

FIBROMYALGIA: ABSTRACTS 2008

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 2008. The studies were selected from the extensive literature on fibromyalgia so as to cover a wide range of subjects in limited space.

Abstracts for 2009 will be posted quarterly during the year. Similar collections of abstracts produced annually from 1999 on can be found on the website of the National Fibromyalgia Partnership: www.fmpartnership.org.

The abstracts are arranged in alphabetical order by lead author.

Abeles M, Solitar BM, Pillinger MH, Abeles AM

Update on fibromyalgia therapy

Primary fibromyalgia, a poorly-understood chronic pain syndrome, is characterized by widespread musculoskeletal pain, nonrestorative sleep, fatigue, psychological distress, and specific regions of localized tenderness, all in the absence of otherwise apparent organic disease. While the etiology of fibromyalgia is unclear, accumulating data suggest that disordered central pain processing likely plays a role in the pathogenesis of symptoms. Although various pharmacological treatments have been studied and espoused for treating fibromyalgia, no single drug or group of drugs has proved to be particularly useful in treating fibromyalgia patients as a whole, and only one drug to date has earned U.S. Food and Drug Administration approval for treating the syndrome in the United States. **This review critically and systematically evaluates clinical investigations of medicinal and nonmedicinal treatments for fibromyalgia dating from 1970 to 2007.**

Am J Med. 2008 Jul; 121(7):555–61

Ablin JN, Buskila D

Emerging therapies for fibromyalgia

BACKGROUND: Fibromyalgia syndrome (FMS) is a disorder characterized by widespread pain, tenderness, and fatigue. High prevalence marks the syndrome which is considered to reflect altered central pain processing. Fibromyalgia syndrome runs a chronic, non-progressive course, extracting a high price owing to

impaired quality of life, restricted vocational capacity, and increased health care utilization. **OBJECTIVE:** To review current and emerging trends in the treatment of FMS. **METHODS:** A rigorous search of published literature, abstract presentations and industry-provided data was performed. **RESULTS/CONCLUSION:** **The recent FDA approval of pregabalin as a first specific medication for FMS may herald a new era for the development of medications with higher specificity and efficacy for this hitherto frustrating condition.**

Expert Opin Emerg Drugs. 2008 Mar; 13(1):53–62

Arnold LM, Crofford LJ, Mease PJ, Burgess SM,
Palmer SC, Abetz L, Martin SA

Patient perspectives on the impact of fibromyalgia

OBJECTIVE: The objective of this study was to elicit and assess important symptom domains and the impact of fibromyalgia on patients' quality of life and functioning from a patient's perspective. The intention was to collect this information as part of an overall effort to overcome shortcomings of existing outcome measures in fibromyalgia. **METHODS:** This was a qualitative study in which six focus group sessions with 48 women diagnosed with fibromyalgia were conducted to elicit concepts and ideas to assess the impact of fibromyalgia on their lives. **RESULTS:** The focus groups conducted with fibromyalgia patients identified symptom domains that had the greatest impact on their quality of life including pain, sleep disturbance, fatigue, depression, anxiety, and cognitive impairment. Fibromyalgia had a substantial negative impact on social and occupational function. Patients reported disrupted relationships with family and friends, social isolation, reduced activities of daily living and leisure activities, avoidance of physical activity, and loss of career or inability to advance in careers or education. **CONCLUSION:** The findings from the focus groups revealed that fibromyalgia has a substantial negative impact on patients' lives. **PRACTICE IMPLICATIONS:** **A comprehensive assessment of the multiple symptoms domains associated with fibromyalgia and the impact of fibromyalgia on multidimensional aspects of function should be a routine part of the care of fibromyalgia patients.**

Patient Educ Couns. 2008 Oct; 73(1):114–20. Epub 2008 Jul 21

Assefi N, Bogart A, Goldberg J, Buchwald D

Reiki for the treatment of fibromyalgia: a randomized controlled trial

OBJECTIVE: Fibromyalgia is a common, chronic pain condition for which patients frequently use complementary and alternative medicine, including Reiki.

Our objective was to determine whether Reiki is beneficial as an adjunctive fibromyalgia treatment. DESIGN: This was a factorial designed, randomized, sham-controlled trial in which participants, data collection staff, and data analysts were blinded to treatment group. SETTING/LOCATION: The study setting was private medical offices in the Seattle, Washington metropolitan area. SUBJECTS: The subjects were comprised 100 adults with fibromyalgia. INTERVENTION: Four (4) groups received twice-weekly treatment for 8 weeks by either a Reiki master or actor randomized to use direct touch or no touch (distant therapy). OUTCOME MEASURES: The primary outcome was subjective pain as measured by visual analog scale at weeks 4, 8, and 20 (3 months following end of treatment). Secondary outcomes were physical and mental functioning, medication use, and health provider visits. Participant blinding and adverse effects were ascertained by self-report. Improvement between groups was examined in an intention-to-treat analysis. RESULTS: **Neither Reiki nor touch had any effect on pain or any of the secondary outcomes.** All outcome measures were nearly identical among the 4 treatment groups during the course of the trial. CONCLUSION: Neither Reiki nor touch improved the symptoms of fibromyalgia. Energy medicine modalities such as Reiki should be rigorously studied before being recommended to patients with chronic pain symptoms.

J Altern Complement Med. 2008 Nov; 14(9):1115–22

Bazzichi L, Giannaccini G, Betti L, Fabbrini L, Schmid L, Palego L, Giacomelli C, Rossi A, Giusti L, De Feo F, Giuliano T, Mascia G, Bombardieri S, Lucacchini A.

ATP, calcium and magnesium levels in platelets of patients with primary fibromyalgia

OBJECTIVES: To evaluate the intracellular levels of the high energy adenosine triphosphate nucleotide ATP and essential divalent cations, calcium and magnesium, in platelets of patients affected by primary fibromyalgia syndrome (FMS). DESIGN AND METHOD: Platelet ATP and cation concentrations were measured in 25 patients affected by FMS and 25 healthy volunteers through a chemiluminescent and a fluorimetric assay, respectively. RESULTS: Significant lower ATP levels were observed inside platelets of FMS patients (fmol ATP/plt: 0.0169±0.0012 vs. healthy controls, fmol ATP/plt: 0.0306±0.0023, mean±SEM) (**P<0.0001). A trend towards higher calcium concentrations (P=0.06) together with significant increased magnesium levels were also reported in platelets of patients by comparison with controls (P=0.02). CONCLUSIONS: This preliminary study suggests that **disturbances in the homeostasis of platelet ATP metabolism-signaling and calcium-magnesium flows might have a relevance in the pathogenesis of FMS.**

Clin Biochem. 2008 Sep; 41(13):1084–90. Epub 2008 Jul 2

Burns JW, Crofford LJ, Chervin RD

Sleep stage dynamics in fibromyalgia patients and controls

OBJECTIVE: To determine whether previously described sleep stage dynamics, reflecting the mean duration of specific sleep stages, may have clinical utility in a sample of patients with fibromyalgia syndrome (FMS) and controls. **METHODS:** Women with FMS (n=15, screened to exclude other sleep disorders) and age-matched women in good health (n=15) were studied with nocturnal polysomnography, multiple sleep latency tests, 2-week pain diaries, and a measure of current pain intensity. **RESULTS:** The FMS subjects, in comparison to controls, did not show differences in several common polysomnographic measures, except for increased numbers of stage shifts (126+/-27 vs. 107+/-22, p=.042). Mean durations for episodes of total sleep, stage 1 sleep, stage 3/4 sleep, and rapid eye movement sleep failed to distinguish FMS and control subjects (Wilcoxon rank sum tests, p>.10 for each), but those for stage 2 sleep were shorter in the FMS subjects (p=.006), possibly because transitions to stage 3/4 sleep occurred more quickly (p=.036). Shorter stage 2 sleep durations predicted higher pain diary scores (Spearman rho=-.56, p=.0014) and current pain intensity (rho=-.71, p<0.0001). **CONCLUSIONS:** Sleep stage dynamic, and, more specifically, **shorter durations of sleep stage 2 periods, distinguish FMS and control female subjects and may predict pain levels experienced in FMS.** Analysis of the lengths of individual sleep stages, in addition to the usual sleep stage amounts and percentages listed in standard polysomnogram reports, may have clinical utility.

