

FIBROMYALGIA: ABSTRACTS 2009

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 2009. The studies were selected from the extensive literature on fibromyalgia so as to cover a wide range of subjects in limited space.

Abstracts for 2010 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.

Arnold LM

Strategies for managing fibromyalgia

The presentation of fibromyalgia is heterogeneous, and the treatment approach should be individualized for each patient, depending on the severity of the patient's pain, the presence of other symptoms or comorbidities, and the degree of functional impairment. The management of fibromyalgia includes the identification and treatment of all pain sources that may be present in addition to fibromyalgia, such as peripheral pain generators (e.g., comorbid osteoarthritis or neuropathic pain) or visceral pain (e.g., comorbid irritable bowel syndrome). It is also important to address other symptoms or disorders that commonly occur in patients with fibromyalgia, such as fatigue, sleep disturbances, cognitive impairment, stiffness, and mood or anxiety disorders. Finally, the treatment should strive to improve the patient's function and global health status. In most cases, the management of fibromyalgia involves both pharmacologic and nonpharmacologic treatments. **This report provides an in-depth review of randomized, controlled trials for pharmacologic and nonpharmacologic approaches to fibromyalgia therapy.** (c) 2009 Elsevier Inc.

Am J Med. 2009 Dec; 122(12 Suppl):S31

Bazzichi L, Palego L, Giannaccini G, Rossi A, De Feo F, Giacomelli C, Betti L, Giusti L, Mascia G, Bombardieri S, Lucacchini A

Altered amino acid homeostasis in subjects affected by fibromyalgia

OBJECTIVES: To evaluate plasma amino acid (AA) concentrations in patients affected by fibromyalgia (FM) and to study the relationships between their levels and FM clinical parameters. **DESIGN AND METHODS:** 20 AAs were assessed in

34 FM patients and in 18 healthy volunteers by means of a modified version of the Waters picotag method. RESULTS: Significant lower plasma taurine, alanine, tyrosine (Tyr), valine, methionine, phenylalanine and threonine concentrations, and the sum of essential AAs were observed in FM patients vs healthy controls ($P<0.05$). Tyr CAA' ratio and the sum of AAs competing with tryptophan for brain uptake were significantly reduced in FM ($P<0.05$). A significant correlation was found between FM clinical parameters and certain AAs. CONCLUSIONS: **Our results suggest probable defects of gut malabsorption of certain AAs in FM patients. Moreover, given the reduced Tyr CAA' ratio in FM patients, a possible impairment of the catecholaminergic system in the FM syndrome may be suggested.**

Clin Biochem. 2009 Mar 10.

Bennett RM, Bushmakin AG, Cappelleri JC, Zlateva G, Sadosky AB

Minimal clinically important difference in the fibromyalgia impact questionnaire

OBJECTIVE: The Fibromyalgia Impact Questionnaire (FIQ) is a disease-specific composite instrument that measures the effect of problems experienced by patients with fibromyalgia (FM). Utilization of the FIQ in measuring changes due to interventions in FM requires derivation of a clinically meaningful change for that instrument. Analyses were conducted to estimate the minimal clinically important difference (MCID), and to propose FIQ severity categories. METHODS: Data from 3 similarly designed, 3-month placebo-controlled, clinical treatment trials of pregabalin 300, 450, and 600 mg/day in patients with FM were modeled to estimate the change in the mean FIQ total and stiffness items corresponding to each category on the Patient Global Impression of Change. FIQ severity categories were modeled and determined using established pain severity cutpoints as an anchor. RESULTS: A total of 2228 patients, mean age 49 years, 93% women, with a mean baseline FIQ total score of 62 were treated in the 3 studies. Estimated MCID on a given measure were similar across the studies. In a pooled analysis the estimated MCID (95% confidence interval) was 14% (13; 15) and for FIQ stiffness it was 13% (12; 14). In the severity analysis a FIQ total score from 0 to < 39 was found to represent a mild effect, ≥ 39 to < 59 a moderate effect, and ≥ 59 to 100 a severe effect. CONCLUSION: **The analysis indicates that a 14% change in the FIQ total score is clinically relevant, and results of these analyses should enhance the clinical utility of the FIQ in research and practice.**

J Rheumatol. 2009 Jun; 36(6):1304–11.

