FIBROMYALGIA: ABSTRACTS 2002
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 2002. The studies were selected from the extensive literature on fibromyalgia so as to cover a wide range of subjects in limited space.

The following studies were published in the period January through December 2002. Abstracts for 2003 will be posted at intervals during the year. Similar collections of abstracts published in 1999, 2000 and 2001 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, Manfredsdottir VF, Creskoff KW

Neuroendocrine abnormalities in fibromyalgia

Fibromyalgia is a disorder of unknown etiology characterized by chronic, widespread musculoskeletal pain and symptoms such as fatigue, poor sleep, gastrointestinal complaints, and psychologic problems that are similar to those experienced by patients with hormone deficiencies. This review summarizes the available data on the neuroendocrine function in fibromyalgia, including data on hormone secretion, circadian phase, and autonomic nervous system function. Studies suggest that there may be lower activity of a number of hypothalamic-pituitary-peripheral gland axes and altered autonomic nervous system function in patients with fibromyalgia. These reductions in activity are mild to moderate and do not result from alterations in circadian rhythms. The reduced hormonal and autonomic responses appear to reflect an impairment in the hypothalamic or central nervous system response to stimuli rather than a primary defect at the level of the pituitary gland or the peripheral glands. A combination of multiple, mild impaired responses may lead to more profound physiologic and clinical consequences as compared with a defect in only one system, and could contribute to the symptoms of fibromyalgia.

Curr Pain Headache Rep 2002 Aug; 6(4):289–98

Argoff CE

Pharmacologic management of chronic pain

Pain is associated with myriad medical conditions and affects millions of Americans. Chronic pain is one of the most common reasons prompting visits to healthcare providers; collectively, it possibly disables more people annually than heart disease and cancer combined. Primary goals of treating patients with chronic pain are to reduce pain as much as possible and facilitate functional restoration. When chronic pain becomes a disease state, it can be controlled, but, at present, it cannot be cured. Better understanding of the pathophysiology of acute and chronic pain has led to numerous advances in pharmacologic management of painful disorders, including low back pain, migraine headache, fibromyalgia, postherpetic neuralgia, osteoarthritis, rheumatoid arthritis, and

cancer-related neuropathic pain. This presentation reviews the available agents and how to use them rationally, either singly or in combination, so practitioners can treat patients with chronic pain as effectively as possible.

J Am Osteopath Assoc 2002 Sep;102(9 Suppl 3):S21–7

Arnold LM, Hess EV, Hudson JI, Welge JA, Berno SE, Keck PE Jr.

A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia

PURPOSE: To assess the efficacy of fluoxetine in the treatment of patients with fibromyalgia. SUBJECTS AND METHODS: Sixty outpatients (all women, aged 21–71 years) with fibromyalgia were randomly assigned to receive fluoxetine (10–80 mg/d) or placebo for 12 weeks in a double-blind, parallel-group, flexible-dose study. The primary outcome measures were the Fibromyalgia Impact Questionnaire total score (score range, 0 [no impact] to 80) and pain score (score range, 0–10). Secondary measures included the McGill Pain Questionnaire, change in the number of tender points, and total myalgic score. RESULTS: In the intent-to-treat analysis, women who received fluoxetine (mean [± SD] dose, 45 ± 25 mg/d) had significant ($p = 0.005$) improvement in the Fibromyalgia Impact Questionnaire total score compared with those who received placebo, with a difference of -12 (95% confidence interval [CI]: -19 to -4). They also had significant ($p = 0.002$) improvement in the Fibromyalgia Impact Questionnaire pain score (difference, -2.2 [95% CI: -3.6 to -0.9]), as well as in the Fibromyalgia Impact Questionnaire fatigue ($p = 0.05$) and depression ($p = 0.01$) scores and the McGill Pain Questionnaire ($p = 0.01$), when compared with subjects who received placebo. Although counts for the number of tender points and total myalgic scores improved more in the fluoxetine group than in the placebo group, these differences were not statistically significant. CONCLUSIONS: In a 12-week, flexible-dose, placebo-controlled trial, fluoxetine was found to be effective on most outcome measures and generally well tolerated in women with fibromyalgia.

Am J Med 2002 Feb 15; 112(3):191–7

Bennett RM

Adult growth hormone deficiency in patients with fibromyalgia

Adult growth hormone (GH) deficiency is a well-described clinical syndrome with many features reminiscent of fibromyalgia. There is evidence that GH deficiency as defined in terms of a low insulin-like growth factor-1 (IGF-1) level occurs in approximately 30% of patients with fibromyalgia and is probably the cause of some morbidity. It seems most likely that impaired GH secretion in fibromyalgia is related to a physiologic dysregulation of the hypothalamic-pituitary-adrenal axis (HPA) with a resulting increase in hypothalamic somatostatin tone. It is postulated that impaired GH secretion is secondary to chronic physical and psychological stressors. It appears that impaired GH secretion is more common than clinically significant GH deficiency with low IGF-1 levels. The severe GH deficiency that occurs in a subset of patients with fibromyalgia is of clinical relevance because it is a treatable disorder with demonstrated benefits to patients.

Curr Rheumatol Rep 2002 Aug; 4(4):306–12

Bennett RM

The rational management of fibromyalgia patients

The exponential increase in pain research over the last 10 years has established fibromyalgia (FM) as a common chronic pain syndrome with similar neurophysiologic aberrations to other chronic pain states. As such, the pathogenesis is considered to involve an interaction of augmented sensory processing (central sensitization) and peripheral pain generators. The notion, that FM symptomatology results from an amplification of incoming sensory impulses, has revolutionized the contemporary understanding of this enigmatic problem and provided a more rational approach to treatment. To date, the management of FM has been mainly palliative, with the aims of reducing pain, improving sleep, maintaining function, treating psychologic distress and diminishing the impact of associated syndromes. The rapidly evolving neurophysiologic, psychophysiologic and molecular biologic basis for chronic pain states has already opened up new avenues for management which should be applicable to this difficult group of patients. Indeed, it is now possible to think about a "rational" approach to managing FM patients that was unthinkable just a few years ago.

