain severity score ($P = 0.015$; estimated difference between groups at week 12 = -0.92 [95% confidence

interval -1.75, -0.71]). A significantly greater proportion of gabapentin-treated patients compared with placebo-treated patients achieved response at end point (51% versus 31%; $P = 0.014$). Gabapentin compared with placebo also significantly improved the BPI average pain interference score, the Fibromyalgia Impact Questionnaire total score, the Clinical Global Impression of Severity, the Patient Global Impression of Improvement, the Medical Outcomes Study (MOS) Sleep Problems Index, and the MOS Short Form 36 vitality score, but not the mean tender point pain threshold or the Montgomery Asberg Depression Rating Scale. Gabapentin was generally well tolerated. **CONCLUSION: Gabapentin (1,200–2,400 mg/day) is safe and efficacious for the treatment of pain and other symptoms associated with fibromyalgia.**

Arthritis Rheum. 2007 Mar 28; 56(4):1336–1344 [Epub ahead of print]

Baliki MN, Geha PY, Apkarian AV

Spontaneous pain and brain activity in neuropathic pain: functional MRI and pharmacologic functional MRI studies

Functional brain imaging studies in chronic neuropathic pain patients have lagged far behind equivalent studies in acute pain. In the past few years, this trend has begun to shift. This article discusses the novel approach of studying brain activity for spontaneous pain and its modulation by pharmacologic manipulation. We argue that the approach provides a solid methodology for studying clinical (especially neuropathic) pain and patient populations and, moreover, that the latest results using this approach imply that **distinct clinical chronic pain conditions seem to involve specific brain circuitry, which is also distinct from the brain activity commonly observed in acute pain.**

Curr Pain Headache Rep. 2007 Jun; 11(3):171–7

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

An internet survey of 2,596 people with fibromyalgia

BACKGROUND: This study explored the feasibility of using an Internet survey of people with fibromyalgia (FM), with a view to providing information on demographics, sources of information, symptoms, functionality, perceived aggravating factors, perceived triggering events, health care utilization, management strategies, and medication use. **METHODS:** A survey questionnaire was developed by the National Fibromyalgia Association (NFA) in conjunction with a task force of “experts in the field.” The questionnaire underwent several rounds of testing to improve its face validity, content validity, clarity and readability before it was mounted on the internet. The questionnaire consisted of 121 items and is available

online at the website of the National Fibromyalgia Association. RESULTS: The questionnaire was completed by 2,569 people. Most were from the United States, with at least one respondent from each of the 50 states. Respondents were predominantly middle-aged Caucasian females, most of whom had FM symptoms for > or = 4 years. The most common problems were morning stiffness, fatigue, nonrestorative sleep, pain, concentration, and memory. Aggravating factors included: emotional distress, weather changes, insomnia, and strenuous activity. Respondents rated the most effective management modalities as rest, heat, pain medications, antidepressants, and hypnotics. The most commonly used medications were: acetaminophen, ibuprofen, naproxen, cyclobenzaprine, amitriptyline, and aspirin. The medications perceived to be the most effective were: hydrocodone preparations, aprazolam, oxycodone preparations, zolpidem, cyclobenzaprine, and clonazepam. CONCLUSION: This survey provides a snapshot of FM at the end of 2005, as reported by a self-selected population of people. This descriptive data has a heuristic function, in that **it identifies several issues for further research, such as the prescribing habits of FM health care providers, the role of emotional precipitants, the impact of obesity, the significance of low back pain and the nature of FM-related stiffness.**

BMC Musculoskelet Disord. 2007 Mar 9; 8:27

Carville SF, Arendt-Nielsen S, Bliddal H, Blotman F, Branco JC, Buskila D, Da Silva JA, Danneskiold-Samsøe B, Dincer F, Henriksson C, Henriksson K, Kosek E, Longley K, McCarthy GM, Perrot S, Puszczewicz MJ, Sarzi-Puttini P, Silman A, Späth M, Choy EH

EULAR evidence-based recommendations for the management of fibromyalgia syndrome

OBJECTIVE: To develop evidence-based recommendations for the management of fibromyalgia syndrome (FMS). METHODS: A multidisciplinary task force was formed representing eleven European countries. The design of the study including search strategy, participants, interventions, outcome measures, data collection and analytical method was defined at the outset. A systematic review was undertaken with the keywords “fibromyalgia”, “treatment or management” and “trial.” Studies were excluded if they did not utilise the ACR classification criteria, were not clinical trials, or included patients with chronic fatigue syndrome or myalgic encephalomyelitis. Primary outcome measures were change in pain assessed by visual analogue scale (VAS) and fibromyalgia impact questionnaire (FIQ). The quality of the studies was categorised based on randomisation, blinding and allocation concealment. Only the highest quality studies were used to base recommendations on. When there was insufficient evidence from the literature, a Delphi process was used to provide basis for recommendation. RESULTS: One hundred and forty-six studies were eligible for the review. Thirty-nine pharmacologic intervention studies and 59 non-pharmacologic were

included in the final recommendation summary tables once those of a lower quality or with insufficient data were separated. The categories of treatment identified were antidepressants, analgesics, and “other pharmacological,” and exercise, cognitive behavioural therapy, education, dietary interventions and “other non-pharmacological.” In many studies sample size was small and the quality of the study was insufficient for strong recommendations to be made. **CONCLUSION: Nine recommendations for the management of FMS were developed using a systematic review and expert consensus.**