Bennett RM, Friend R, Jones KD, Ward R, Han BK, Ross RL

The Revised Fibromyalgia Impact Questionnaire (FIQR): validation and psychometric properties

INTRODUCTION: The Fibromyalgia Impact Questionnaire (FIQ) is a commonly used instrument in the evaluation of fibromyalgia (FM) patients. Over the last 18 years, since the publication of the original FIQ, several deficiencies have become apparent and the cumbersome scoring algorithm has been a barrier to widespread clinical use. The aim of this paper is to describe and validate a revised version of the FIQ: the FIQR. **METHODS:** The FIQR was developed in response to known deficiencies of the FIQ with the help of a patient focus group. The FIQR has the same 3 domains as the FIQ (that is, function, overall impact and symptoms). It differs from the FIQ in having modified function questions and the inclusion of questions on memory, tenderness, balance and environmental sensitivity. All questions are graded on a 0–10 numeric scale. The FIQR was administered online and the results were compared to the same patient's online responses to the 36-Item Short Form Health Survey (SF-36) and the original FIQ. **RESULTS:** The FIQR was completed online by 202 FM patients, 51 rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) patients (31 RA and 20 SLE), 11 patients with major depressive disorder (MDD) and 213 healthy controls (HC). The mean total FIQR score was 56.6 +/- 19.9 compared to a total FIQ score of 60.6 +/- 17.8 ($P < 0.03$). The total scores of the FIQR and FIQ were closely correlated ($r = 0.88$, $P < 0.001$). Each of the 3 domains of the FIQR correlated well with the 3 related FIQ domains ($r = 0.69$ to 0.88 , $P < 0.01$). The FIQR showed good correlation with comparable domains in the SF-36, with a multiple regression analysis showing that the three FIQR domain scores predicted the 8 SF-36 subscale scores. The FIQR had good discriminant ability between FM and the 3 other groups; total FIQR scores were HC (12.1 +/- 11.6), RA/SLE (28.6 +/- 21.2) and MDD (17.3 +/- 11.8). The patient completion time was 1.3 minutes; scoring took about 1 minute. **CONCLUSIONS:** **The FIQR is an updated version of the FIQ that has good psychometric properties, can be completed in less than 2 minutes and is easy to score.** It has scoring characteristics comparable to the original FIQ, making it possible to compare past FIQ results with future FIQR results.

Arthritis Res Ther. 2009; 11(4):R120.

Boomershine CS, Crofford LJ

A symptom-based approach to pharmacologic management of fibromyalgia

Fibromyalgia is a prevalent disorder that is characterized by widespread pain along with numerous other symptoms, including fatigue, poor sleep, mood disorders, and stiffness. Previous guidelines for the management of fibromyalgia recommended an approach that integrates pharmacologic and nonpharmacologic therapies selected according to the symptoms experienced by individual patients. However, they offered no recommendations for a system of patient assessment that would provide a basis for individualized treatment selection. **We present a simple, rapid and easily remembered system for symptom quantitation and pharmacologic management of fibromyalgia** that combines visual analogue

scale symptom scores from a modified form of the disease-neutral Fibromyalgia Impact Questionnaire, with a review of medications that can be used to treat the individual symptoms. This symptom-based approach is amenable to caring for patients with fibromyalgia in a busy clinical practice.

Nat Rev Rheumatol. 2009 Apr; 5(4):191–9

Branco JC, Bannwarth B, Failde I, Abello Carbonell J, Blotman F, Spaeth M, Saraiva F, Nacci F, Thomas E, Caubère JP, Le Lay K, Taieb C, Matucci-Cerinic M