Rheum Dis Clin North Am 2002 May; 28(2):181–99, v

Berglund B, Harju EL, Kosek E, Lindblom U

Quantitative and qualitative perceptual analysis of cold dysesthesia and hyperalgesia in fibromyalgia

Somatosensory perception thresholds, perceived intensity, and quality of perceptions were assessed in 20 women with fibromyalgia syndrome (FMS) and in 20 healthy age-matched female controls. All patients and controls scaled perceived intensity and described perceived quality of randomized thermal (Thermotest) and tactile (von Frey filaments) stimulation. Perceived intensity was scaled by free-number magnitude estimation, and inter-individual comparability was accomplished by Master Scaling. Perceived quality was assessed by choosing verbal descriptors from a list. Thenar was used as a reference for each modality tested. All patients were able to reliably scale perceived intensity at thenar, as well as in pain-affected body areas. Perception thresholds for cold pain, heat pain, cold-pain tolerance and heat-pain tolerance were significantly lower in patients than controls. For cold and tactile stimulation, the master scaled perceived intensities were significantly higher in patients' pain-affected areas, whereas for warmth/heat stimulation, the intensities were significantly lower. In the qualitative perceptual analysis the most striking and significant finding was the aberration of cold-evoked perceptions in all patients: most stimuli in the range of 30–10 degrees C were reported as heat or other paresthetic or dysesthetic perceptions. The perceptual quality of warmth, and of touch, did not differ from the controls. Another aberration was observed in the nociceptive range of thermal and of tactile stimulation as significantly more frequent pain-related descriptors than in controls. This indicates a general nociceptive facilitation in addition to the lower thermal pain thresholds. The combination of cold hyperesthesia, cold dysesthesia, and multimodal hyperalgesia suggests a selective pathophysiology at a particular level of integration, possibly in the insular cortex. It is suggested that the aberrations revealed by the supraliminal sensory evaluation may be generic for FMS. Particularly, the aberrations established in all patients for perceived quality and intensity in the cold sensory channel may be an additional diagnostic criterion.

Pain 2002 Mar; 96(1–2):177–87

Burckhardt CS

Nonpharmacologic management strategies in fibromyalgia

Clinicians using the results of the extant research base can take an optimistic view of the role of nonpharmacologic treatment strategies for fibromyalgia. There were no negative outcomes in any of the reviewed studies, although in a few studies the experimental treatment did not prove to be more effective than the attention control. Rather than viewing this negatively, one could look more closely at the attention control groups and attempt to better understand what they contained that worked as an active treatment. A number of trials include a follow-up component and all but one of them find maintenance of at least one outcome change. Maintenance of changes is more likely to occur when the patient continues to participate in the experimental activity long-term. Patients especially need strategies that help them continue in exercise regimens. Unlike cognitive skills strategies that once learned are likely to become part of a person's coping repertoire, both exercise and behavioral strategies, like progressive muscle relaxation, need to be performed on a consistent basis in order to have their effect. The goals of increased self-efficacy, symptom reduction, increased functional status and quality of life along with decreased inappropriate use of health care resources are realistic when patients persevere in their use of strategy combinations and receive support from their providers.

Rheum Dis Clin North Am 2002 May; 28(2):291–304

Carli G, Suman AL, Biasi G, Marcolongo R

Reactivity to superficial and deep stimuli in patients with chronic musculoskeletal pain

In this study, we evaluated pain sensitivity in patients with fibromyalgia or other types of chronic, diffuse musculoskeletal pain to establish whether fibromyalgia represents the end of a continuum of dysfunction in the nociceptive system. One hundred and forty-five patients and 22 healthy subjects (HS) completed an epidemiological questionnaire to provide information about fatigue, stiffness, sleep, the intensity of pain (VAS 0-100) and its extent both at onset and at present. Algometry was performed at all American College of Rheumatology (ACR) tender points and at ten control points. Patients were divided into five main groups: fibromyalgia (FS) patients, secondary-concomitant fibromyalgia (SCFS) patients, patients with widespread pain (WP) but not reaching the ACR criterion of 11 tender points, patients with diffuse multi-regional pain (MP) not reaching the ACR criteria (widespread pain, tender point counts), and patients with multi-regional pain associated with at least 11 tender points (MPTE). Von Frey monofilaments were used to assess superficial punctate pressure pain thresholds. Heat and cold pain thresholds were determined with a thermal stimulator. Ischemic pain was assessed by the cold pressure test and the submaximal effort tourniquet test. The scores for stiffness and present pain intensity gradually increased concomitantly with the increase in tender point count and pain extent. The pressure pain thresholds for positive tender and positive control points were significantly lower in the SCFS, FS and MPTE groups than in HS, MP and WP groups, the latter three groups displaying similar values. In all groups, there were no differences in pain thresholds between positive tender and positive control points. The heat pain threshold and the pain threshold in the cold pressure test were lower in the FS and SCFS groups than in HS. The cold pressure tolerance was lower in patients with widespread pain than in HS. In the von Frey test, all patient groups except MP had similar values, which were significantly lower than in HS. Finally, all patient groups displayed lower tourniquet tolerance than HS. In each psychophysical test, patients with widespread pain

and patients with multi-regional pain showed similar thresholds; however, the thresholds in the MP or MPTE groups differed from those in the FS and SCFS groups. In the FS group, pain thresholds and pain tolerance did not differ according to the presence of ongoing pain at the stimulated site and were not correlated to ongoing pain**.** The results indicate that dysfunction in the nociceptive system is already present in patients with multiregional pain with a low tender point count; it becomes more and more severe as the positive tender point count and pain extent increase and it is maximal in fibromyalgia patients.