Sleep Med. 2008 Feb 29 [Epub ahead of print]

Buskila D, Atzeni F, Sarzi-Puttini P

Etiology of fibromyalgia: The possible role of infection and vaccination

Fibromyalgia syndrome (FMS), a condition characterized by widespread pain and diffuse tenderness, is considered a multifactorial disorder. FMS is now recognized as one of the “central” pain syndromes. Environmental and genetic factors play a role in the pathogenesis of FMS. Various triggers including trauma and stress as well as infections, may precipitate the development of FMS. **Certain infections including hepatitis C virus, HIV and Lyme disease have been temporally associated with the development of FMS.** There is some evidence for the possible role of vaccinations in triggering the development of FMS and related syndromes; however, this association remains to be established.

Autoimmun Rev. 2008 Aug 12. [Epub ahead of print]

Caro XJ, Winter EF, Dumas AJ

A subset of fibromyalgia patients have findings suggestive of chronic inflammatory demyelinating polyneuropathy and appear to respond to IVIg

OBJECTIVES: The aetiopathogenesis of the fibromyalgia syndrome (FMS) remains unknown. Recent reports, however, suggest that a subgroup of FMS subjects has an immune-mediated disease. Therefore, our primary objective was to study FMS subjects for evidence of an immune-mediated demyelinating polyneuropathy. Our secondary objective was to determine the effects of treating these FMS subjects with the immune modulator, intravenous immunoglobulin (IVIg). **METHODS:** Fifty-eight FMS subjects, 26 rheumatic non-FMS subjects and 52 non-rheumatic non-FMS subjects were studied. Subjective measures of paraesthesias, weakness, stocking hypaesthesia, pain, fatigue and stiffness were made. Objective measures of tenderness, proximal muscle strength and electrodiagnostic (EDX) evidence of polyneuropathy and demyelination were also made. Eleven other FMS subjects underwent sural nerve biopsy. **RESULTS:** Paraesthesias, subjective weakness and stocking hypaesthesia were more common in FMS than in rheumatic non-FMS ($P < \text{or} = 0.0001$). Proximal muscle strength was less in FMS than in rheumatic non-FMS ($P < \text{or} = 0.0001$). **EDX demonstrated a distal demyelinating polyneuropathy, suggestive of chronic inflammatory demyelinating polyneuropathy (CIDP), in 33% of FMS subjects.** No rheumatic non-FMS subject had polyneuropathy ($P = 0.005$), or demyelination ($P = 0.05$). Fifteen FMS/CIDP subjects were subsequently treated with IVIg (400 mg/kg each day for 5 days). Pain ($P = 0.01$), tenderness ($P = 0.001$) and strength ($P = 0.04$) improved significantly. Fatigue and stiffness trended towards improvement. **CONCLUSIONS:** IVIg treatment shows promise in treating this subset. These observations have implications for better understanding and treating some FMS patients.

Rheumatology (Oxford). 2008 Feb; 47(2):208–11

Clauw DJ, Mease P, Palmer RH, Gendreau RM, Wang Y

Milnacipran for the treatment of fibromyalgia in adults: a 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial

BACKGROUND: Preclinical and clinical studies have suggested that milnacipran, a dual norepinephrine-serotonin reuptake inhibitor, may be efficacious in the treatment of fibromyalgia (FM). **OBJECTIVE:** This study was conducted to evaluate the efficacy and tolerability of milnacipran in treating the multiple domains of FM. **METHODS:** This was a multicenter, double-blind, placebo-controlled trial. Adult patients (age 18–70 years) who met 1990 American College

of Rheumatology criteria for FM were randomized to receive milnacipran 100 mg/d, milnacipran 200 mg/d, or placebo for 15 weeks. Because this was a pivotal registration trial, the primary end points were chosen to investigate efficacy for 2 potential indications: the treatment of FM and the treatment of FM pain. Thus, the 2 primary efficacy end points were rates of FM composite responders and FM pain composite responders. FM composite responders were defined as patients concurrently experiencing clinically meaningful improvements in the following 3 domain criteria: pain (> or = 30% improvement, as recorded in an electronic diary); patients' global status (a rating of very much improved or much improved on the Patient Global Impression of Change [PGIC] scale); and physical function (a > or = 6-point improvement on the 36-item Short-Form Health Survey [SF-36] Physical Component Summary score). FM pain composite responders were defined as those who met the pain and PGIC criteria. Adverse events reported by patients or observed by investigators were recorded throughout the trial. RESULTS: Of 2270 patients screened, 1196 were randomized to receive milnacipran 100 mg/d (n = 399), milnacipran 200 mg/d (n = 396), or placebo (n = 401). The majority of patients were female (96.2%) and white (93.5%). The population had a mean age of 50.2 years, a mean baseline weight of 180.8 pounds, and a mean baseline body mass index of 30.6 kg/m². Compared with placebo, significantly greater proportions of milnacipran-treated patients were FM composite responders (100 mg/d: P = 0.01; 200 mg/d: P = 0.02) and FM pain composite responders (100 mg/d: P = 0.03; 200 mg/d: P = 0.004). Milnacipran was associated with significant improvements in pain after 1 week of treatment (100 mg/d: P = 0.004; 200 mg/d: P = 0.04), as well as significant improvements in multiple secondary efficacy end points, including global status (PGIC: P<0.001 for both doses), physical function (SF-36 physical functioning domain—100 mg/d: P < 0.001; 200 mg/d: P = 0.02), and fatigue (Multidimensional Fatigue Inventory—100 mg/d: P = 0.04). The most commonly reported adverse events with milnacipran were nausea (100 mg/d, 34.3%; 200 mg/d, 37.6%), headache (18.0% and 17.7%, respectively), and constipation (14.3% and 17.9%). **Adverse events resulted in premature study discontinuation in 19.5% and 23.7% of those who received milnacipran 100 and 200 mg/d, respectively, compared with 9.5% of placebo recipients.** CONCLUSION: **In these adult patients with FM, both doses of milnacipran (100 and 200 mg/d) were associated with significant improvements in pain and other symptoms.** Clinical Trials Identification Number: NCT00098124.