Prevalence of fibromyalgia: A survey in five European countries

OBJECTIVE: A survey was performed in 5 European countries (France, Germany, Italy, Portugal, and Spain) to estimate the prevalence of fibromyalgia (FM) in the general population. **METHODS:** In each country, the London Fibromyalgia Epidemiological Study Screening Questionnaire (LFESSQ) was administered by telephone to a representative sample of the community over 15 years of age. A positive screen was defined as the following: (1) meeting the 4-pain criteria alone (LFESSQ-4), or (2) meeting both the 4-pain and the 2-fatigue criteria (LFESSQ-6). The questionnaire was also submitted to all outpatients referred to the 8 participating rheumatology clinics for 1 month. These patients were examined by a rheumatologist to confirm or exclude the FM diagnosis according to the 1990 American College of Rheumatology classification criteria. The prevalence of FM in the general population was estimated by applying the positive-predictive values to eligible community subjects (ie, positive screens). **RESULTS:** Among rheumatology outpatients, 46% screened positive for chronic widespread pain (LFESSQ-4), 32% for pain and fatigue (LFESSQ-6), and 14% were confirmed FM cases. In the whole general population, 13% and 6.7% screened positive for LFESSQ-4 and LFESSQ-6, respectively. The estimated overall prevalence of FM was 4.7% (95% CI: 4.0 to 5.3) and 2.9% (95% CI: 2.4 to 3.4), respectively, in the general population. The prevalence of FM was age- and sex-related and varied among countries. **CONCLUSION: FM appears to be a common condition in these 5 European countries, even if data derived from the most specific criteria set (LFESSQ-6) are considered.**

Semin Arthritis Rheum. 2009 Feb 26.

Choy EH, Mease PJ, Kajdasz DK, Wohlreich MM, Crits-Christoph P, Walker DJ, Chappell AS

Safety and tolerability of duloxetine in the treatment of patients with fibromyalgia: pooled analysis of data from five clinical trials

The purpose of this report is to describe the overall safety profile of both short- and longer-term duloxetine treatment of fibromyalgia. Data from four double-

blind, randomized, placebo-controlled studies (two with 6-month open-label extension phases) and a 1-year, open-label safety study were included. Safety measures included treatment-emergent adverse events (TEAEs), adverse events leading to discontinuation, serious adverse events (SAEs), clinical laboratory tests, vital signs, and electrocardiograms. The most common TEAEs for short-term treatment with duloxetine were nausea (29.3%), headache (20.0%), dry mouth (18.2%), insomnia (14.5%), fatigue (13.5%), constipation (14.5%), diarrhea (11.6%), and dizziness (11.0%; all $p < 0.05$ vs. placebo). Most TEAEs emerged early and were mild to moderate in severity. The profile of adverse events in patients enrolled at least 6 months, and for patients in the 1-year study, was similar to that found in the short-term treatment studies, with no new adverse events emerging at a notable rate. About 20% of patients discontinued due to adverse events in the short-term treatment studies and in the 1-year study. SAEs were uncommon, and none occurred at a significantly higher frequency for duloxetine compared with placebo. Mean changes in vital signs and weight were small. Rates of treatment-emergent potentially clinically significant (PCS) vital sign, laboratory, and electrocardiogram measures were low, with only PCS rates of alanine aminotransferase being significantly higher for duloxetine compared with placebo in the placebo-controlled treatment studies. In the 1-year study, four patients (1.1%) had suicide-related behavior. **The data provided here summarize short- and long-term safety from five clinical studies in patients treated with duloxetine for fibromyalgia.** In addition, postmarketing surveillance continues for adverse events reported with duloxetine in fibromyalgia, as in other indications.

Clin Rheumatol. 2009 Jun 18.

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

The deficit of pain inhibition in fibromyalgia is more pronounced in patients with comorbid depressive symptoms

BACKGROUND: On pathophysiologic grounds, fibromyalgia (FM) is characterized by a deficit in diffuse noxious inhibitory controls (DNIC), but the role of depressive symptoms on these mechanisms has not been investigated. We hypothesized that the deficit in pain inhibition would be more pronounced in FM patients with depressive symptoms (FM+D), relative to patients without such symptoms (FM-D). **METHODS:** Fifty-two women diagnosed with FM (American College of Rheumatology criteria) and 10 healthy women participated in this study. Thermal stimuli were used to measure pain thresholds and DNIC efficacy (spatial summation paradigm). Clinical pain was measured using visual analog scales. **RESULTS:** We found that the amplitude of DNIC was smaller in FM+D patients, relative to the FM-D group; and that daily pain (unpleasantness) was higher in the FM+D group, relative to FM-D patients. **DISCUSSION:** **We found that FM+D patients have a more pronounced deficit in pain inhibition as well increased clinical pain.** As such, these results show the usefulness of combining

psychologic factors and psychophysical measures to identify subgroups of FM patients. These results may have implications for future treatment of FM patients with and without comorbid depressive symptoms.