Pain 2002 Dec; 100(3):259–69

Daoud KF, Barkhuizen A

Rheumatic mimics and selected triggers of fibromyalgia

Fibromyalgia is a chronic pain syndrome of unknown etiology characterized by diffuse pain and tender points, which have been present for more than 3 months. Many patients with systemic illnesses can have diffuse pain similar to that found in fibromyalgia, including rheumatic diseases such as polymyalgia rheumatica, rheumatoid arthritis, idiopathic inflammatory myopathy, systemic lupus erythematosus, and joint hypermobility. Osteomalacia and thyroid disease are also in the differential diagnosis of diffuse pain and are imminently treatable. In addition, there has been interest throughout the past 10 years in infectious diseases including hepatitis C, Lyme disease, coxsackie B, HIV, and parvovirus infection, which may cause or trigger fibromyalgia. This paper provides a framework to use when identifying these diseases as part of the evaluation of a patient with chronic widespread musculoskeletal pain.

Curr Pain Headache Rep 2002 Aug; 6(4):284–8

Dick B, Eccleston C, Crombez G

Attentional functioning in fibromyalgia, rheumatoid arthritis, and musculoskeletal pain patients

OBJECTIVES: To investigate whether chronic pain patients have deficits in attentional functioning compared with pain-free controls, and whether fibromyalgia patients have larger deficits in attentional functioning compared with rheumatoid arthritis and musculoskeletal pain patients. METHODS: Sixty patients (20 in each of 3 patient groups) and 20 pain-free controls completed measures assessing pain intensity, mood, pain-related disability, somatic awareness, and catastrophic thinking about pain. Attentional functioning was assessed using an age-standardized, ecologically valid test battery. Analyses were made of between-group differences. RESULTS: Sixty percent of patients had at least one score in the clinical range of neuropsychological impairment, independent of demography and mood. Fibromyalgia patients were more anxious and somatically aware than rheumatoid arthritis or musculoskeletal pain patients, but did not show larger attentional deficits than other patient groups. CONCLUSION: All 3 groups of chronic pain patients, regardless of diagnosis, had impaired cognitive functioning on an ecologically sensitive neuropsychological test of everyday attention.

Arthritis Rheum 2002 Dec 15; 47(6):639–44

Gracely RH, Petzke F, Wolf JM, Clauw DJ

Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia

OBJECTIVE: To use functional magnetic resonance imaging (fMRI) to evaluate the pattern of cerebral activation during the application of painful pressure and determine whether this pattern is augmented in patients with fibromyalgia (FM) compared with controls. METHODS: Pressure was applied to the left thumbnail beds of 16 right-handed patients with FM and 16 right-handed matched controls. Each FM patient underwent fMRI while moderately painful pressure was being applied. The functional activation patterns in FM patients were compared with those in controls, who were tested under 2 conditions: the "stimulus pressure control" condition, during which they received an amount of pressure similar to that delivered to patients, and the "subjective pain control" condition, during which the intensity of stimulation was increased to deliver a subjective level of pain similar to that experienced by patients. RESULTS: Stimulation with adequate pressure to cause similar pain in both groups resulted in 19 regions of increased regional cerebral blood flow in healthy controls and 12 significant regions in patients. Increased fMRI signal occurred in 7 regions common to both groups, and decreased signal was observed in 1 common region. In contrast, stimulation of controls with the same amount of pressure that caused pain in patients resulted in only 2 regions of increased signal, neither of which coincided with a region of activation in patients. Statistical comparison of the patient and control groups receiving similar stimulus pressures revealed 13 regions of greater activation in the patient group. In contrast, similar stimulus pressures produced only 1 region of greater activation in the control group. CONCLUSION: The fact that comparable subjectively painful conditions resulted in activation patterns that were similar in patients and controls, whereas similar pressures resulted in no common regions of activation and greater effects in patients, supports the hypothesis that FM is characterized by cortical or sub-cortical augmentation of pain processing.

Arthritis Rheum 2002 May; 46(5):1333–43

Graven-Nielsen T, Arendt-Nielsen L

Peripheral and central sensitization in musculoskeletal pain disorders: an experimental approach

This report provides a brief introduction to the manifestations of peripheral and central sensitization involved in musculoskeletal pain disorders. It has become increasingly evident that muscle hyperalgesia, referred pain, referred hyperalgesia, and widespread hyperalgesia play an important role in chronic musculoskeletal pain. A better understanding of the involved basic mechanisms and better methods to assess muscle pain in the clinic may provide new possibilities for designing rational therapies and for targeting the pharmacologic intervention optimally. Peripheral sensitization plays an important role for increased sensitivity of deep tissue. However, central sensitization may be equally important but less addressed. Quantitative sensory testing provides the possibility to evaluate these manifestations in a standardized way in patients with musculoskeletal pain or in healthy volunteers (e.g., experimentally induced referred pain can be used to assess the potential involvement of central sensitization in musculoskeletal pain conditions). Central sensitization may play a role in the persistence, amplification, and spread of pain. Interventions should take this aspect into consideration.

Curr Rheumatol Rep 2002 Aug;4(4): 313–21

Gur A, Karakoc M, Nas K, Remzi, Cevik, Denli A, Sarac J

Cytokines and depression in cases with fibromyalgia

OBJECTIVE: Fibromyalgia (FM) is a chronic, painful musculoskeletal disorder characterized by widespread pain, pressure, hyperalgesia, morning stiffness, and an increased incidence of depressive symptoms. The etiology, however, has remained elusive. The aim of the present study was to examine the inflammatory response system in FM and to investigate the effect of depression level on serum cytokines. METHODS: Serum interleukin-1 (IL-1), IL-2 receptor (IL-2r), IL-6, and IL-8 and the Hamilton Depression Rating Scale (HDRS) score were determined in 32 healthy volunteers and in 81 patients with FM, classified according to the American College of Rheumatology criteria. RESULTS: In our study, serum IL-1 and IL-6 were not statistically significant, but serum IL-8, IL2r, and HDRS score were significantly higher in patients with FM than the control group ($p < 0.01$). In addition, in patients with FM, IL-8 was found to be related to pain intensity ($r = 0.35$; $p < 0.01$). CONCLUSION: IL-8 may play an important role in the occurrence of pain in FM.