Ann Rheum Dis. 2007 Oct 3 [Epub ahead of print]

Cook DB, Stegner AJ, McLoughlin MJ

Imaging pain of fibromyalgia

Brain imaging studies have provided objective evidence of abnormal central regulation of pain in fibromyalgia (FM). Resting brain blood flow studies have reported mixed findings for several brain regions, whereas decreased thalamic blood flow has been noted by several investigators. Studies examining the function of the nociceptive system in FM have reported augmented brain responses to both painful and non-painful stimuli that may be influenced by psychologic dispositions such as depressed mood and catastrophizing. Treatment approaches are beginning to demonstrate the potential for brain imaging to improve our understanding of pain-alleviating mechanisms. Data from other chronic conditions suggest that **idiopathic pain may be maintained by similar central abnormalities as in FM, whereas chronic pain conditions with a known nociceptive source may not be.** Future neuroimaging research in FM is clearly warranted and should continue to improve our understanding of factors involved in pain maintenance and symptom exacerbation.

Curr Pain Headache Rep. 2007 Jun; 11(3):190–200

Cöster L, Kendall S, Gerdle B, Henriksson C,
Henriksson KG, Bengtsson A

Chronic widespread musculoskeletal pain – A comparison of those who meet criteria for fibromyalgia and those who do not

Fibromyalgia is currently classified as chronic widespread pain with widespread allodynia to pressure pain. There are few data describing pain characteristics, quality of life, consequences for daily living, and psychosocial status in patients who meet the classification criteria for fibromyalgia proposed by the American College of Rheumatology compared with patients with chronic widespread pain but not widespread allodynia. This study used a randomly selected sample from the general population. A postal questionnaire and a pain mannequin were sent to

9952 people. The response rate was 76.7%. The pain drawings showed that 345 people had widespread pain; that is, they noted pain in all four extremities and axially. Clinical examination, which included a manual tender point examination, was performed in 125 subjects. These people answered commonly used questionnaires on pain, quality of life, coping strategies, depression, and anxiety. Compared with chronic widespread pain without widespread allodynia, fibromyalgia was associated with more severe symptoms/consequences for daily life and higher pain severity. Similar coping strategies were found. **Chronic widespread pain without widespread allodynia to pressure pain was found in 4.5% in the population and fibromyalgia in 2.5%.**

Eur J Pain. 2007 Nov 14 [Epub ahead of print]

Goldenberg DL

Pharmacological treatment of fibromyalgia and other chronic musculoskeletal pain

The pharmacologic management of fibromyalgia is based on the emerging evidence that pain in this disorder is primarily related to central pain sensitization. There is strong evidence that tricyclic antidepressants are effective, and moderate evidence for the effectiveness of serotonin reuptake inhibitors and dual serotonin-norepinephrine reuptake inhibitors. Recent work suggests that the anti-seizure medications pregabalin and gabapentin are also effective. **The only analgesic demonstrated to be helpful is tramadol.**

Best Pract Res Clin Rheumatol. 2007 Jun; 21(3):499–511

Haak T, Scott B

The effect of Qigong on fibromyalgia (FMS): A controlled randomized study

PURPOSE. To evaluate the effect of a 7-week Qigong intervention on subjects with Fibromyalgia Syndrome (FMS). **METHODS.** The study was a controlled randomized study with repeated measures. Fifty-seven FMS female subjects were randomly assigned to an intervention group (n = 29) or a waiting-list control group (n = 28). After completion of the experimental part, the control group received the same intervention. Collection of data was made at pre- and post-treatment and at 4-month follow-up for both groups. **RESULTS.** During the experimental part of the study, significant improvements were found for the intervention group, at post-treatment, regarding different aspects of pain and psychological health and distress. Almost identical results were found for the combined group. At 4-month follow-up, the majority of these results were either maintained or improved. **CONCLUSION.** The overall results show that Qigong has

positive and reliable effects regarding FMS. A high degree of completion, 93%, and contentment with the intervention further support the potential of the treatment. The results of the study are encouraging and suggest that **Qigong intervention could be a useful complement to medical treatment** for subjects with FMS.