Clin Ther. 2008 Nov; 30(11):1988–2004

Crofford LJ

Pain management in fibromyalgia

PURPOSE OF REVIEW: Pain is the primary presenting symptom in the vast majority of inflammatory and noninflammatory rheumatic diseases. Patients tell

us that improved pain relief is a principal concern. Many pain complaints respond incompletely to the treatment of the primary rheumatic disorder and pain syndromes such as fibromyalgia do not respond to traditional analgesic medications. Therefore, proper management requires consideration of additional medications for symptomatic relief. This review addresses newer strategies for the treatment of pain in patients with fibromyalgia that may be also useful in patients with other rheumatic diseases. **RECENT FINDINGS:** New medications have been developed with a better understanding of chronic pain mechanisms that principally address pain neurobiology at the levels of the spinal cord and the brain. **Clinical studies demonstrate the effectiveness of the alpha-2-delta ligands (gabapentin and pregabalin) and the norepinephrine/serotonin reuptake inhibitors (duloxetine and milnacipran) in fibromyalgia.** **SUMMARY:** Patients with chronic pain, best classified as fibromyalgia, either primary or in association with other rheumatic disorders, may experience benefit from new therapies targeting central pain mechanisms.

Curr Opin Rheumatol. 2008 May; 20(3):246–50

de Souza JB, Goffaux P, Julien N, Potvin S, Charest J, Marchand S

Fibromyalgia subgroups: profiling distinct subgroups using the Fibromyalgia Impact Questionnaire. A preliminary study

The main goal of this project was to identify the presence of fibromyalgia (FM) subgroups using a simple and frequently used clinical tool, the Fibromyalgia Impact Questionnaire (FIQ). A total of 61 women diagnosed with FM participated in this study. FM subgroups were created by applying a hierarchical cluster analysis on selected items of the FIQ (pain, fatigue, morning tiredness, stiffness, anxiety and depressive symptoms). We also tested for group differences on experimental pain, psychosocial functioning and demographic characteristics. Two cluster profiles best fit our data. FM-Type I was characterized by the lowest levels of anxiety, depressive and morning tiredness symptoms, while FM-Type II was characterized by elevated levels of pain, fatigue, morning tiredness, stiffness, anxiety and depressive symptoms. Both FM subgroups showed hyperalgesic responses to experimental pain. **These results suggest that pain and stiffness are universal symptoms of the disorder but that psychological distress is a feature present only in some patients.**

Rheumatol Int. 2008 Sep 27. [Epub ahead of print]

Dick BD, Verrier MJ, Harker KT, Rashid S

Disruption of cognitive function in fibromyalgia syndrome

Accumulating evidence points to significant cognitive disruption in individuals with fibromyalgia syndrome (FMS). This study was carried out in order to

examine specific cognitive mechanisms involved in this disruption. Standardized experimental paradigms were used to examine attentional function and working memory capacity in 30 women with FMS and 30 matched controls. Cognitive function was examined using performance on these tests and between group results were analysed in the context of important psychological and behavioural measures. Performance of standardized everyday attentional tasks was impaired in the FMS group compared to controls. Working memory was also found to be impaired in this group. Stimulus interference was found to be significantly worse in the FMS group as the demands of the tasks increased. These effects were found to exist independent of the measures of mood and sleep disruption. However, when pain levels were accounted for statistically, no differences existed between groups on cognitive measures. These findings point to disrupted working memory as a specific mechanism that is disrupted in this population. **The results of this study suggest that pain in FMS may play an important role in cognitive disruption.** It is likely that many factors, including disrupted cognition, play a role in the reduced quality of life reported by individuals with FMS.

Pain. 2008 Aug 6. [Epub ahead of print]

Geisser ME, Glass JM, Rajcevska LD, Clauw DJ, Williams DA, Kileny PR, Gracely RH

A psychophysical study of auditory and pressure sensitivity in patients with fibromyalgia and healthy controls

Fibromyalgia (FM) is characterized by widespread tenderness. Studies have also reported that persons with FM are sensitive to other stimuli, such as auditory tones. We hypothesized that subjects with FM would display greater sensitivity to both pressure and auditory tones and report greater sensitivity to sounds encountered in daily activities. FM subjects ($n = 30$) and healthy control subjects ($n = 28$) were administered auditory tones and pressure using the same psychophysical methods to deliver the stimuli and a common way of scaling responses. Subjects were also administered a self-report questionnaire regarding sensitivity to everyday sounds. Participants with FM displayed significantly greater sensitivity to all levels of auditory stimulation ($P < .05$). The magnitude of difference between FM patients' lowered auditory sensitivity (relative to control subjects) was similar to that seen with pressure, and pressure and auditory ratings were significantly correlated in both control subjects and subjects with FM. FM patients also were more sensitive to everyday sounds ($t = 8.65$, $P < .001$). These findings support that FM is associated with a global central nervous system augmentation in sensory processing. Further research is needed to examine the neural substrates associated with this abnormality and its role in the etiology and maintenance of FM. PERSPECTIVE: Muscle tenderness is the hallmark of FM, but the findings of this study and others suggest that persons with FM display sensitivity to a number of sensory stimuli. **These findings suggest that FM is**

associated with a global central nervous system augmentation of sensory information. These findings may also help to explain why persons with FM display a number of comorbid physical symptoms other than pain.

J Pain. 2008 May; 9(5):417–22. Epub 2008 Feb 15

Goebel A, Buhner S, Schedel R, Lochs H, Sprotte G

Altered intestinal permeability in patients with primary fibromyalgia and in patients with complex regional pain syndrome

OBJECTIVES. The pain intensity of patients with FM has recently been reported to be correlated with the degree of small intestinal bacterial overgrowth (SIBO). SIBO is often associated with an increased intestinal permeability (IP). Increased IP, if shown in FM, may have pathogenetic relevance because it leads to the exposure of immune cells to luminal antigens and consequent immune modulation. It is currently unknown whether IP is altered in FM. We therefore examined the IP in a group of patients with primary FM and in two control groups, healthy volunteers and patients with an unrelated chronic pain syndrome, complex regional pain syndrome (CRPS). We hypothesized that patients with FM, but not volunteers or those patients with CRPS, would have altered IP. **METHODS.** Both gastroduodenal and small IP were assessed using an established three-sugar test, where urinary disaccharide excretion reflecting intestinal uptake was measured using HPLC. **Results.** Forty patients with primary FM, 57 age- and sex-matched volunteers and 17 patients with CRPS were enrolled in this study. In the FM group, 13 patients had raised gastroduodenal permeability and 15 patients had raised small intestinal permeability, but only one volunteer had increased gastroduodenal permeability ($P < 0.0001$, chi-square test for the three groups). The IP values were significantly increased in the patient groups ($P < 0.0003$ for all comparisons, one-way analysis of variance). **CONCLUSIONS.** **The IPs in primary FM and, unexpectedly, CRPS are increased.** This study should stimulate further research to determine the implication of altered IP in the disease pathophysiology of FM and CRPS.