J Rheumatol 2002 Feb; 29(2):358–61

Gur A, Karakoc M, Erdogan S, Nas K, Cevik R, Sarac AJ

Regional cerebral blood flow and cytokines in young females with fibromyalgia

OBJECTIVE: To determine whether there is any difference in regional cerebral blood flow (rCBF) and serum cytokine levels and association between clinical parameters and rCBF and serum cytokine levels in young females with fibromyalgia (FM). The other aim was to search whether the depression state has any effect on these two parameters. METHODS: Nineteen women with FM and 20 healthy women had 99mTc-HMPAO brain single-photon-emission computed tomography (SPECT) to evaluate rCBF. Serum interleukin (IL) levels (IL 1 beta, IL 2r, IL 6 and IL 8) were measured. Clinical and psychological evaluation was also carried out in FM patients and healthy controls. RESULTS: The patients with FM had significantly higher radioactivity uptake ratio in right and left caudate nucleus ($p = 0.009$, $p = 0.001$, respectively) than healthy controls. There was statistically significant decrease in the 99mTc-HMPAO uptake in the right superior parietal ($p = 0.041$), gyrus rectalis ($p = 0.036$) and pons ($p = 0.023$). FM patients had significantly higher serum IL 2r and IL 8 levels ($p = 0.023$, $p = 0.011$, respectively) than controls. Additionally, FM patients had significantly higher Fibromyalgia Impact Questionnaire (FIQ), Health Assessment Questionnaire (HAQ), and Hamilton Depression Rate scale (HDRS) scores ($p = 0.000$) than controls. Interestingly, the patients with mild depressive symptoms or without (i.e. HDRS-score < or = 16) had significantly higher serum IL 8 levels ($p = 0.027$) and increased radioactivity uptake ratio in the pons ($p = 0.036$) than the patients with more severe depressive symptoms (i.e. HDRS-score > 16). With regard to regional cerebral blood flow, significant correlations were detected between RSP and morning stiffness ($r = 0.70$, $p < 0.01$) and sleep disturbance ($r = -0.53$, $p < 0.05$), and between gyrus rectalis and FIQ score. There were significant correlations between LCN and IL-2 ($p = 0.025$), between RSP and morning stiffness ($p = 0.006$), sleep disturbance ($p = 0.021$) according to multiple regression analysis test[ing]. CONCLUSION: This study shows a significant increase in rCBF of caudate nuclei, a reduction in the pons, some cortical regions activity and a increase in IL 8, IL2r levels of young female patients with FM. These findings are more prominent in patients with low HDRS scores.

Clin Exp Rheumatol 2002 Nov–Dec; 20(6):753–60

Hein G, Franke S

Are advanced glycation end-product-modified proteins of pathogenetic importance in fibromyalgia?

OBJECTIVE: To quantify the serum levels of the advanced glycation end-product (AGE) pentosidine in 41 patients with fibromyalgia (FM) and 46 healthy controls. The formation of pentosidine is closely related to oxidative stress. METHODS: Pentosidine was measured by reverse-phased high-performance liquid chromatography with gradient separation on a RP-18 column. RESULTS: Patients with FM have significantly higher pentosidine serum levels than healthy subjects. CONCLUSION: AGE modification of proteins leads to reduced solubility and high resistance to proteolytic digestion of such altered proteins (e.g. AGE-modified collagens). AGEs are also able to stimulate different kinds of cells via activation of the NFkappaB, 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 phenomena in FM patients.

Rheumatology (Oxford) Oct; 41(10):1163–1167

Jones KD, Burckhardt CS, Clark SR, Bennett RM, Potempa KM

A randomized controlled trial of muscle strengthening versus flexibility training in fibromyalgia

OBJECTIVE: To determine the effectiveness of a muscle strengthening program compared to a stretching program in women with fibromyalgia (FM). METHODS: Sixty-eight women with FM were randomly assigned to a 12-week, twice weekly exercise program consisting of either muscle strengthening or stretching. Outcome measures included muscle strength (main outcome variable), flexibility, weight, body fat, tender point count, and disease and symptom severity scales. RESULTS: No statistically significant differences between groups were found on independent t tests. Paired t tests revealed twice the number of significant improvements in the strengthening group compared to the stretching group. Effect size scores indicated that the magnitude of change was generally greater in the strengthening group than the stretching group. CONCLUSION: Patients with FM can engage in a specially tailored muscle strengthening program and experience an improvement in overall disease activity, without a significant exercise induced flare in pain. Flexibility training alone also results in overall improvements, albeit of a lesser degree.

J Rheumatol 2002 May; 29(5):1041–8

Jones KD, Clark SR

Individualizing the exercise prescription for persons with fibromyalgia

"Exercise is good for you; you must exercise, and just do it" are common admonitions to fibromyalgia (FM) patients by health professionals. "I can't exercise; I hurt too much to exercise; and, I don't have enough energy to exercise" are equally common responses from patients with FM. Such exchanges can lead to frustration for both patient and provider. The factor that neither participant in the dialogue is addressing is that exercise carries both risks and benefits for persons with FM. Although for decades exercise has been acknowledged to be a key component of the treatment of FM, the majority of FM patients remain aerobically unfit, with poor muscle strength and limited flexibility. Unfit muscle is theoretically more prone to muscle microtrauma, which

causes localized pain and may trigger widespread pain through disordered central processing. The purpose of this article is to provide practicing health care providers with guidelines for prescribing exercise to FM patients that take into account the risk/benefit ratio. A sample exercise prescription is included.