Disabil Rehabil. 2007 Jun 15: 1–9 [Epub ahead of print]

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

Decreased central mu-opioid receptor availability in fibromyalgia

The underlying neurophysiology of acute pain is fairly well characterized, whereas the central mechanisms operative in chronic pain states are less well understood. Fibromyalgia (FM), a common chronic pain condition characterized by widespread pain, is thought to originate largely from altered central neurotransmission. We compare a sample of 17 FM patients and 17 age- and sex-matched healthy controls, using mu-opioid receptor (MOR) positron emission tomography. We demonstrate that FM patients display reduced MOR binding potential (BP) within several regions known to play a role in pain modulation, including the nucleus accumbens, the amygdala, and the dorsal cingulate. MOR BP in the accumbens of FM patients was negatively correlated with affective pain ratings. Moreover, MOR BP throughout the cingulate and the striatum was also negatively correlated with the relative amount of affective pain (McGill, affective score/sensory score) within these patients. **These findings indicate altered endogenous opioid analgesic activity in FM and suggest a possible reason why exogenous opiates appear to have reduced efficacy in this population.**

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

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

Growth hormone perturbations in fibromyalgia: A review

OBJECTIVE: Fibromyalgia (FM) is a syndrome characterized by chronic widespread pain, fatigue, disrupted sleep, depression, and physical deconditioning. In this article, we review the literature on the normal activity of the hypothalamic-pituitary-growth hormone-insulin-like growth factor-1 (HP-GH-IGF-1) axis and its perturbations in FM subjects. **METHODS:** Studies included in this review were accessed through an English language search of Cochrane Collaboration Reviews. Keyword MeSH terms included “fibromyalgia,” “growth hormone” (GH), or “insulin-like growth factor” (IGF-1). **RESULTS:** Twenty-six studies enrolling 2006 subjects were reviewed. Overall, low levels of IGF-1 were found in a subgroup of subjects. Growth hormone stimulation tests often revealed a suboptimal response, which did not always correlate with IGF-1 levels. No consistent defects in pituitary function were found. Of the 3 randomized placebo

controlled studies, only 9 months of daily injectable recombinant GH reduced FM symptoms and normalized IGF-1. **CONCLUSIONS: These studies suggest that pituitary function is normal in FM and that reported changes in the HP-GH-IGF-1 axis are most likely hypothalamic in origin. The therapeutic efficacy of supplemental GH therapy in FM requires further study before any solid recommendations can be made.**

Semin Arthritis Rheum. 2007 Jan 12; [Epub ahead of print]

Kashikar-Zuck S, Lynch AM, Graham TB, Swain NF, Mullen SM, Noll RB

Social functioning and peer relationships of adolescents with juvenile fibromyalgia syndrome

OBJECTIVE: To assess peer relationships of adolescents with juvenile primary fibromyalgia syndrome (JPFS) compared with matched classroom comparison peers (MCCPs) without a chronic illness. JPFS is characterized by chronic musculoskeletal pain, sleep disturbance, fatigue, and difficulty with daily functioning. Adolescents with JPFS often report problems with school and participating in peer activities, placing them at risk for social isolation from their peers and psychosocial adjustment problems. **METHODS:** Participants were 55 adolescents with JPFS (ages 12-18 years) from a pediatric outpatient rheumatology clinic and 55 MCCPs. Data on peer reputation and peer acceptance were collected from teachers, peers, and self report in a classroom setting with no focus on JPFS. **RESULTS:** Adolescents with JPFS were perceived (by peer and self reports) as being more isolated and withdrawn and less popular. Adolescents with JPFS were less well liked, were selected less often as a best friend, and had fewer reciprocated friendships. **CONCLUSION: Our findings suggest that adolescents with JPFS are experiencing problems with peer relationships.** Given the central role that peer relationships play in psychological development of children, and because **peer rejection and isolation have been associated with subsequent adjustment problems, these findings are concerning.** Longitudinal studies of adolescents with JPFS are needed to ascertain whether these patients are at long-term risk and will provide a foundation for the need for early interventions. Results are discussed within the context of earlier findings for other adolescents with chronic illness and rheumatic conditions, such as juvenile idiopathic arthritis, who demonstrated no social problems.

Arthritis Rheum. 2007 Mar 29; 57(3):474-480 [Epub ahead of print]

Katz DL, Greene L, Ali A, Faridi Z

The pain of fibromyalgia syndrome is due to muscle hypoperfusion induced by regional vasomotor dysregulation

Fibromyalgia syndrome (FMS) is a condition of chronic muscle pain and fatigue of unknown etiology and pathogenesis. There is limited support for the various hypotheses espoused to account for the manifestations of FMS, including immunogenic, endocrine, and neurological mechanisms. Treatment, partially effective at best, is directed toward symptomatic relief without the benefit of targeting known, underlying pathology. **A noteworthy commonality among partially effective therapies is a vasodilatory effect.** This is true both of conventional treatments, unconventional treatments such as intravenous micronutrient therapy, and lifestyle treatments, specifically graduated exercise. The pain of fibromyalgia is described in terms suggestive of the pain in muscles following extreme exertion and anaerobic metabolism. Taken together, these characteristics suggest that the pain could be induced by vasomotor dysregulation, and vasoconstriction in muscle, leading to low-level ischemia and its metabolic sequelae. Vasodilatory influences, including physical activity, relieve the pain of FMS by increasing muscle perfusion. There are some preliminary data consistent with this hypothesis, and nothing known about FMS that refutes it. **The hypothesis that the downstream cause of FMS symptoms is muscle hypoperfusion due to regional vasomotor dysregulation has clear implications for treatment; is testable with current technology; and should be investigated.**