Rheumatology (Oxford). 2008 Jun 7. [Epub ahead of print]

Guedj E, Cammilleri S, Niboyet J, Dupont P, Vidal E, Dropinski JP, Mundler O

Clinical correlate of brain SPECT perfusion abnormalities in fibromyalgia

The purpose of this study was to investigate the specific clinical correlate of brain SPECT perfusion abnormalities reported in fibromyalgia. **METHODS:** We per-

formed a whole-brain voxel-based correlation analysis involving regional cerebral blood flow and various parameters related to pain (Visual Analog Scale, Tubingen Pain Behavior Scale, and Questionnaire Douleur de Saint-Antoine Scale), disability (Fibromyalgia Impact Questionnaire [FIQ]), and anxiety and depression status (Hospital Anxiety and Depression scale) in 20 patients with fibromyalgia (P voxel < 0.005). Ten healthy control women were also included, in order to determine areas of significant hypo- and hyperperfusions in patients. RESULTS: FIQ total score was positively correlated with bilateral parietal perfusion, including postcentral cortex. These clusters of correlation were included in the areas of significant hyperperfusion. FIQ total score was also negatively correlated with perfusion of a left anterior temporal cluster, included in the areas of significant hypoperfusions. No other clinical correlation was observed with regional cerebral blood flow. CONCLUSION: **These results show that brain perfusion abnormalities in patients with fibromyalgia are correlated with the clinical severity of the disease.**

J Nucl Med. 2008 Nov; 49(11): 1798–803. Epub 2008 Oct 16

Harris RE, Sundgren PC, Pang Y, Hsu M, Petrou M, Kim SH, McLean SA, Gracely RH, Clauw DJ

Dynamic levels of glutamate within the insula are associated with improvements in multiple pain domains in fibromyalgia

OBJECTIVE: Fibromyalgia (FM) is a chronic widespread pain condition that is thought to arise from augmentation of central neural activity. Glutamate (Glu) is an excitatory neurotransmitter that functions in pain-processing pathways. This study was carried out to investigate the relationship between changing levels of Glu within the insula and changes in multiple pain domains in patients with FM. METHODS: Ten patients with FM underwent 2 sessions of proton magnetic resonance spectroscopy (H-MRS) and 2 sessions of functional magnetic resonance imaging (fMRI), each conducted before and after a nonpharmacologic intervention to reduce pain. During H-MRS, the anterior and posterior insular regions were examined separately using single-voxel spectroscopy. The levels of Glu and other metabolites were estimated relative to levels of creatine (Cr) (e.g., the Glu/Cr ratio). During fMRI, painful pressures were applied to the thumbnail to elicit neuronal activation. Experimental pressure-evoked pain thresholds and clinical pain ratings (on the Short Form of the McGill Pain Questionnaire [SF-MPQ]) were also assessed prior to each imaging session. RESULTS: Both experimental pain ($P = 0.047$ versus pretreatment) and SF-MPQ-rated clinical pain ($P = 0.043$ versus pretreatment) were reduced following treatment. Changes from pre- to posttreatment in Glu/Cr were negatively correlated with changes in experimental pain thresholds ($r = -0.95$, $P < 0.001$) and positively correlated with changes in clinical pain ($r = 0.85$, $P = 0.002$). Changes in the fMRI-determined blood oxygenation level-dependent effect (a measure of neural activation) were

positively correlated with changes in Glu/Cr within the contralateral insula ($r = 0.81$, $P = 0.002$). **CONCLUSION: Changes in Glu levels within the insula are associated with changes in multiple pain domains in patients with FM.** Thus, H-MRS data may serve as a useful biomarker and surrogate end point for clinical trials of FM.

Arthritis Rheum. 2008 Mar; 58(3):903–7

Huynh CN, Yanni LM, Morgan LA

Fibromyalgia: diagnosis and management for the primary healthcare provider

Fibromyalgia is a disorder of chronic generalized musculoskeletal pain affecting 2% of the general population, with an increased frequency in women. Clinical diagnosis relies on history and research-supported tender point criteria. As in other chronic pain syndromes, a multidimensional approach optimizes treatment response. Empirical data and consensus support the use of nonpharmacological modalities, such as education, aerobic exercise, and cognitive behavioral therapy, in the management of fibromyalgia. Evidence-supported pharmacological interventions include tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, alpha-2-delta ligands, and other serotonergic-noradrenergic analgesic agents, such as tramadol. **This paper offers the primary healthcare provider a systematic approach to the diagnosis of fibromyalgia and management strategies based on available evidence, consensus, and empirical data.**

J Womens Health (Larchmt). 2008 Oct; 17(8):1379–87

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

Family factors, emotional functioning, and functional impairment in juvenile fibromyalgia syndrome

OBJECTIVE: Family factors and emotional functioning can play an important role in the ability of adolescents with juvenile primary fibromyalgia syndrome (JPFS) to cope with their condition and function in their everyday lives. The primary objectives of this study were to determine 1) whether adolescents with JPFS and their caregivers differed from healthy age-matched comparison peers and their caregivers in terms of emotional distress and functional impairment; 2) whether there were any differences in the family environment of adolescents with JPFS compared with healthy comparison peers; and 3) which individual-, caregiver-, and family-level variables were associated with functional impairment in adolescents with JPFS. **METHODS:** Participants were 47 adolescents with JPFS recruited from a pediatric rheumatology clinic and 46 comparison peers without

chronic illness matched for age, sex, and race. Participants and their caregivers (all mothers) completed a battery of standardized measures administered in their homes. **RESULTS:** Adolescents with JPFS had greater internalizing and externalizing symptoms than healthy comparison peers. Mothers of adolescents with JPFS reported twice as many pain conditions and significantly greater depressive symptoms than mothers of comparison peers. The JPFS group also had poorer overall family functioning and more conflicted family relationships. In adolescents with JPFS, maternal pain history was associated with significantly higher functional impairment. **CONCLUSION: Increased distress and chronic pain are evident in families of adolescents with JPFS, and family relationships are also impacted.** Implications for child functional impairment and the need for inclusion of caregivers in treatment are discussed.

Arthritis Rheum. 2008 Sep 29; 59(10):1392–1398. [Epub ahead of print]

Khasar SG, Burkham J, Dina OA, Brown AS, Bogen O, Alessandri-Haber N, Green PG, Reichling DB, Levine JD

Stress induces a switch of intracellular signaling in sensory neurons in a model of generalized pain

Stress dramatically exacerbates pain in diseases such as fibromyalgia and rheumatoid arthritis, but the underlying mechanisms are unknown. We tested the hypothesis that stress causes generalized hyperalgesia by enhancing pronociceptive effects of immune mediators. Rats exposed to nonhabituating sound stress exhibited no change in mechanical nociceptive threshold, but showed a marked increase in hyperalgesia evoked by local injections of prostaglandin (2) or epinephrine. This enhancement, which developed more than a week after exposure to stress, required concerted action of glucocorticoids and catecholamines at receptors located in the periphery on sensory afferents. The altered response to pronociceptive mediators involved a switch in coupling of their receptors from predominantly stimulatory to inhibitory G-proteins (G(s) to G(i)), and for prostaglandin E(2), emergence of novel dependence on protein kinase C epsilon. Thus, **an important mechanism in generalized pain syndromes may be stress-induced coactivation of the hypothalamo-pituitary-adrenal and sympatho-adrenal axes, causing a long-lasting alteration in intracellular signaling pathways**, enabling normally innocuous levels of immune mediators to produce chronic hyperalgesia.

J Neurosci. 2008 May 28; 28(22):5721–30

Kroese ME, Schulpen GJ, Bessems MC, Severens JL, Nijhuis FJ, Geusens PP, Landewé RB

Substitution of specialized rheumatology nurses for rheumatologists in the diagnostic process of fibromyalgia: a randomized controlled trial

OBJECTIVE: To evaluate the substitution of specialized rheumatology nurses for rheumatologists in diagnosing fibromyalgia (FM). **METHODS:** Referred patients with FM symptoms (n = 193) were randomized to a study group diagnosed by a specialized rheumatology nurse (SRN group, n = 97) or to a control group diagnosed by a rheumatologist (RMT group, n = 96). SRN patients were seen within 3 weeks by a nurse who took structured history and initiated routine laboratory tests. During a 5-minute supervision session, the rheumatologist was informed by the nurse about medical history, performed a brief physical examination, and confirmed or rejected the nurse's diagnosis. RMT patients were seen by a rheumatologist after a regular waiting period of 3 months. Outcome measures were initial agreement between the nurse and rheumatologist in the SRN group, final diagnosis after 12–24 months of followup, patient satisfaction, and diagnostic costs. **RESULTS:** The mean waiting time after randomization was 2.8 and 12.1 weeks in the SRN and RMT groups, respectively. Eight RMT patients cancelled their appointments because of the waiting time. Excellent agreement ($\kappa = 0.91$) between rheumatologists and nurses was found. After 12–24 months of followup, none of the initial diagnoses were recalled in either group. SRN patients were significantly more satisfied than RMT patients. Mean diagnostic costs were lower in the SRN group (euro-219) than in the RMT group (euro-281) (95% uncertainty interval euro-103, euro-20). **CONCLUSION:** **Substituting specialized nurses for rheumatologists in the diagnostic process of FM is a trustworthy and successful approach that saves waiting time, provides greater patient satisfaction, and is cost-effective.**

Arthritis Rheum. 2008 Sep 15; 59(9):1299–305

Lawson K

Pharmacological treatments of fibromyalgia: do complex conditions need complex therapies?