Rheum Dis Clin North Am 2002 May; 28(2):419–36, x–xi

Lidbeck J

Central hyperexcitability in chronic musculoskeletal pain: A conceptual breakthrough with multiple clinical implications

Recent investigations of dysfunctional pain processing in the central nervous system have contributed much knowledge about the development of chronic musculoskeletal pain. Many common chronic musculoskeletal pain syndromes— including regional myofascial pain syndromes, whiplash pain syndromes, refractory work-related neck-shoulder pain, certain types of chronic low back pain, fibromyalgia and others—may essentially be explained by abnormalities in central pain modulation. The growing awareness of dysfunctional central pain modulation may be a conceptual breakthrough leading to a better understanding of common chronic pain disorders. A new paradigm will have multiple clinical implications, including re-evaluation of clinical practice routines and rehabilitation methods, and will focus on controversial issues of medico-legal concern. The concept of dysfunctional central pain processing will also necessitate a mechanism-based classification of pain for the selection of individual treatment and rehabilitation programs for subgroups of patients with chronic musculoskeletal pain due to different pathophysiological mechanisms.

Pain Res Manag 2002 Summer; 7(2):81–92

Lundberg G, Gerdle B

Tender point scores and their relations to signs of mobility, symptoms, and disability in female home care personnel and the prevalence of fibromyalgia syndrome

OBJECTIVE: In this study of female home care personnel employed in a municipality (N = 643; participation rate 94%) we investigated (1) the prevalence of tender points and fibromyalgia (FM); (2) the relationships between tender point score and other signs and symptoms; (3) if subgroups based on the tender point score differed with respect to signs, symptoms, disability, and health related quality of life; and (4) signs that showed the strongest intercorrelations with disability and health. METHODS: The following variables were registered: (1) Signs: joint mobility, spinal posture and mobility, tender points, and segmental mobility and pain provocation at L4-S1 levels of the low back. (2) Symptoms: pain and pain intensity and other symptoms. (3) Disability (i.e., self-rated reduced capacity for everyday activities and employment) and health: 3 indices and sick leave. RESULTS: The tender point score correlated with the number of pain regions and the pain intensities, and the amount of other symptoms, sick leave, and disability. Tender point score was the strongest regressor of the investigated signs in regression of the 2 disability indices. Segmental pain showed the strongest correlation with tender point score. Three subgroups identified by tender point score showed significant differences in segmental pain, prevalence and intensity of different symptoms, disability, and health-related quality of life. The prevalence of FM was 2.0%. CONCLUSION: Tender point score together with different symptoms

showed relatively strong correlations with disability. A relatively high prevalence of FM was found in occupationally active female home care personnel.

J Rheumatol 2002 Mar; 29(3):603–13

Martinez-Lavin M, Vidal M, Barbosa RE, Pineda C, Casanova JM, Nava A

Norepinephrine-evoked pain in fibromyalgia. A randomized pilot study

BACKGROUND: Fibromyalgia syndrome displays sympathetically maintained pain features such as frequent post-traumatic onset and stimuli-independent pain accompanied by allodynia and paresthesias. Heart rate variability studies showed that fibromyalgia patients have changes consistent with ongoing sympathetic hyperactivity. [In this study, a] norepinephrine-evoked pain test is used to assess sympathetically maintained pain syndromes. Our objective was to define if fibromyalgia patients have norepinephrine-evoked pain. METHODS: Prospective double blind controlled study. Participants: Twenty FM patients, and two age/sex matched control groups: 20 rheumatoid arthritis patients and 20 healthy controls. Ten micrograms of norepinephrine diluted in 0.1 ml of saline solution were injected in a forearm. The contrasting substance, 0.1 ml of saline solution alone, was injected in the opposite forearm. Maximum local pain elicited during the 5 minutes post-injection was graded on a visual analog scale (VAS). Norepinephrine-evoked pain was diagnosed when norepinephrine injection induced greater pain than placebo injection. Intensity of norepinephrine-evoked pain was calculated as the difference between norepinephrine minus placebo-induced VAS scores. RESULTS: Norepinephrine-evoked pain was seen in 80% of FM patients (95% confidence intervals 56.3 – 94.3), in 30% of rheumatoid arthritis patients and in 30% of healthy controls (95% confidence intervals 11.9 – 54.3) ($p < 0.05$). Intensity of norepinephrine-evoked pain was greater in FM patients (mean ± SD 2.5 ± 2.5) when compared to rheumatoid arthritis patients (0.3 ± 0.7), and healthy controls (0.3 ± 0.8) ($p < 0.0001$). CONCLUSIONS: Fibromyalgia patients have norepinephrine-evoked pain. This finding supports the hypothesis that fibromyalgia may be a sympathetically maintained pain syndrome.

BMC Musculoskelet Disord 2002; 3(1):2

Miller LJ, Kubes KL

Serotonergic agents in the treatment of fibromyalgia syndrome

OBJECTIVE: To evaluate literature that discusses the treatment of fibromyalgia syndrome (FMS) with agents that involve the neurotransmitter serotonin. DATA SOURCES: Biomedical literature accessed through MEDLINE (1966–August 2001) and International Pharmaceutical Abstracts. DATA SYNTHESIS: The cause and pathophysiology of FMS remain elusive, although abnormalities in the serotonin pathway have been implicated. Several serotonergic agents have been studied for use in FMS. Trials and case reports focusing on the use of newer agents: the selective serotonin reuptake inhibitors, venlafaxine and tramadol, were reviewed. CONCLUSIONS: Current research suggests that the serotonergic agents may reduce at least some of the symptoms of FMS. However, medications that act on multiple neurotransmitters may prove to be more effective in symptom management. Additional long-term studies are required in order to validate these results.