Med Hypotheses. 2007 Mar 19; [Epub ahead of print]

Leblebici B, Pektaay ZO, Ortancil O, Harcan EC, Bagis S, Akman MN

Coexistence of fibromyalgia, temporomandibular disorder, and masticatory myofascial pain syndromes

The purpose of this study was to determine the association of fibromyalgia (FM) with temporomandibular disorder (TMD) and masticatory myofascial pain (MMP). Thirty-one consecutive women diagnosed as having FM according to American College of Rheumatology criteria and 21 consecutive women diagnosed as having TMD were included in this prospective study. All patients were examined by a dentist and a physiatrist to identify the coexistence of FM and TMD. In the FM group, TMD was found in 25 (80%) patients, and only 6 (19%) [of those] patients had arthrogenous origin with MMP, whereas 19 (81%) had MMP without arthrogenous origin...In the TMD group, the prevalence of FM was 52%, which was significantly higher in those with TMD of arthrogenous origin with MMP. **Our results indicate that coexistence of FM and TMD with MMP is high. Pain and tenderness in the masticatory muscles appear to be an important element in FM, so in some patients it may be the leading complaint.**

Rheumatol Int. 2007 Apr; 27(6):541–4. Epub 2006 Nov 10

Martinez-Lavin M

Biology and therapy of fibromyalgia. Stress, the stress response system, and fibromyalgia

Stress is a state of disharmony, or threatened homeostasis. A stressor could have a psychological origin or a biological origin. Societies have become more intricate with industrialization, and modern individuals try to adapt to the new defiance by forcing their stress response system. The main component of the stress response network is the autonomic nervous system. **The present article reviews current knowledge on autonomic dysfunction in fibromyalgia.** Sympathetic hyperactivity has been consistently described by diverse groups of investigators. Fibromyalgia is proposed to be a sympathetically maintained neuropathic pain syndrome, and genomic data support this contention. Autonomic dysfunction may also explain other fibromyalgia features not related to pain.

Arthritis Res Ther. 2007 Jul 6; 9(4):216 [Epub ahead of print]

Martinez-Lavin M, Infante O, Lerma C

Hypothesis: The chaos and complexity theory may help our understanding of fibromyalgia and similar maladies

BACKGROUND: Modern clinicians are often frustrated by their inability to understand fibromyalgia and similar maladies since these illnesses cannot be explained by the prevailing linear-reductionist medical paradigm. **OBJECTIVE:** This article proposes that new concepts derived from the Complexity Theory may help understand the pathogenesis of fibromyalgia, chronic fatigue syndrome, and Gulf War syndrome. **METHODS:** This hypothesis is based on the recent recognition of chaos fractals and complex systems in human physiology. **RESULTS:** These nonlinear dynamics concepts offer a different perspective to the notion of homeostasis and disease. They propose that **the essence of disease is dysfunction and not structural damage.** Studies using novel nonlinear instruments have shown that fibromyalgia and similar maladies may be caused by the degraded performance of our main complex adaptive system. This dysfunction explains the multifaceted manifestations of these entities. **CONCLUSIONS:** To understand and alleviate the suffering associated with these complex illnesses, a paradigm shift from reductionism to holism based on the Complexity Theory is suggested. **This shift perceives health as resilient adaptation and some chronic illnesses as rigid dysfunction.**

Semin Arthritis Rheum. 2007 Jun 13; [Epub ahead of print]

McVeigh JG, Finch MB, Hurley DA, Basford JR, Sim J, Baxter GD

Tender point count and total myalgic score in fibromyalgia: changes over a 28-day period

Tender point count (TPC) is central to fibromyalgia syndrome (FMS), and with total myalgic score (TMS) is often used to monitor the patient's condition. This study aimed to determine the stability of TPC and TMS over time, and to examine how well these measures reflected patients' perceptions of their condition. Twenty-four patients with FMS completed the Fibromyalgia Impact Questionnaire (FIQ) and a visual analogue scale (VAS) measuring well-being at entrance into the study, and 7 and 28 days later. There was no significant change in TPC ($P = 0.074$), FIQ score ($P = 0.291$) or VAS ($P = 0.079$) of well-being with time. However, **mean TMS score did change over time** ($P = 0.021$). There was no correlation between total FIQ score and the other measures (all P -values > 0.05). **The significant change in TMS over time may reflect the natural fluctuation in the clinical presentation of FMS.**