Clin J Pain. 2009 Feb; 25(2):123–7

Goffaux P, de Souza JB, Potvin S, Marchand S

Pain relief through expectation supersedes descending inhibitory deficits in fibromyalgia patients

In healthy adults, expectations can modulate the activity of inhibitory bulbo-spinal projections, and can even block the analgesic properties of counter-irritation—a phenomenon that triggers descending inhibition. Since descending inhibition is known to be deficient in fibromyalgia (FM) patients, we tested the possibility that expectancy-mediated analgesia would improve, or even kick-start, the deficient inhibitory responses of FM patients. By measuring subjective pain ratings, spinal withdrawal reflexes, and somatosensory evoked potentials (SEP), it was possible to test whether or not expectancy-mediated analgesia involved descending inhibition in FM patients. Here, we show that expectations of analgesia radically change the subjective experience of pain, but do not eliminate evidence of spinal hyperexcitability in FM patients. We found that expectations of analgesia reduce subjective pain ratings and decrease SEP amplitudes, confirming that expectations influence thalamocortical processes. However, even when analgesia was experienced, the spinal activity of FM patients was abnormal, showing heightened reflex responses. This demonstrates that, **unlike healthy subjects, the modulation of pain by expectations in FM fails to influence spinal activity.** These results indicate that FMs are capable of expectancy-induced analgesia but that, for them, this form of analgesia does not depend on the recruitment of descending inhibitory projections.

Pain. 2009 Jun 11

Häuser W, Bernardy K, Arnold B, Offenbächer M, Schiltenwolf M

Efficacy of multicomponent treatment in fibromyalgia syndrome: a meta-analysis of randomized controlled clinical trials

OBJECTIVE: To systematically review the efficacy of multicomponent treatment of fibromyalgia syndrome (FMS). **METHODS:** We screened Medline, PsychINFO, Scopus, and the Cochrane Library (through December 2007), as well as reference sections of original studies, reviews, and evidence-based guidelines. Randomized controlled trials (RCTs) on the multicomponent treatment (at least 1 educational or other psychological therapy with at least 1 exercise therapy) of FMS were analyzed. **RESULTS:** We included 9 (of 14) RCTs with 1,119 subjects (median treatment time 24 hours) in the meta-analysis. Effects were summarized using

standardized mean differences (SMDs) or weighted mean differences (WMDs). There was strong evidence that multicomponent treatment reduces pain (SMD -0.37; 95% confidence interval [95% CI] -0.62, -0.13), fatigue (WMD -0.85; 95% CI -1.50, -0.20), depressive symptoms (SMD -0.67; 95% CI -1.08, -0.26), and limitations to health-related quality of life (HRQOL) (SMD -0.59; 95% CI -0.90, -0.27) and improves self-efficacy pain (SMD 0.54; 95% CI 0.26, 0.82) and physical fitness (SMD 0.30; 95% CI 0.02, 0.57) at post-treatment. **There was no evidence of its efficacy on pain, fatigue, sleep disturbances, depressive symptoms, HRQOL, or self-efficacy pain in the long term.** There was strong evidence that positive effects on physical fitness (SMD 0.30; 95% CI 0.09, 0.51) can be maintained in the long term (median followup 7 months). **CONCLUSIONS:** There is strong evidence that **multicomponent treatment has beneficial short-term effects** on the key symptoms of FMS. Strategies to maintain the benefits of multicomponent treatment in the long term need to be developed.