Ann Pharmacother 2002 Apr; 36(4):707–12

Moldofsky H

Management of sleep disorders in fibromyalgia

In summary, the treatment of patients with FM requires a proper assessment of the reason for the unrefreshing sleep, which is an important component of the FM syndrome. Sleep laboratory investigations provides a suitable rationale for management where a specific primary sleep disorder is determined. Nonspecific treatments include various behavioral approaches to improve sleep hygiene, fitness, and regular proper nutrition that serve to regularize disturbances in circadian sleep-wake rhythms. As yet, no medication is known to improve the EEG sleep arousal disorders that include phasic (alpha-delta), tonic alpha non-REM sleep disorders, or the periodic K alpha cycling alternating pattern disorder. Traditional hypnotic agents, while helpful in initiating and maintaining sleep and reducing daytime tiredness, do not provide restorative sleep or reduce pain. Tricyclic drugs, such as amitriptyline and cyclobenzaprine, may provide long-term benefit for improving sleep but may not have a continuing benefit beyond one month for reducing pain. The use of a biologic agent that facilitates sleep-related neuroendocrine functions, for example growth hormone, is reported to improve symptoms but the need for injection and high cost restrict its use. No systematic studies have been reported on the use of remedial measures for the management of PLMS/restless legs syndrome and sleep apnea that occur in some patients with FM.

Rheum Dis Clin North Am 2002 May; 28(2):353–65

Moulin DE

Systemic drug treatment for chronic musculoskeletal pain

OBJECTIVE: The purpose of this review was to determine how effective different classes of analgesic agents are in the management of chronic pain. METHODOLOGY: The literature search identified five systematic reviews and 18 randomized controlled trials to provide evidence about systemic drug treatment for chronic pain. RESULTS: Studies in the systematic reviews were mainly of low back pain, and studies in the randomized controlled trials were mainly of fibromyalgia. Other studies investigated rheumatic pain, musculoskeletal pain, chronic low back pain, and temporomandibular pain. Classes of analgesic agents reviewed were antidepressants, nonsteroidal anti-inflammatory drugs, muscle relaxants, opioid analgesics, and a number of miscellaneous agents. CONCLUSIONS: For chronic pain, opioid analgesics provide benefit for up to 9 weeks (level 2). For chronic low back pain, the evidence shows that various types of nonsteroidal anti-inflammatory drugs are equally effective or ineffective, and that antidepressants provide no benefit in the short to intermediate term (level 2). Muscle relaxants showed limited effectiveness (level 3) for chronic neck pain and for chronic low back pain for up to 4 weeks. For fibromyalgia, there is limited evidence (level 3) of the effectiveness of amitryptiline, ondansetron, zolpidem, or growth hormone, and evidence of no effectiveness for nonsteroidal anti-inflammatory drugs, malic acid with magnesium, calcitonin injections, or s-adenyl-L-methionine. For temporomandibular pain, oral sumatriptan is not effective (level 2). The remaining evidence was inadequate (level 4a) or contradictory (level 4b).

Clin J Pain 2001 Dec; 17(4 Suppl):S86–93

Price D, Staud R, Robinson M, Mauderli A, Cannon R, Vierck C

Enhanced temporal summation of second pain and its central modulation in fibromyalgia patients

We have previously shown that fibromyalgia (FMS) patients have enhanced temporal summation (windup) and prolonged decay of heat-induced second pain in comparison to control subjects, consistent with central sensitization. It has been hypothesized that sensory abnormalities of FMS patients are related to deficient pain modulatory mechanisms. Therefore, we conducted several analyses to further characterize enhanced windup in FMS patients and to determine whether it can be centrally modulated by placebo, naloxone, or fentanyl. Pre-drug baseline ratings of FMS and normal control (NC) groups were compared with determine whether FMS had higher pain sensitivity in response to several types of thermal tests used to predominantly activate A-delta heat, C heat, or cold nociceptors. Our results confirmed and extended our earlier study in showing that FMS patients had larger magnitudes of heat tap as well as cold tap-induced windup when compared with age- and sex-matched NC subjects. The groups differed less in their ratings of sensory tests that rely predominantly on A-delta-nociceptive afferent input. Heat and cold-induced windup were attenuated by saline placebo injections and by fentanyl (0.75 and 1.5 &mgr;g/kg). However, naloxone injection had the same magnitudes of effect on first or second pain as that produced by placebo injection. Hypoalgesic effects of saline placebo and fentanyl on windup were at least as large in FMS as compared to NC subjects and therefore do not support the hypothesis that pain modulatory mechanisms are deficient in FMS. To the extent that temporal summation of second pain (windup) contributes to processes underlying hyperalgesia and persistent pain states, these results indirectly suggest that these processes can be centrally modulated in FMS patients by endogenous and exogenous analgesic manipulations.

Pain 2002 Sep; 99(1–2):49

Rao SG

The neuropharmacology of centrally-acting analgesic medications in fibromyalgia

As demonstrated above, the anatomy and neuropharmacology of the pain pathways within the CNS, even to the level of the midbrain, are extraordinarily complex. Indeed, discussions of the effects of these agents on the neuropharmacology of the thalamus, hypothalamus, and cortex were excluded from this review owing to their adding further to this complexity. Also, the dearth of data regarding FMS pain pathophysiology necessitated a relatively generic analysis of the pain pathways. As mentioned in the introduction, the current thought is that central sensitization plays an important role in FMS. However, we see in this chapter that the behavioral state of central sensitization may be a result of iterations in either the ascending systems or in one or more descending systems. Studies to assess the presence or relative importance of such changes in FMS are difficult to perform in humans, and to date there are no animal models of FMS. Accepting these limitations, it is apparent that many drugs considered to date for the treatment of FMS do target a number of appropriate sites within both the ascending and descending pain pathways. The data regarding clinical efficacy on some good candidate agents, however, is extremely preliminary. For example, it is evident from the present analysis that SNRIs, alpha 2 agonists, and NK1 antagonists may be particularly well suited to FMS, although current data supporting their use is either anecdotal or from open-label trials [114,149]. Other sites within the pain pathways have not yet been targeted. Examples of these include the use of CCKB antagonists to block on-cell activation or of nitric oxide synthetase antagonists to block the

downstream mediators of NMDA activation. Efficacy of such agents may give considerable insight into the pathophysiology of FMS. Finally, as indicated previously, FMS consists of more than just chronic pain, and the question of how sleep abnormalities, depression, fatigue and so forth tie into disordered pain processing is being researched actively. Future research focusing on how the various manifestations of FMS relate to one another undoubtedly will lead to a more rational targeting of drugs in this complex disorder.