Rheumatol Int. 2007 Sep; 27(11):1011–8. Epub 2007 Jul 20

Munguía-Izquierdo D, Legaz-Arrese A

Exercise in warm water decreases pain and improves cognitive function in middle-aged women with fibromyalgia

OBJECTIVES: To compare the cognitive function performance in patients with fibromyalgia (FM) with respect healthy controls and to evaluate the short-term efficacy of exercise therapy in a warm, chest-high pool on pain and cognitive function in women with FM. **METHODS:** Sixty middle-aged women with FM were randomly assigned to either an exercise training group ($n = 35$) to perform 3 sessions per week of aquatic training (32 degrees C) including mobility, aerobic, strengthening, and relaxation exercises for 16 weeks, or a control group ($n = 25$). Twenty-five healthy women matched for age, weight, body mass index, and educational and physical activity levels were recruited. Pain was assessed in patients using a syringe calibrated like a pressure dolorimeter, and a visual analog scale. The severity of FM was evaluated using the Fibromyalgia Impact Questionnaire. Cognitive function was measured in healthy individuals and patients using several standardized neuropsychological tests. All patients were measured at baseline and post-treatment. **RESULTS:** At baseline, the healthy group evidenced cognitive performance that was significantly superior to the group of patients with FM in all of the neuropsychological tests. The exercise group significantly improved their pain threshold, tender point count, self-reported pain, severity of FM, and cognitive function, while in the control group the differences were not significant. **CONCLUSION: An exercise therapy three times per week for 16 weeks in a warm-water pool is an adequate treatment to decrease the**

pain and severity of FM as well as to improve cognitive function in previously unfit women with FM and heightened painful symptomatology.

Clin Exp Rheumatol. 2007 Nov-Dec; 25(6):823–30

Nielsen LA, Henriksson KG

Pathophysiological mechanisms in chronic musculoskeletal pain (fibromyalgia): the role of central and peripheral sensitization and pain disinhibition

Chronic musculoskeletal pain has biological, psychological and social components. This review deals with the biological factors, with emphasis on the fibromyalgia syndrome (FMS). Studies on central sensitization of pain-transmitting neurons, changes in endogenous pain modulation that give rise to pain disinhibition, referred pain, pain-related decrease in muscle strength and endurance, and pain generators in deep tissues are reviewed. In FMS there is strong scientific support for the statement that **the biological part of the syndrome is a longstanding or permanent change in the function of the nociceptive nervous system that can be equated with a disease**. Further research is necessary in order to determine which methods are best for diagnosis of the pain hypersensitivity in clinical practice. FMS may be the far end of a continuum that starts with chronic localized/regional musculoskeletal pain and ends with widespread chronic disabling pain.

Best Pract Res Clin Rheumatol. 2007 Jun; 21(3):465–80

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

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

OBJECTIVE: Psychosocial stress is a risk factor for musculoskeletal pain, but how stress affects musculoskeletal pain is poorly understood. We wanted to examine the relationship between low-grade autonomic activation and stress-related pain in patients with fibromyalgia and localised chronic shoulder/neck pain. **METHODS:** Twenty-three female patients with fibromyalgia, 29 female patients with chronic shoulder-neck pain, and 35 healthy women performed a stressful task lasting 60min. With a blinded study design, we recorded continuous blood pressure, heart rate, finger skin blood flow and respiration frequency before (10min), during (60min) and after (30min) the stressful task. The physiological responses were compared with subjective reports of pain. **RESULTS:** The increase in diastolic blood pressure and heart rate in response to the stressful task were smaller in fibromyalgia patients compared with the healthy controls. Furthermore, fibromyalgia patients had reduced finger skin blood flow at the end of the

stressful task compared to healthy controls. We also found an inverse relationship between the heart rate response and development and recovery of the stress-related pain in fibromyalgia patients. **CONCLUSION: We found abnormal cardiovascular responses to a 60min long stressful task in fibromyalgia patients. Furthermore, we found a negative association between the heart rate response and the pain which developed during the stressful task in the fibromyalgia group, possibly a result of reduced stress-induced analgesia for fibromyalgia patients.**

Eur J Pain. 2007 Jan 13; [Epub ahead of print]

Owen RT

Pregabalin: Its efficacy, safety and tolerability profile in fibromyalgia syndrome

Fibromyalgia syndrome (FMS) is characterized by chronic widespread pain and accompanied by a variety of other symptoms such as fatigue, sleep dysfunction, depression, anxiety and cognitive disturbance. Current guidelines recommend tricyclic antidepressants or SSRIs (selective serotonin reuptake inhibitors) as first-line therapies to treat the multiple symptom domains. Until recently, however, there were no licensing authority approved treatments for FMS. The alpha 2 delta modulator pregabalin has anxiolytic, anticonvulsant and antinociceptive properties which has prompted its investigation in FMS. In a series of short-term randomized, double-blind, placebo-controlled trials of 8-14 weeks duration, **pregabalin proved effective in reducing the pain and accompanying symptoms of FMS and improved quality of life domains.** A 6-month double-blind, placebo-controlled trial demonstrated the durability of its effects on pain and a variety of secondary measures such as fatigue and sleep disturbance. Overall, **pregabalin was well tolerated with no new adverse events emerging that have not been reported with its use in other indications.**

Drugs Today (Barc). 2007 Dec; 43(12):857-63

Palomino RA, Nicassio PM, Greenberg MA, Medina EP Jr.