Fibromyalgia (FM) is a chronic pain condition, with auxiliary symptoms, such as sleep disturbances and fatigue. Although many of the mechanisms of action targeted by the drugs used to treat FM have been focused to the management of single symptoms, **drugs (e.g. pregabalin, duloxetine) have now been identified that demonstrate a multidimensional effect. However, such drugs often fail to demonstrate acceptable efficacy in the majority of the patient population.** Thus, the mechanisms of action of the drugs studied as treatments for FM are

either identifying subgroups within the pathophysiology of the condition or suggesting that a mechanism of action that will offer universal efficacy has, as yet, to be identified.

Drug Discov Today. 2008 Apr; 13(7-8):333–40. Epub 2008 Mar 7

Le Page JA, Iverson GL, Collins P

The impact of judges' perceptions of credibility in fibromyalgia claims

Fibromyalgia (FM) is a confusing and controversial diagnosis, characterized by widespread pain and tenderness at specific anatomical sites. The cause of this syndrome is unknown, and the course of the condition is difficult to predict. Without a known cause, predictable course, or effective treatment, it is not surprising that FM is a contentious diagnosis from a medical perspective, as well as a civil litigation and disability insurance industry perspective. The purpose of this study was to investigate judges' perceptions of credibility in litigated cases involving FM claims in the Canadian courts, and the relation between perceived credibility and awards granted. A systematic review was conducted of every trial-by-judge litigated FM claim in Canada (N=194 cases) up to 2003. The cases were examined in relation to credibility factors. The role and responsibility of the plaintiff was central in claims involving issues of misrepresentation, fraud, non-disclosure, failure to mitigate, and contributory negligence. The presence of these issues suggested a possible decrease or loss in the claim as a result of the plaintiff's conduct. In regards to the actions of defendants, the presence of investigative and surveillance information alone did not affect the awards granted. However, the credibility of that information had a large effect on the amount of award granted. Plaintiff credibility played a similar role, indicating that **plaintiffs perceived as more credible were typically granted greater awards. An examination of medical expert credibility revealed that judges appear to perceive experts as more credible overall than plaintiffs, regardless of the expert's role in the case.**

Int J Law Psychiatry. 2008 Jan-Feb; 31(1):30–40. Epub 2008 Jan 8

Luerding R, Weigand T, Bogdahn U, Schmidt-Wilcke T

Working memory performance is correlated with local brain morphology in the medial frontal and anterior cingulate cortex in fibromyalgia patients: structural correlates of pain-cognition interaction

Fibromyalgia (FM) is a disorder of unknown aetiology, characterized by chronic widespread pain, stiffness and sleep disturbances. In addition, patients frequently complain of memory and attention deficits. Accumulating evidence suggests that FM is associated with CNS dysfunction and with an altered brain morphology. However, few studies have specifically investigated neuropsychological issues in patients suffering from FM. We therefore sought to determine whether neuropsychological deficits found in FM patients may be correlated with changes in local brain morphology specifically in the frontal, temporal or cingulate cortices. Twenty FM patients underwent extensive testing for potential neuropsychological deficits, which demonstrated significantly reduced working memory and impaired non-verbal long-term memory (limited to free recall condition) in comparison with normative data from age- and education-matched control groups. Voxel-based morphometry (VBM) was used to evaluate for potential correlations between test results and local brain morphology. Performance on non-verbal working memory was positively correlated with grey matter values in the left dorsolateral prefrontal cortex, whereas performance on verbal working memory (digit backward) was positively correlated with grey matter values in the supplementary motor cortex. On the other hand, pain scores were negatively correlated with grey matter values in the medial frontal gyrus. White matter analyses revealed comparable correlations for verbal working memory and pain scores in the medial frontal and prefrontal cortex and in the anterior cingulate cortex. **Our data suggest that, in addition to chronic pain, FM patients suffer from neurocognitive deficits that correlate with local brain morphology in the frontal lobe and anterior cingulate gyrus, which may be interpreted to indicate structural correlates of pain-cognition interaction.**

Brain. 2008 Sep 26. [Epub ahead of print]

Lutz J, Jäger L, de Quervain D, Krauseneck T, Padberg F, Wichnalek M, Beyer A, Stahl R, Zirngibl B, Morhard D, Reiser M, Schelling G

White and gray matter abnormalities in the brain of patients with fibromyalgia: a diffusion-tensor and volumetric imaging study

OBJECTIVE: To use a combination of magnetic resonance diffusion-tensor imaging (MR-DTI) and MR imaging of voxel-based morphometry (MR-VBM) in patients with fibromyalgia syndrome (FMS) to determine microstructural and volume changes in the central neuronal networks involved in the sensory-discriminative and affective-motivational characteristics of pain, anxiety, memory, and regulation of the stress response. **METHODS:** Thirty female patients with FMS and 30 healthy female control subjects were studied. Predefined areas of the brain were measured for volume of gray matter by MR-VBM and for diffusivity and fractional anisotropy (FA) by MR-DTI. Higher FA values and reduced

diffusivity are thought to reflect increased complexity of brain-tissue microstructure. RESULTS: MR-VBM and MR-DTI demonstrated a striking pattern of changes in brain morphology in patients with FMS. Both thalami, the thalamo-cortical tracts, and both insular regions showed significant decreases in FA. In contrast, increases in FA and decreases in gray matter volume were seen in the postcentral gyri, amygdalae, hippocampi, superior frontal gyri, and anterior cingulate gyri. Increased pain intensity scores were correlated with changes in MR-DTI measurements in the right superior frontal gyrus. Increased fatigue was correlated with changes in the left superior frontal and left anterior cingulate gyrus, and self-perceived physical impairment was correlated with changes in the left postcentral gyrus. Higher intensity scores for stress symptoms were correlated negatively with diffusivity in the thalamus and FA in the left insular cortex. No relationship was found between MR-VBM measurements and symptom intensity scores. CONCLUSION: **MR-DTI allows the visualization of microstructural changes in the brain of patients with FMS, appears to be more sensitive than MR-VBM, and may serve as an additional diagnostic technique in FMS and probably other dysfunctional pain syndromes.**

Arthritis Rheum. 2008 Dec; 58(12):3960–9

Lyseng-Williamson KA, Siddiqui MA

Pregabalin: a review of its use in fibromyalgia

Oral pregabalin, a calcium channel alpha(2)delta-subunit ligand with analgesic, anxiolytic and antiepileptic activity, has shown efficacy in the treatment of fibromyalgia. It has a multidimensional effect in the treatment of this complex condition, and is associated with rapid and clinically significant improvements in several outcome measures relating to core symptoms of the syndrome, including pain and sleep, in patients with long-standing fibromyalgia. Pregabalin treatment is also associated with improvements in the overall health status of these patients. **The beneficial effects of pregabalin are durable in patients with an initial response to the drug. The most common adverse events associated with the drug are dizziness and somnolence,** which are generally mild to moderate in intensity and are tolerated by many patients. Pregabalin is, therefore, a valuable option in the first-line treatment of patients with fibromyalgia.