Rheum Dis Clin North Am 2002 May; 28(2):235–59

Raphael J, Southall J, Treharne G, Kitas G

Efficacy and adverse effects of intravenous lignocaine therapy in fibromyalgia syndrome

BACKGROUND: To investigate the effects of intravenous lignocaine infusions (IV lignocaine) in fibromyalgia. METHODS: Prospective study of the adverse effects of IV lignocaine in 106 patients with fibromyalgia; retrospective questionnaire study of the efficacy of IV lignocaine in 50 patients with fibromyalgia. RESULTS: Prospective study: Two major (pulmonary oedema and supra-ventricular tachycardia) and 42 minor side-effects were reported. None had long-term sequelae. The commonest was hypotension (17 cases). Retrospective study: Pain and a range of psychosocial measures (on single 11-point scales) improved significantly after treatment. There was no effect of the treatment on work status. The average duration of pain relief after the 6-day course of treatment was 11.5 ±; 6.5 weeks. CONCLUSIONS: Intravenous lignocaine appears to be both safe and of benefit in improving pain and quality of life for patients with fibromyalgia. This needs to be confirmed in prospective randomised controlled trials.

BMC Musculoskelet Disord 2002 Sep 8; 3(1):21

Russell IJ

The promise of substance >P inhibitors in fibromyalgia

The discovery of SP and its potent biological activities have led to the discovery of other tachykinins and to receptors for them, including the NK1 receptor. Blockade of the NK1 receptor has a number of potentially beneficial effects in medical care including the management of drug-induced emesis and the treatment of depression. The analgesic potential of NK1 receptor antagonists that, in theory, seemed so promising has not met early expectations. However, there is still reason to predict valuable clinical uses for more potent NK1 receptor antagonists in a variety of medical conditions, including FMS.

Rheum Dis Clin North Am 2002 May; 28(2):329–42

Spath M

Current experience with 5-HT3 receptor antagonists in fibromyalgia

Pain is perceived, transmitted, processed and modulated within an extensive network of neurotransmitters and hormones. Despite increasing knowledge about the biologic principles, even on the molecular level, the more we learn about the precise mechanisms of their interactions the more questions arise. It is also pertinent to remember that clinical scientists studying pain modulating pharmacologic agents always have to consider possible placebo effects [57–61]. Most

of our knowledge regarding the function of neurotransmitter systems in the CNS has been provided by animal studies. Thus we cannot be sure that they have exactly parallel counterparts in humans. For instance, animal studies suggest an inverse relationship between brain and spinal cord concentrations of substance P. If these observations are converted to an interpretation of human fibromyalgia, low brain-tissue levels of both serotonin and substance P should be expected, while spinal cord serotonin concentrations would be low and spinal cord substance P would be high [1]. There is good evidence that 5-HT, its receptors, and their interactions with other neurotransmitters are essential for nociception and antinociception. The activities of 5-HT receptors can be studied by agonist and, in humans especially, by antagonist use. But even with a direct spinal application of selective agonists and antagonists, observations may still be confounded by (1) dose, as there can be a dose-dependent activation of different receptor subtypes; (2) type of nociceptive tests (e.g., thermal versus pressure versus chemical models), which may have differences in the way they are regulated; and (3) influences due to effects on temperature, blood flow or motor function. With this potential for variability, it is perhaps not surprising that there is some variability in the results of studies reporting on the effects of various 5-HT agonists and antagonists on nociceptive transmission within the spinal cord [62]. For instance, different 5-HT3 receptor densities could exist in various neuronal systems, one density type being completely inhibited at low concentrations, and the others only at higher concentrations of 5-HT3 receptor antagonists, thus resulting in contrary effects. Finally, the "endogeneous 5-HT tone" may greatly influence agonist and antagonist action. Considering this complexity of serotonin-mediated reactions, it is not surprising that treatment of pain by 5-HT3 receptor antagonists appears to yield inconsistent results. As fibromyalgia is now regarded as a pain amplification syndrome with a broad variety of additional non-pain symptoms, the interrelations are complicated even more. Fibromyalgia associated symptoms (e.g., fatigue, insomnia, and irritable bowel syndrome) can be modulated by 5-HT3 receptor antagonists. From the data evaluated so far, there is evidence that 5-HT3 receptor antagonists provide significant benefit in some fibromyalgia patients. In our practice, the data justify a careful application in clinical use according to the study results. The dosage, route of application, long term adverse reactions and duration of therapy still need to be studied in greater detail. Recently reported adverse events from therapy of irritable bowel syndrome with alosetron [63–67] provide a note for caution before hastily using 5-HT3 receptor antagonists without more studies. One can surmise that, much as the biochemistry of depression has been elucidated by the development of the SSRIs, a greater understanding of the role of 5-HT3 receptor antagonists in treating fibromyalgia patients may provide some insights into disease mechanisms of this enigmatic disorder.