Helplessness and loss as mediators between pain and depressive symptoms in fibromyalgia

This study evaluated the contribution of condition-specific helplessness and loss to depression in fibromyalgia (FM). Two models were tested. The first model examined whether loss, measured by the West Haven-Yale Multidimensional Pain Inventory (WHYMPI) Interference Scale, would mediate the relationship between disability and depression. The second model determined whether condition-specific helplessness and loss would mediate the relationship between pain and

depression with disability controlled. Eighty patients with confirmed diagnoses of FM were recruited throughout Southern California from general medical clinics, newspaper advertisements, and rheumatology practices. The study design was cross-sectional, using self-report, observational, and interview measures. A composite measure of depression was adopted, consisting of the Center for Epidemiological Studies-Depression Scale and the Hamilton Rating Scale for Depression. Hierarchical multiple regression analyses were conducted using a path analytic framework to examine each model. In Model 1, loss fully mediated the relationship between disability and depression. In Model 2, condition-specific helplessness mediated the relationship between pain and depression, but the contribution of loss was not significant. The findings confirm the importance of helplessness and demonstrate that **the cognitive meaning of having FM plays a more central role in predicting depressive symptomatology than illness-related stressors, such as pain or disability.**

Pain. 2007 Feb 28; [Epub ahead of print]

Patkar AA, Masand PS, Krulewicz S, Mannelli P, Peindl K, Beebe KL, Jiang W

A randomized, controlled trial of controlled release paroxetine in fibromyalgia

PURPOSE: We investigated the efficacy and tolerability of paroxetine controlled release, a selective serotonin reuptake inhibitor in fibromyalgia. **METHODS:** After excluding patients with current major depression and anxiety disorders, 116 subjects with fibromyalgia were enrolled in a 12-week, randomized, double-blind, placebo-controlled, trial of paroxetine controlled release (12.5-62.5 mg/day). The primary outcome measure was proportion of responders as defined as a $>$ or $=$ 25% reduction in scores on the Fibromyalgia Impact Questionnaire (FIQ) from randomization to end of treatment. Secondary outcome measures included changes in FIQ scores, Clinical Global Impression-Improvement (CGI-I) and Severity (CGI-S) scores, Visual Analogue Scale for pain scores, number of tender points, and scores on the Sheehan Disability Scale (SDS). **RESULTS:** Significantly more patients in the paroxetine controlled release group (57%) showed a $>$ or $=$ 25% reduction in FIQ compared to placebo (33%) ($P=.016$). Paroxetine controlled release was significantly superior to placebo in reducing the FIQ total score ($P=.015$). The CGI-I ratings significantly favored the drug over placebo ($P<.005$). The improvements on other secondary outcome measures between the 2 groups were not statistically significant. Drowsiness, dry mouth, blurred vision, genital disorders, and anxiety were reported more frequently with paroxetine controlled release. The mean dose of paroxetine controlled release was 39.1 mg/day. **CONCLUSIONS:** **Paroxetine controlled release appears to be well tolerated and to improve the overall symptomatology in patients with fibromyalgia**

without current mood or anxiety disorders. However, its effect on pain measures seems to be less robust.

Am J Med. 2007 May; 120(5):448–4

Sarchielli P, Di Filippo M, Nardi K, Calabresi P

Sensitization, glutamate, and the link between migraine and fibromyalgia

Recent advances have shed insight on the pathophysiologic mechanisms of fibromyalgia and migraine, especially in the chronic form. A growing body of evidence supports the involvement of peripheral and central sensitization disturbances of pain-related processes underlying both disorders. They involve increased glutamate transmission through interaction with its ionotropic and metabotropic receptors. **[A] few studies supporting the implication of this excitatory amino acid in chronic migraine and primary fibromyalgia demonstrated increased levels of glutamate in the cerebrospinal fluid of affected patients.** These findings have implications for future therapies directed against glutamate receptors (in particular, N-methyl-D-aspartate receptors). Limited clinical experience in this regard, although promising, does not exclude additional mechanisms contributing to the maintenance of pain, which can be the target of therapeutic approaches in both disorders.