Drugs. 2008; 68(15):2205–23

Martinez-Lavin M, Solano C

Dorsal root ganglia, sodium channels, and fibromyalgia sympathetic pain

Fibromyalgia (FM) is the most frequent cause of generalized pain in the community. Trauma and infection are frequent FM triggering events. A consistent line of

investigation suggests that autonomic dysfunction may explain the multi-system features of FM, and that FM is a sympathetically maintained neuropathic pain syndrome. Dorsal root ganglia (DRG) are potential sympathetic-nociceptive short-circuit sites. Sodium channels located in DRG (particularly Nav1.7) act as molecular gatekeepers of pain detection at peripheral nociceptors. Different infecting agents may lie dormant in DRG. Trauma or infection can induce neuroplasticity with an over-expression of sympathetic fibers and sodium channels in DRG. Nerve growth factor (NGF) mediates these phenotypic changes, which enable catecholamines and/or sympathetic impulses to activate nociceptors. Several DRG sodium "channelopathies" have been recently associated to rare painful-dysautonomic syndromes, such as primary erythromelgia [erythromelalgia] and paroxysmal extreme pain disorder (formerly familial rectal pain syndrome). **We propose that enhanced DRG excitability may play a key role in FM pain.** Individuals at risk would be those with genetically determined sympathetic hyperactivity, or those with inherent sodium channelopathies. Today's stressful environment may contribute to permanent sympathetic hyperactivity. Trauma or infection would induce sodium channels' up-regulation and sympathetic sprouting in DRG through NGF over-expression. High levels of NGF have been reported in the cerebro-spinal fluid of FM patients. These post-traumatic (or post-infective) phenotypic changes would induce a sympathetically maintained neuropathic pain syndrome resulting in widespread pain, allodynia and paresthesias—precisely the key clinical features of FM. If this hypothesis proves to be true, then **sodium channel blockers could become therapeutic options for FM pain.**

Med Hypotheses. 2009 Jan; 72(1):64–6. Epub 2008 Oct 8

May A

Chronic pain may change the structure of the brain

Recently, local morphologic alterations of the brain in areas ascribable to the transmission of pain were detected in patients suffering from phantom pain, chronic back pain, irritable bowel syndrome, fibromyalgia and two types of frequent headaches. These alterations were different for each pain syndrome, but overlapped in the cingulate cortex, the orbitofrontal cortex, the insula and dorsal pons. These regions function as multi-integrative structures during the experience and the anticipation of pain. As it seems that chronic pain patients have a common "brain signature" in areas known to be involved in pain regulation, the question arises whether these changes are the cause or the consequence of chronic pain. **The author suggests that the gray matter change observed in chronic pain patients are the consequence of frequent nociceptive input and should thus be reversible when pain is adequately treated.**

Pain. 2008 Jul; 137(1):7–15. Epub 2008 Apr 14

Mease PJ, Russell IJ, Arnold LM, Florian H, Young JP Jr, Martin SA, Sharma U

A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia

OBJECTIVE: To evaluate the efficacy and safety of pregabalin for symptomatic relief of pain associated with fibromyalgia (FM) and for management of FM. **METHODS:** This multicenter, double-blind, placebo-controlled trial randomly assigned 748 patients with FM to receive placebo or pregabalin 300, 450, or 600 mg/day (dosed twice daily) for 13 weeks. The primary outcome variable for study objective 1, symptomatic relief of pain associated with FM, was comparison of endpoint mean pain scores between each pregabalin group and placebo. The outcome variable for study objective 2, management of FM, included endpoint mean pain scores, Patient Global Impression of Change (PGIC), and Fibromyalgia Impact Questionnaire (FIQ)-Total Score. Secondary outcomes included assessments of sleep, fatigue, and mood disturbance. **RESULTS:** Patients in all pregabalin groups showed statistically significant improvement in endpoint mean pain score and in PGIC response compared with placebo. Improvements in FIQ-Total Score for the pregabalin groups were numerically but not significantly greater than those for the placebo group. Compared with placebo, all pregabalin treatment groups showed statistically significant improvement in assessments of sleep and in patients' impressions of their global improvement. Dizziness and somnolence were the most frequently reported adverse events. **CONCLUSION:** Pregabalin at 300, 450, and 600 mg/day was efficacious and safe for treatment of pain associated with FM. **Pregabalin monotherapy provides clinically meaningful benefit to patients with FM.**

J Rheumatol. 2008 Mar; 35(3):502–14. Epub 2008 Feb 15

Mease PJ, Seymour K

Fibromyalgia: should the treatment paradigm be monotherapy or combination pharmacotherapy?

Fibromyalgia (FM) is a disorder characterized by chronic widespread pain, tenderness, and associated symptoms such as fatigue, sleep disturbance, mood disorder, and cognitive dysfunction. Research on the pathophysiology of FM has focused on dysregulation of sensory processing in the central nervous system, as well as genetic and sociobiologic background factors. Abnormalities include excessive pronociceptive input and deficiency of modulatory signaling via noradrenergic and serotonergic pathways. Effective pharmacotherapy of FM includes medications that inhibit pronociceptive input and augment modulatory signaling. Several other dysregulated pathways may be involved and be potential targets for therapeutic intervention. **This article reviews positive results of recent monotherapy**

trials of several norepinephrine and serotonin reuptake inhibitors. Although there has been little assessment of combination therapy in FM, this review outlines the basis for rational treatment using this approach (in order to most effectively treat multiple symptom domains). Controlled monotherapy trials of medications currently being approved for FM demonstrate significant effect on pain, patient global impression of change, and function. **Trials are currently being developed to assess the potential additive or synergistic effects of combined central pharmacotherapy** and to assess the safety and tolerability of this approach.

Curr Pain Headache Rep. 2008 Dec; 12(6):399–405

Moldofsky H

The significance of the sleeping-waking brain for the understanding of widespread musculoskeletal pain and fatigue in fibromyalgia syndrome and allied syndromes

The clinical focus of rheumatologists on the widespread pain and numerous tender points in specific anatomic regions in their patients who show no evidence for disease pathology has led to the characterization of such peripheral symptoms as a specific disorder of the musculoskeletal system, now commonly known as fibromyalgia. This rheumatologic diagnostic entity has resulted in relative inattention to an understanding of their patients' common complaints of unrefreshing sleep, chronic fatigue and psychological distress. Experimental evidence from humans and animal studies indicate that there is an inter-relationship of disturbances in the physiology of the sleeping-waking brain with the widespread musculoskeletal pain, chronic fatigue, and psychological distress in patients with hitherto unexplained pain/fatigue illnesses, e.g., fibromyalgia and chronic fatigue syndromes. **The emerging knowledge of the dysfunction of the nervous system in such patients has led to the study of novel medications that affect neurotransmitter functions, e.g., pregabalin, serotonin/noradrenaline compounds and sodium oxybate that are shown to improve many of the symptoms of such patients.**

Joint Bone Spine. 2008 May 2. [Epub ahead of print]