Arthritis Rheum. 2009 Feb 15; 61(2):216–24

Häuser W, Bernardy K, Uçeyler N, Sommer C

Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis

CONTEXT: Fibromyalgia syndrome (FMS) is a chronic pain disorder associated with multiple debilitating symptoms and high disease-related costs. Effective treatment options are needed. **OBJECTIVES:** To determine the efficacy of antidepressants in the treatment of FMS by performing a meta-analysis of randomized controlled clinical trials. **DATA SOURCES:** MEDLINE, PsycINFO, Scopus, and the Cochrane Library databases were searched through August 2008. Reference sections of original studies, meta-analyses, and reviews on antidepressants in FMS were reviewed. **STUDY SELECTION:** Randomized placebo-controlled trials with tricyclic and tetracyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs) were analyzed. **DATA EXTRACTION AND DATA SYNTHESIS:** Two authors independently extracted data. Effects were summarized using standardized mean differences (SMDs) by a random-effects model. **RESULTS:** Eighteen randomized controlled trials (median duration, 8 weeks; range, 4–28 weeks) involving 1427 participants were included. Overall, there was strong evidence for an association of antidepressants with reduction in pain (SMD, -0.43; 95% confidence interval [CI], -0.55 to -0.30), fatigue (SMD, -0.13; 95% CI, -0.26 to -0.01), depressed mood (SMD, -0.26; 95% CI, -0.39 to -0.12), and sleep disturbances (SMD, -0.32; 95% CI, -0.46 to -0.18). There was strong evidence for an association of antidepressants with improved health-related quality of life (SMD, -0.31; 95% CI, -0.42 to -0.20). Effect sizes for pain reduction were large for TCAs (SMD, -1.64; 95% CI, -2.57 to -0.71), medium for MAOIs (SMD, -0.54; 95% CI, -1.02 to -0.07), and small for SSRIs (SMD, -0.39; 95% CI, -0.77 to -0.01) and SNRIs (SMD, -0.36; 95% CI, -0.46 to -0.25). **CONCLUSION:**

Antidepressant medications are associated with improvements in pain, depression, fatigue, sleep disturbances, and health-related quality of life in patients with FMS.

JAMA. 2009 Jan 14; 301(2):198–209

Hudson JI, Arnold LM, Bradley LA, Choy EH, Mease PJ, Wang F, Ahl J, Wohlreich MM

What makes patients with fibromyalgia feel better?

Correlations between Patient Global Impression of Improvement and changes in clinical symptoms and function: a pooled analysis of 4 randomized placebo-controlled trials of duloxetine

OBJECTIVE: To investigate the relationship between changes in clinical rating scale items and endpoint Patient Global Impression of Improvement (PGI-I). **METHODS:** Data were pooled from 4 randomized, double-blind, placebo-controlled studies of duloxetine in patients with fibromyalgia (FM). Variables included in the analyses were those that assessed symptoms in FM domains of pain, fatigue, sleep, cognitive difficulties, emotional well-being, physical function, and impact on daily living. The association of endpoint PGI-I with changes from baseline in individual variables was assessed using Pearson product-moment correlations (r). Stepwise linear regression was used to identify those variables for which changes from baseline were statistically significant independent predictors of the endpoint PGI-I ratings. **RESULTS:** Changes in pain variables and interference of symptoms with the ability to work were highly correlated ($r \geq 0.5$ or $r \leq -0.5$) with endpoint PGI-I. Moderate correlation with endpoint PGI-I ($0.30 \leq r < 0.5$ or $-0.5 < r \leq -0.30$) included changes in variables that assessed physical functioning, depression, anxiety, fatigue, and several variables related to impact on daily living. Independent predictor variables of endpoint PGI-I identified by stepwise linear regression included assessments for pain, physical function, vitality, anxiety, social function, and tender point thresholds. **CONCLUSION:** **In addition to pain reduction, what makes patients with FM feel better may include improvement in fatigue, physical functioning, mood, and impact on daily living. An assessment of these domains may be important in clinical trials of FM and in the management of patients with FM.**

J Rheumatol. 2009 Nov; 36(11):2517–22. Epub 2009 Oct 15

Hsu MC, Harris RE, Sundgren PC, Welsh RC, Fernandes CR, Clauw DJ, Williams DA

No consistent difference in gray matter volume between individuals with fibromyalgia and age-matched healthy subjects when controlling for affective disorder