Rheum Dis Clin North Am 2002 May; 28(2):319–28

Staud R

Evidence of involvement of central neural mechanisms in generating fibromyalgia pain

Fibromyalgia syndrome (FMS) is characterized by widespread pain, fatigue, sleep abnormalities, and distress. Because FMS lacks consistent evidence of tissue abnormalities, recent investigations have focused on central nervous system mechanisms of pain. Abnormal temporal summation of second pain (wind-up) and central sensitization have been described recently in patients with FMS. Wind-up and central sensitization, which rely on central pain mechanisms, occur after prolonged C-nociceptor input and depend on activation of nociceptor-specific neurons and wide dynamic range neurons in the dorsal horn of the spinal cord. Other abnormal central pain

mechanisms recently detected in patients with FMS include diffuse noxious inhibitory controls. These pain inhibitory mechanisms rely on spinal cord and supraspinal systems involving pain facilitatory and pain inhibitory pathways. Brain-imaging techniques that can detect neuronal activation after nociceptive stimuli have provided additional evidence for abnormal central pain mechanisms in FMS. Brain images have corroborated the augmented reported pain experience of patients with fibromyalgia during experimental pain stimuli. In addition, thalamic activity, which contributes significantly to pain processing, was decreased in fibromyalgia. However, central pain mechanisms of fibromyalgia may not depend exclusively on neuronal activation. Neuroglial activation has been found to play an important role in the induction and maintenance of chronic pain. These findings may have important implications for future research and the treatment of fibromyalgia pain.

Curr Rheumatol Rep 2002 Aug; 4(4):299–305

Staud R, Smitherman ML

Peripheral and central sensitization in fibromyalgia: pathogenetic role

Characteristic symptoms of fibromyalgia syndrome include widespread pain, fatigue, sleep abnormalities, and distress. Patients with fibromyalgia show psychophysical evidence of mechanical, thermal, and electrical hyperalgesia. Peripheral and central abnormalities of nociception have been described in fibromyalgia. Important nociceptor systems in the skin and muscles seem to undergo profound changes in patients with fibromyalgia through unknown mechanisms. They include sensitization of vanilloid receptor, acid-sensing ion channel receptors, and purino-receptors. Tissue mediators of inflammation and nerve growth factors can excite these receptors and cause extensive changes in pain sensitivity, but patients with fibromyalgia lack consistent evidence for inflammatory soft tissue abnormalities. Therefore, recent investigations have focused on central nervous system mechanisms of pain in fibromyalgia.

Curr Pain Headache Rep 2002 Aug; 6(4):259–66

Strusberg I, Mendelberg RC, Serra HA, Strusberg AM

Influence of weather conditions on rheumatic pain

OBJECTIVE: To evaluate the influence of the weather in Cordoba City, Argentina, on pain in patients with rheumatic pain; to correlate different climate variables with the patients' impression of weather sensitivity; and to assess correlations between pain and climate conditions on 5 days preceding and following painful episodes. METHODS: Self-reported questionnaires to assess the presence and features of spontaneous daily pain during one year (1998) were completed by 151 outpatients with osteoarthritis (OA) (n = 52), rheumatoid arthritis (RA) (n = 82), and fibromyalgia (FM) (n = 17) and 32 healthy subjects. Data were correlated with daily temperature, atmospheric pressure, and relative humidity obtained during the same period. Only p values < 0.001 were considered significant. RESULTS: Low temperature, high atmospheric pressure, and high humidity were significantly correlated with pain in RA (r = -0.30, r = 0.34, r = 0.23, respectively; $p < 0.001$); in OA, pain correlated with low temperature and high humidity (r = –0.23, r = 0.24; $p < 0.001$); in FM, [pain correlated] with low temperature and high atmospheric pressure (r = -0.255, r = 0.22; $p < 0.001$) and no correlation was found in controls. Patients self-described as being weather sensitive correlated only with high humidity (r = 0.45; $p < 0.001$). There was no better correlation with climate variables, except for humidity, 5 days before or after the day of the painful episode. CONCLUSION: These results support the belief that weather

influences rheumatic pain, albeit in different ways depending on the subjacent pathology and subjective weather sensitivity. This influence may not depend on weather conditions of the previous or following days, indicating that climate would not be a pain predictor and vice versa.

J Rheumatol 2002 Feb; 29(2):335–8

Targino RA, Imamura M, Kaziyama HH, Souza LP,
Hsing WT, Imamura ST

Pain treatment with acupuncture for patients with fibromyalgia

Fibromyalgia is a chronic, painful musculoskeletal syndrome of unknown etiopathogenesis. In addition to medica[tions] and physical and psychologic therapies, several other adjunct therapies have been used as alternatives in the attempt to obtain analgesia and decrease the symptoms that are characteristic of this problem. This article presents a literary review on the use of acupuncture as an adjunct or chief treatment for patients with fibromyalgia, comparing it with an ongoing clinical experience that has been carried out at Hospital das Clinicas in the city of Sao Paulo. The results were found by applying traditional acupuncture, which demonstrated positive rates in the Visual Analogue Scale, myalgic index, number of tender points, and improvement in quality of life based on the SF-36 questionnaire.

Curr Pain Headache Rep 2002 Oct; 6(5):379–83

Verne GN, Price DD

Irritable bowel syndrome as a common precipitant of central sensitization

Animal models of neuropathic pain have significantly advanced our knowledge of abnormalities in central pain processing mechanisms in chronic pain disorders. New neuroimaging techniques using functional magnetic resonance imaging and positron emission tomography scanning are beginning to provide insight into cortical participation in the processing of pain. Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders seen by physicians. Visceral hypersensitivity or decreased pain thresholds to distension of the gut is considered to be a biologic marker for IBS and is present in most patients with this gastrointestinal disorder. Patients with IBS also have many extra-intestinal symptoms consistent with a central hyperalgesic state. Recent studies suggest that patients with IBS may also have cutaneous hyperalgesia similar to that seen in other chronic pain disorders such as fibromyalgia. This suggests that abnormalities of central nociceptive processing are present in IBS.

Curr Rheumatol Rep 2002 Aug; 4(4):322–8