Perrot S, Dickenson AH, Bennett RM

Fibromyalgia: Harmonizing science with clinical practice considerations

This review summarizes the present and emerging knowledge base on the pathophysiology, diagnosis, and management of fibromyalgia. Epidemiology: Fibromyalgia is the most common chronic pain syndrome encountered in general medicine and rheumatology. Historically, contemporary concepts of fibromyalgia

have evolved in terms of its clinical description and parallel advances in the understanding of its pathophysiology. Pathophysiology: A generally accepted paradigm postulates that fibromyalgia is the clinical expression of a rheumatologic disorder in which the associated pain is driven primarily by central sensitization and possibly through changes in several neuronal systems but not necessarily reliant on peripheral processes. Management: **Several agents, including serotonin-norepinephrine reuptake inhibitors (ie, duloxetine and milnacipran), opioids (ie, tramadol), and the alpha2-delta ligand pregabalin**, which recently received U.S. regulatory approval for the treatment of fibromyalgia, **have been evaluated in clinical trials, demonstrating benefit in terms of pain reduction and improvement in core symptoms** (i.e., fatigue and sleep disturbance). The European League Against Rheumatism has developed updated guidelines for the management of fibromyalgia.

Pain Pract. 2008 Mar 18 [Epub ahead of print]

Rooks DS

Talking to patients with fibromyalgia about physical activity and exercise

PURPOSE OF REVIEW: The purpose of this article is to describe the application of basic exercise principles to individuals with fibromyalgia to encourage clinicians to discuss with their patients ways of becoming more physically active. **RECENT FINDINGS:** The goals of increased physical activity and exercise for individuals with fibromyalgia are to improve or maintain general fitness, physical function, emotional well being, symptoms and overall health, and provide them with a feeling of control over their well being. Describing ways of increasing activity through home, work and leisure-related tasks or exercise provides a universal approach to increasing physical activity that applies to individuals with fibromyalgia and fits a counseling model of health behavior familiar to clinicians. The patient-clinician relationship provides a unique opportunity for health professionals to counsel individuals with fibromyalgia to become and remain more physically active. **SUMMARY:** Regular physical activity and exercise has numerous physical, psychological, and functional benefits for individuals with fibromyalgia and should be included in treatment plans. **Clinicians can help patients adopt a more physically active lifestyle through targeted discussions, support and consistent follow up.**

Curr Opin Rheumatol. 2008 Mar; 20(2):208–12

Russell IJ

Fibromyalgia syndrome: approach to management

The management of fibromyalgia syndrome (FMS) has traditionally been multimodal and multidisciplinary, including education, physical modalities, and

medication. In this article, an acronym is offered to help the clinician remember the important components of management. An improved understanding of the pathogenesis of FMS has allowed substantial refinements in its treatment. This is particularly true for medications that target specific symptom domains, allowing individualization of therapy. Since all FMS patients experience pain, there has been emphasis on that domain although medications are now available to address two or more domains with monotherapy. In addition, **a logical basis is provided to help the clinician design strategic polypharmacy.**

CNS Spectr. 2008 Mar; 13(3 Suppl 5):27–33

Russell IJ, Raphael KG

Fibromyalgia syndrome: presentation, diagnosis, differential diagnosis, and vulnerability

Fibromyalgia syndrome (FMS) presents with widespread soft tissue pain. Common comorbidities include severe insomnia, body stiffness, affective symptoms, irritable bowels, and urethral syndrome. A 1990 research classification depends on a history of widespread pain and prominent tenderness to palpation at 11 or more of 18 specific tender points. It is a criteria-based diagnosis rather than one by exclusion and can accompany other medical conditions. FMS occurs worldwide, and can present any age, but is most common in adult females. Although numerous studies and reviews contend that FMS may be caused by psychological stress such as sexual abuse, critical epidemiological review fails to support that concept. Existing data suggest that **some individuals with FMS may have a dysregulated physiological stress response system that predates the onset of symptoms.**

CNS Spectr. 2008 Mar; 13(3 Suppl 5):6–11

Russo EB

Clinical endocannabinoid deficiency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions?

OBJECTIVES: This study examines the concept of clinical endocannabinoid deficiency (CECD), and the prospect that it could underlie the pathophysiology of migraine, fibromyalgia, irritable bowel syndrome, and other functional conditions alleviated by clinical cannabis. **METHODS:** Available literature was reviewed, and literature searches pursued via the National Library of Medicine database and other resources. **RESULTS:** Migraine has numerous relationships to endocannabinoid function. Anandamide (AEA) potentiates 5-HT_{1A} and inhibits 5-HT_{2A} receptors supporting therapeutic efficacy in acute and preventive migraine

treatment. Cannabinoids also demonstrate dopamine-blocking and anti-inflammatory effects. AEA is tonically active in the periaqueductal gray matter, a migraine generator. THC modulates glutamatergic neurotransmission via NMDA receptors. Fibromyalgia is now conceived as a central sensitization state with secondary hyperalgesia. Cannabinoids have similarly demonstrated the ability to block spinal, peripheral and gastrointestinal mechanisms that promote pain in headache, fibromyalgia, IBS and related disorders. The past and potential clinical utility of cannabis-based medicines in their treatment is discussed, as are further suggestions for experimental investigation of CECD via CSF examination and neuro-imaging. **CONCLUSION: Migraine, fibromyalgia, IBS and related conditions display common clinical, biochemical and pathophysiological patterns that suggest an underlying clinical endocannabinoid deficiency that may be suitably treated with cannabinoid medicines.**

Neuro Endocrinol Lett. 2008 Apr; 29(2):192–200

Republished from: *Neuro Endocrinol Lett.* 2004 Feb-Apr; 25(1-2):31–9

Schweinhardt P, Sauro KM, Bushnell MC

Fibromyalgia: A disorder of the brain?

This article presents evidence that fibromyalgia patients have alterations in CNS anatomy, physiology, and chemistry that potentially contribute to the symptoms experienced by these patients. There is substantial psychophysical evidence that fibromyalgia patients perceive pain and other noxious stimuli differently than healthy individuals and that normal pain modulatory systems, such as diffuse noxious inhibitory control mechanisms, are compromised in fibromyalgia. Furthermore, functional brain imaging studies revealing enhanced pain-related activations corroborate the patients' reports of increased pain. Neurotransmitter studies show that fibromyalgia patients have abnormalities in dopaminergic, opioidergic, and serotonergic systems. Finally, **studies of brain anatomy show structural differences between the brains of fibromyalgia patients and healthy individuals.** The cerebral alterations offer a compelling explanation for the multiple symptoms of fibromyalgia, including widespread pain and affective disturbances. The frequent comorbidity of fibromyalgia with stress-related disorders, such as chronic fatigue, posttraumatic stress disorder, irritable bowel syndrome, and depression, as well as the similarity of many CNS abnormalities, suggests at least a partial common substrate for these disorders. Despite the numerous cerebral alterations, fibromyalgia might not be a primary disorder of the brain but may be a consequence of early life stress or prolonged or severe stress, affecting brain modulatory circuitry of pain and emotions in genetically susceptible individuals.