Fibromyalgia (FM) is thought to involve abnormalities in central pain processing. Recent studies involving small samples have suggested alterations in gray matter volume (GMV) in brains of FM patients. Our objective was to verify these findings in a somewhat larger sample using voxel-based morphometry (VBM), while controlling for the presence of affective disorders (AD). T1-weighted magnetic resonance image (MRI) brain scans were obtained on 29 FM patients with AD, 29 FM patients without AD, and 29 age-matched healthy controls (HCs) using a 3T scanner. Segmentation, spatial normalization, and volumetric modulation were performed using an automated protocol within SPM5. Smoothed gray matter segments were entered into a voxel-wise one-way ANOVA, and a search for significant clusters was performed using thresholding methods published in previous studies (whole-brain threshold of $p < .05$ correcting for multiple comparisons; region-of-interest (ROI) threshold of $p < \text{or} = .001$ uncorrected, or $p < .05$ small-volume corrected). The whole-brain analysis did not reveal any significant clusters. ROI-based analysis revealed a significant difference in left anterior insula GMV among the three groups ($xyz = \{-28, 21, 9\}$; $p = .026$, corrected). However, on post-hoc testing, **FM patients without AD did not differ significantly from HC with respect to mean GMV extracted from this cluster.** A significant negative correlation was found between mean cluster GMV and scores of trait anxiety (State-Trait Personality Inventory, Trait Anxiety scale; $\rho = -.470$, $p < .001$). No other significant clusters were found on ROI-based analysis. Our results emphasize the importance of correcting for AD when carrying out VBM studies in chronic pain.

Pain. 2009 Jun; 143(3):262–7

Jensen KB, Kosek E, Petzke F, Carville S, Fransson P, Marcus H, Williams SC, Choy E, Giesecke T, Mainguy Y, Gracely R, Ingvar M

Evidence of dysfunctional pain inhibition in fibromyalgia reflected in rACC during provoked pain

Over the years, many have viewed fibromyalgia syndrome (FMS) as a so-called "functional disorder" and patients have experienced a concomitant lack of interest and legitimacy from the medical profession. The symptoms have not been explained by peripheral mechanisms alone nor by specific central nervous system mechanisms. In this study, we objectively evaluated the cerebral response to individually calibrated pain provocations of a pain-free body region (thumbnail). The study comprised 16 female FMS patients and 16 individually age-matched controls. Brain activity was measured using functional magnetic resonance imaging (fMRI) during individually calibrated painful pressures representing 50 mm on a visual analogue scale (VAS) ranging from 0 to 100 mm. Patients exhibited higher sensitivity to pain provocation than controls as they required less pressure to evoke equal pain magnitudes ($U(A) = 48$, $p < .002$). Despite lower pressures applied in patients at VAS 50 mm, the fMRI-analysis revealed no difference in activity in brain regions relating to attention and affect or regions

with sensory projections from the stimulated body area. However, in the primary link in the descending pain regulating system (the rostral anterior cingulate cortex [rACC]) the patients failed to respond to pain provocation. **The attenuated response to pain in this brain region is the first demonstration of a specific brain region where the impairment of pain inhibition in FMS patients is expressed.** These results validate previous reports of dysfunctional endogenous pain inhibition in FMS and advance the understanding of the central pathophysiologic mechanisms, providing a new direction for the development of successful treatments in FMS.

Pain. 2009 Jul;144(1-2): 95-100

Jones KD, Horak FB, Winters-Stone K, Irvine JM, Bennett RM

Fibromyalgia is associated with impaired balance and falls

BACKGROUND/OBJECTIVE: The purpose of this study was to determine whether fibromyalgia (FM) patients differ from matched healthy controls in clinical tests of balance ability and fall frequency. **METHODS:** Thirty-four FM patients and 32 age-matched controls were administered the Balance Evaluation-Systems Test (BESTest), rated their balance confidence with the Activities-Specific Balance Confidence (ABC) Scale, and reported the number of falls in the last 6 months. The Fibromyalgia Impact Questionnaire was used to assess FM severity. **RESULTS:** FM patients had significantly impaired balance in all components of the BESTest compared with controls. They also scored more poorly on balance confidence. Overall FM severity (Fibromyalgia Impact Questionnaire) correlated significantly with the BESTest and the ABC scale. The BESTest and ABC correlated significantly with 6 commonly reported FM symptoms (excluding pain). FM patients reported a total of 37 falls over the last 6-months compared with 6 falls in healthy controls. **CONCLUSION: FM is associated with balance problems and increased fall frequency.** Patients were aware of their balance problems. These results suggest that FM may affect peripheral and/or central mechanisms of postural control. Further objective study is needed to identify the relative contributions of various neural and musculoskeletal and other impairments to postural stability in FM to provide clinicians with methods to maximize postural stability and help fall prevention.