Curr Pain Headache Rep. 2007 Oct;11(5):343–51

Seidel MF, Weinreich GF, Stratz T, Müller W

5-HT₃ receptor antagonists regulate autonomic cardiac dysfunction in primary fibromyalgia syndrome

Fibromyalgia syndrome (FMS) frequently presents with autonomic and/or functional symptoms. Tropicsetron, a selective serotonin-3 antagonist, is widely used for the treatment of this disease. However, its effects on autonomic function are not well known. In the present study, we evaluated whether tropisetron improved cardiac autonomic symptoms in FMS. Thirty-six patients were treated with physiotherapy and 5 mg tropisetron intravenously for 5 days. An additional 36 patients were treated with physiotherapy alone. Thirty-six volunteers served as healthy controls. The ISAX apparatus was used for spectral analyses of cardiac R-R intervals. High frequencies and mid frequencies were analysed to assess sympathetic and parasympathetic activity. The findings were correlated with pain intensity. ISAX findings were significantly different in FMS patients compared to healthy controls and did not correlate with pain perception. Ten of 12 pathological parameters disappeared during treatment in the tropisetron group. Our results

indicate that **tropisetron reduced not only pain perception but also had a favourable effect on cardiac dysfunction during treatment.**

Rheumatol Int. 2007 Sep; 27(11):1025–1030. Epub 2007 Jul 19

Sephton SE, Salmon P, Weissbecker I, Ulmer C, Floyd A, Hoover K, Studts JL

Mindfulness meditation alleviates depressive symptoms in women with fibromyalgia: results of a randomized clinical trial

OBJECTIVE: Depressive symptoms are common among patients with fibromyalgia, and behavioral intervention has been recommended as a major treatment component for this illness. The objective of this study was to test the effects of the Mindfulness-Based Stress Reduction (MBSR) intervention on depressive symptoms in patients with fibromyalgia. **METHODS:** This randomized controlled trial examined effects of the 8-week MBSR intervention on depressive symptoms in 91 women with fibromyalgia who were randomly assigned to treatment (n = 51) or a waiting-list control group (n = 40). Eligible patients were at least 18 years old, willing to participate in a weekly group, and able to provide physician verification of a fibromyalgia diagnosis. Of 166 eligible participants who responded to local television news publicizing, 49 did not appear for a scheduled intake, 24 enrolled but did not provide baseline data, and 2 were excluded due to severe mental illness, leaving 91 participants. The sample averaged 48 years of age and had 14.7 years of education. The typical participant was white, married, and employed. Patients randomly assigned to treatment received MBSR. Eight weekly 2.5-hour sessions were led by a licensed clinical psychologist with mindfulness training. Somatic and cognitive symptoms of depression were assessed using the Beck Depression Inventory administered at baseline, immediately postprogram, and at followup 2 months after the conclusion of the intervention. **RESULTS:** Change in depressive symptoms was assessed using slopes analyses of intervention effects over time. Depressive symptoms improved significantly in treatment versus control participants over the 3 assessments. **CONCLUSION: This meditation-based intervention alleviated depressive symptoms among patients with fibromyalgia.**

Arthritis Rheum. 2007 Feb 15; 57(1):77–85

Staud R

Treatment of fibromyalgia and its symptoms

The main symptoms of fibromyalgia syndrome (FM) are pain, stiffness, subjective weakness and muscle fatigue. Pain in FM usually fluctuates, as well as being 'deep' and is always associated with local or generalized tenderness (hyperalgesia

and allodynia). The pathogenesis of such peripheral and/or CNS changes in FM is unclear, but peripheral tissue changes, specifically in muscles, have been implicated. Indirect evidence from interventions that attenuate tonic peripheral impulse input in patients with FM suggest that overall FM pain is dependent on nociception. More importantly, FM-associated widespread mechanical hyperalgesia and allodynia can also be improved or abolished by removal of peripheral pain impulse input. In addition, **FM patients show evidence of abnormal stress reactivity, including blunting of the hypothalamic-pituitary-adrenal axis and increased autonomic nervous system responsiveness.** Thus, therapeutic interventions in FM should target not only pain reductions, but also improvements of peripheral/central sensitization and neuroendocrine/autonomic abnormalities. Despite the complexity of FM, there are pharmacologic and non-pharmacologic interventions that are available that have clinical benefit. **Present evidence indicates efficacy of antidepressants, cardiovascular exercise and cognitive behavioural therapy.** Based on this evidence, a stepwise program emphasizing education, medications, exercise and cognitive therapy can be recommended.

Expert Opin Pharmacother. 2007 Aug; 8(11):1629–42

van Koulil S, Effting M, Kraaimaat FW, van Lankveld W, van Helmond T, Cats H, van Riel PL, de Jong AJ, Haverman JF, Evers AW

Cognitive-behavioural therapies and exercise programmes for patients with fibromyalgia: state of the art and future directions

This review provides an overview of the effects of non-pharmacological treatments for patients with fibromyalgia (FM), including cognitive-behavioural therapy, exercise training programmes, or a combination of the two. After summarising and discussing preliminary evidence of the rationale of non-pharmacological treatment in patients with FM, we reviewed randomised, controlled trials for possible predictors of the success of treatment such as patient and treatment characteristics. In spite of support for their suitability in FM, the effects of non-pharmacological interventions are limited and positive outcomes largely disappear in the long term. However, within the various populations with FM, treatment outcomes showed considerable individual variations. In particular, **specific subgroups of patients characterised by relatively high levels of psychological distress seem to benefit most from non-pharmacological interventions.** Preliminary evidence of retrospective treatment analyses suggests that the efficacy may be enhanced by offering tailored treatment approaches at an early stage to patients who are at risk of developing chronic physical and psychological impairments.