Neuroscientist. 2008 Feb 12 [Epub ahead of print]

Staud R, Bovee CE, Robinson ME, Price DD

Cutaneous C-fiber pain abnormalities of fibromyalgia patients are specifically related to temporal summation

Temporal summation of “second pain” (TSSP) is considered to be the result of C-fiber-evoked responses of dorsal horn neurons, termed ‘windup’. TSSP is dependent on stimulus frequency (0.33Hz) and is relevant for central sensitization and chronic pain. We have previously shown that compared to normal controls (NC), fibromyalgia (FM) subjects show abnormal TSSP, requiring lower stimulus intensities/frequencies to achieve similar TSSP. However, it is unknown whether abnormal TSSP in FM is influenced by peripheral sensitization of C-fiber nociceptors and/or bias in pain ratings. Thus, we evaluated 14 FM subjects and 19 NC with pain threshold tests to selective C-fiber stimulation, 30s heat stimuli, and repetitive brief (1.5s) heat pulses at 0.33Hz using a contact heat stimulator (CHEPS). The intensity of heat pulses was varied to achieve maximal TSSP ratings of 45+/-10 (numerical pain scale 0–100) in both FM and NC groups. We found that NC and FM subjects had similar pain thresholds to C-fiber stimulation and yet FM subjects required lower heat pulse temperatures to generate the same magnitudes of TSSP ($p < .05$). This combination of findings does not support peripheral sensitization and suggests central TSSP abnormalities in FM subjects. In a second experiment, all aspects of individually adjusted TSSP heat pulses were kept the same except that the baseline temperature (BT) between heat pulses was surreptitiously alternated between 35 degrees C and 40 degrees C. These changes of BT resulted in significantly greater TSSP ratings of FM subjects compared to NC subjects, both at 35 degrees C and at 40 degrees C, but did not change their response to the first heat pulse of a stimulus train. **These findings provide strong support for alterations of central pain sensitivity and not peripheral sensitization or rating bias as responsible for TSSP differences between NC and FM subjects.**

Pain. 2008 Jun 4. [Epub ahead of print]

Staud R, Koo EB

Are cannabinoids a new treatment option for pain in patients with fibromyalgia?

Preliminary studies suggest that the synthetic cannabinoid nabilone might be an effective therapy in patients with fibromyalgia. Skrabek et al. performed a double-blind, randomized, placebo-controlled clinical trial to analyze the effects of nabilone on pain and quality of life in patients with fibromyalgia. After 4 weeks of treatment (0.5 mg once daily in week 1, 0.5 mg twice daily in week 2, 0.5 mg in the morning and 1 mg in the evening in week 3, and 1 mg twice daily in week 4), **patients who received nabilone (n = 15) experienced significant improvements in clinical pain**, measured on a visual analog scale ($P < 0.02$), Fibro-

myalgia Impact Questionnaire score ($P < 0.02$) and the 10-point anxiety scale of the Fibromyalgia Impact Questionnaire ($P < 0.02$). After a 4-week wash-out period at the end of the trial, all benefits were lost in the nabilone cohort, which returned to their baseline levels of pain and quality of life. **Patients who received placebo (n = 18) experienced no change throughout the study.** Although nabilone was not associated with serious adverse effects, some patients did experience drowsiness, dry mouth, vertigo and ataxia as a result of treatment.

Nat Clin Pract Rheumatol. 2008 Jul; 4(7):348–9. Epub 2008 Jun 3

Trivedi MH, Desai D, Ossanna MJ, Pritchett YL, Brannan SK, Detke MJ

Clinical evidence for serotonin and norepinephrine reuptake inhibition of duloxetine

Most antidepressants in clinical use are believed to function by enhancing neurotransmission of serotonin [5-hydroxytryptamine (5-HT)] and/or norepinephrine (NE) via inhibition of neurotransmitter reuptake. Agents that affect reuptake of both 5-HT and NE (serotonin-norepinephrine reuptake inhibitors) have been postulated to offer greater efficacy for the treatment of major depressive disorder (MDD). These dual-acting agents also display a broader spectrum of action, including efficacy for MDD and associated painful physical symptoms, diabetic peripheral neuropathic pain, generalized anxiety disorder, and fibromyalgia syndrome. Substantial preclinical evidence shows that duloxetine, an approved drug for the treatment of MDD, generalized anxiety disorder, and the management of diabetic peripheral neuropathic pain, inhibits reuptake of both 5-HT and NE. This paper reviews clinical and neurochemical evidence of duloxetine's effects on 5-HT and NE reuptake inhibition. The clinical evidence supporting duloxetine's effects on NE reuptake inhibition includes indirect measures such as altered excretion of NE metabolites, cardiovascular effects, and treatment-emergent adverse event profiles similar to those for other drugs believed to act through the inhibition of NE reuptake. In summary, **the data presented in this report provide clinical evidence of a mechanism for duloxetine involving both 5-HT and NE reuptake inhibition in humans and are consistent with preclinical evidence for 5-HT/NE reuptake inhibition.**

Int Clin Psychopharmacol. 2008 May; 23(3):161–9

Valet M, Gündel H, Sprenger T, Sorg C, Mühlau M, Zimmer C, Henningsen P, Tölle TR

Patients with pain disorder show gray-matter loss in pain-processing structures: A voxel-based morphometric study

OBJECTIVE: To investigate whether the functional changes in pain disorder might be reflected by structural brain changes. Pain disorder assessed with the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria is characterized by persistent and distressing chronic pain at one or more body sites which cannot be fully explained by a physiological process or somatic disorder. Psychological factors are thought to play a major role. Recent neuroimaging studies evidenced altered pain processing in patients suffering from this disorder. **METHODS:** Fourteen right-handed women fulfilling the DSM-IV criteria for pain disorder and 25 healthy age-matched women were investigated with magnetic resonance imaging. In the voxel-based morphometry analysis, we compared both groups for changes of gray-matter density. We included age and Beck Depression Inventory scores as nuisance variables to minimize possible confounding effects of age or depressive comorbidity. **RESULTS:** In the patient group, we found significant gray-matter decreases in the prefrontal, cingulate, and insular cortex. These regions are known to be critically involved in the modulation of subjective pain experiences. **CONCLUSIONS:** In the context of similar results in patients with other functional pain syndromes, such as fibromyalgia and chronic back pain, **we suggest that structural changes in fronto-limbic brain circuits represent not only an objective marker of these pain syndromes but also constitute a critical pathophysiological element.** These findings represent a further proof of the important role of central changes in pain disorder.

Psychosom Med. 2008 Dec 10. [Epub ahead of print]

Wood PB

Role of central dopamine in pain and analgesia

Recent insights have demonstrated a central role for dopaminergic neurotransmission in modulating pain perception and natural analgesia within supraspinal regions, including the basal ganglia, insula, anterior cingulate cortex, thalamus and periaqueductal gray. In addition, while the participation of serotonin and norepinephrine in spinal descending inhibition of pain is well known, a critical role for dopamine in descending inhibition has also been demonstrated. Decreased levels of dopamine likely contribute to the painful symptoms that frequently occur in Parkinson's disease. **Moreover, abnormalities in dopaminergic neurotransmission have been objectively demonstrated in painful clinical conditions, including burning mouth syndrome, fibromyalgia and restless legs syndrome.** Evidence from animal models and indirect evidence from pharmaceutical trials also suggest a role for dopamine in chronic regional pain syndrome and painful diabetic neuropathy. Several novel classes of medication with analgesic properties have bearing on dopaminergic activity as evident in the capacity of dopamine antagonists to attenuate their analgesic capacity. An expanded appreciation for the role of dopamine in natural analgesia provides the

impetus for further study involving preclinical models and advanced neuroimaging techniques in humans, which may lead to the development of novel therapeutic strategies.

Expert Rev Neurother. 2008 May; 8(5):781–97