J Clin Rheumatol. 2009 Feb; 15(1):16-21

Karsdorp PA, Vlaeyen JW

Active avoidance but not activity pacing is associated with disability in fibromyalgia

Activity pacing has been suggested as a behavioural strategy that may protect patients with fibromyalgia (FM) against activity dysregulation and disability. The aim of the present study was to empirically test whether the construct of activity

pacing is distinct from other behavioural strategies assessed with the Chronic Pain Coping Inventory (CPCI), such as guarding, resting, asking for assistance, relaxation, task persistence, exercise/stretch, seeking social support, and coping self-statements. The second objective was to test whether pacing was associated with physical disability when controlling for pain catastrophizing, pain severity and the other behavioural strategies as measured with CPCI. A random sample of patients with FM (N=409) completed the CPCI, the Pain Catastrophizing Scale (PCS), the Physical Index of the Fibromyalgia Impact Questionnaire (FIQ-PH) and the Pain Disability Index (PDI). The results demonstrated that the Dutch version of the CPCI including the pacing subscale has adequate internal consistency and construct validity. **Moreover, guarding and asking for assistance, but not pacing, were associated with disability.** These findings are in line with fear-avoidance models and suggest that specifically active avoidance behaviours are detrimental in FM. The authors recommend developing cognitive-behavioural and exposure-based interventions and challenge the idea that pacing as an intervention is essential in pain self-management programs.

Pain. 2009 Aug 26

Löfgren M, Norrbrink C

Pain relief in women with fibromyalgia: a cross-over study of superficial warmth stimulation and transcutaneous electrical nerve stimulation

OBJECTIVE: To compare the effects of portable superficial warmth with transcutaneous electrical nerve stimulation on pain in patients with fibromyalgia. **METHODS:** The study had a randomized cross-over design. A total of 32 patients with fibromyalgia were randomly assigned to 2 groups. After instruction, the patients treated themselves using a portable device providing superficial warmth (42 degrees C) or a transcutaneous electrical nerve stimulation [TENS] apparatus. After 3 weeks the patients switched therapy. The patients rated pain intensity on a 0-100 numerical rating scale before and after each treatment. After 6 weeks, patients were questioned concerning therapy preference. **RESULTS:** There was no difference in level of pain relief when comparing the 2 treatment modes. Median pain intensity in patients using warmth therapy decreased from 77.5 on the numerical rating scale before treatment to 62.5 after treatment and in patients using transcutaneous electrical nerve stimulation from 80 to 62.5. Ten patients reported a reduction of 20 units or more on the numerical rating scale after warmth therapy, as did 10 after transcutaneous electrical nerve stimulation. Seventeen of 32 patients preferred warmth therapy and 10 preferred transcutaneous electrical nerve stimulation. **CONCLUSION: Sensory stimulation with superficial warmth or transcutaneous electrical nerve stimulation yielded comparable temporary pain reduction in patients with fibromyalgia.** Both procedures are self-administered, safe and inexpensive.

J Rehabil Med. 2009 Jun; 41(7):557-62

Lombardi VC, Ruscetti FW, Das Gupta J, Pfof MA, Hagen KS, Peterson DL, Ruscetti SK, Bagni RK, Petrow-Sadowski C, Gold B, Dean M, Silverman RH, Mikovits JA

Detection of an infectious retrovirus, XMRV, in blood cells of patients with chronic fatigue syndrome

Chronic fatigue syndrome (CFS) is a debilitating disease of unknown etiology that is estimated to affect 17 million people worldwide. Studying peripheral blood mononuclear cells (PBMCs) from CFS patients, we identified DNA from a human gammaretrovirus, xenotropic murine leukemia virus-related virus (XMRV), in 68 of 101 patients (67%) compared to 8 of 218 (3.7%) healthy controls. Cell culture experiments revealed that patient-derived XMRV is infectious and that both cell-associated and cell-free transmission of the virus are possible. Secondary viral infections were established in uninfected primary lymphocytes and indicator cell lines following exposure to activated PBMCs, B cells, T cells, or plasma derived from CFS patients. These findings raise the possibility that XMRV may be a contributing factor in the pathogenesis of CFS.