Ann Rheum Dis. 2007 May; 66(5):571–81. Epub 2006 Aug 17

Williams DA, Gracely RH

Biology and therapy of fibromyalgia. Functional magnetic resonance imaging findings in fibromyalgia

Techniques in neuroimaging such as functional magnetic resonance imaging (fMRI) have helped to provide insights into the role of supraspinal mechanisms in pain perception. This review focuses on studies that have applied fMRI in an attempt to gain a better understanding of the mechanisms involved in the processing of pain associated with fibromyalgia. **This article provides an overview of the nociceptive system as it functions normally, reviews functional brain imaging methods, and integrates the existing literature utilizing fMRI to study central pain mechanisms in fibromyalgia.**

Arthritis Res Ther. 2006; 8(6):224

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

Fibromyalgia patients show an abnormal dopamine response to pain

Fibromyalgia is characterized by chronic widespread pain and bodily tenderness and is often accompanied by affective disturbances. Accumulating evidence indicates that fibromyalgia may involve a dysfunction of modulatory systems in the brain. While brain dopamine is best known for its role in pleasure, motivation and motor control, recent evidence suggests that it is also involved in pain modulation. Because dopamine is implicated in both pain modulation and affective processing, we hypothesized that fibromyalgia may involve a disturbance of dopaminergic neurotransmission. Fibromyalgia patients and matched healthy control subjects were subjected to deep muscle pain produced by injection of hypertonic saline into the anterior tibialis muscle. In order to determine the endogenous release of dopamine in response to painful stimulation, we used positron emission tomography to examine binding of [(11)C]-raclopride (D2/D3 ligand) in the brain during injection of painful hypertonic saline and nonpainful normal saline. Fibromyalgia patients experienced the hypertonic saline as more painful than healthy control subjects. Control subjects released dopamine in the basal ganglia during the painful stimulation, whereas fibromyalgia patients did not. In control subjects, the amount of dopamine release correlated with the amount of perceived pain but in fibromyalgia patients no such correlation was observed. **These findings provide the first direct evidence that fibromyalgia patients have an abnormal dopamine response to pain.** The disrupted dopaminergic reactivity in fibromyalgia patients could be a critical factor underlying the widespread pain and discomfort in fibromyalgia and suggests that **the therapeutic effects of dopaminergic treatments for this intractable disorder should be explored.**

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

Yuen KC, Bennett RM, Hryciw CA, Cook MB, Rhoads SA, Cook DM

Is further evaluation for growth hormone (GH) deficiency necessary in fibromyalgia patients with low serum insulin-like growth factor (IGF-1) levels?

OBJECTIVE: Fibromyalgia (FM) is characterized by diffuse pain, fatigue, and sleep disturbances, symptoms that resemble the adult growth hormone (GH) deficiency syndrome. Many FM patients have low serum GH levels, with a hypothesized aetiology of dysregulated GH/insulin-like growth factor (IGF-1) axis. The aim of this study was to assess the GH reserve in FM patients with low serum IGF-1 levels using the GH-releasing hormone (GHRH)-arginine test. **DESIGN:** We retrospectively reviewed the GHRH-arginine data of 77 FM patients with low serum IGF-1 levels referred to our tertiary unit over a 4-year period. **RESULTS:** Of the 77 FM patients, 13 patients (17%) failed the GHRH-arginine test. Further evaluation with pituitary imaging revealed normal pituitary glands (n=7), coincident microadenomas (n=4), empty sella (n=1) and pituitary cyst (n=1), and relevant medical histories such as previous head injury (n=4), Sheehan's syndrome (n=1), and whiplash injury (n=1). In contrast, the remaining 64 patients (83%) that responded to the GHRH-arginine test demonstrated higher peak GH levels compared to age and BMI-matched controls (n=24). **CONCLUSION:** Our data shows that a subpopulation of FM patients with low serum IGF-1 levels will fail the GHRH-arginine test. We, thus, recommend that the GH reserve of these patients should be evaluated further, as **GH replacement may potentially improve the symptomatology of those with true GH deficiency. Additionally, the increased GH response rates to GHRH-arginine stimulation in the majority of FM patients with low serum IGF-1 levels further supports the hypothesis of a dysregulated GH/IGF-1 axis in the pathophysiology of FM.**

Growth Horm IGF Res. 2007 Feb; 17(1):82–8. Epub 2007 Feb 6