Science. 2009 Oct 8. [Epub ahead of print]

Maletic V, Raison CL

Neurobiology of depression, fibromyalgia and neuropathic pain

This article synthesizes recent data suggesting that the high rates of comorbidity observed between major depression, fibromyalgia and neuropathic pain likely result from the fact that these disorders share multiple biological and environmental underpinnings. This perspective suggests that these biologically complex conditions result from similar genetic vulnerabilities interacting with environmental adversity. **Shared genetic determinants include poorly functional alleles regulating monoaminergic, glutamatergic, neurotrophic, opioid and inflammatory cytokine signaling. Chief among environmental risk factors are psychosocial stress and illness**, both of which promote, in vulnerable individuals, relative resistance to glucocorticoids, increased sympathetic/decreased parasympathetic activity and increased production and release of proinflammatory mediators. **Dysregulation of stress/inflammatory pathways promotes alterations in brain circuitry that modulates mood, pain and the stress response.** Over time, these functional changes likely promote disruptions in neurotrophic support and disturbances of glia-neuronal communication. These changes, in turn, have been associated with the related processes of central sensitization in pain disorders and “kindling” in depression, both of which may account for the progressive and self-perpetuating nature of these disorders, especially when inadequately treated.

Front Biosci. 2009; 14:5291–338

Mannerkorpi K, Nordeman L, Ericsson A, Arndorw M; GAU Study Group
Collaborators: Lind M, Melin E, Fredrikson A, Hjerpe M, Holmestrand A, Hjelm M, Enhörning E, Neuman AK, Pehrsson NG

Pool exercise for patients with fibromyalgia or chronic widespread pain: a randomized controlled trial and subgroup analyses

OBJECTIVE: To evaluate the effects of pool exercise in patients with fibromyalgia and chronic widespread pain and to determine characteristics influencing the effects of treatment. **METHODS:** A total of 134 women with fibromyalgia and 32 with chronic widespread pain were randomized to a 20-session pool exercise and a 6-session education programme or to a control group undertaking the same education programme. The primary outcomes were the Fibromyalgia Impact Questionnaire (FIQ) total score and the 6-minute walk test (6MWT). FIQ Pain and other health variables were included. **RESULTS:** The FIQ total ($p = 0.04$) improved in the intervention group, with an effect size of 0.32. Patients who had participated in at least 60% of the exercise sessions improved in the FIQ total (effect size 0.44), the 6MWT (effect size 0.43) and FIQ Pain (effect size 0.69) compared with controls ($p < 0.05$). Long-term follow-up revealed lasting, but small, improvement (effect size < 0.29) in the 6MWT among the active participants ($p < 0.05$). Analyses within the subgroups showed that patients with milder stress, pain or depression improved most by treatment on the FIQ total (effect size > 0.50 , $p < 0.05$) compared with controls. **CONCLUSION: The exercise-education programme showed significant, but small, improvement in health status in patients with fibromyalgia and chronic widespread pain, compared with education only.** Patients with milder symptoms improved most with this treatment.

J Rehabil Med. 2009 Sep; 41(9):751–60

Mease PJ

Further strategies for treating fibromyalgia: the role of serotonin and norepinephrine reuptake inhibitors

Fibromyalgia and associated conditions such as irritable bowel syndrome and temporomandibular disorder involve dysfunctions in central sensitization and pain modulation. Central nervous system dysfunction may also contribute to other symptoms characteristic of fibromyalgia, such as fatigue and sleep disturbance. Two key neurotransmitters in the pain modulation pathway are serotonin and norepinephrine. Preclinical studies using animal models of chronic pain have shown that pharmacologic agents that combine serotonergic and noradrenergic reuptake inhibition, thus augmenting the function of these neurotransmitters, have stronger analgesic effects than agents that inhibit reuptake of either neurotransmitter alone. Although tricyclic antidepressants (TCAs) inhibit reuptake

of both serotonin and norepinephrine and have shown efficacy for the treatment of fibromyalgia, long-term use of these drugs is limited owing to poor tolerability. **Unlike TCAs, the newer dual reuptake inhibitors of serotonin and norepinephrine, such as the drugs approved by the US Food and Drug Administration (FDA) for fibromyalgia, milnacipran and duloxetine, do not possess significant affinity for other neurotransmitter systems, resulting in diminished side effects and enhanced tolerability.** Both duloxetine and milnacipran have shown efficacy in clinical trials by improving pain and other symptoms associated with fibromyalgia. Both compounds inhibit the serotonin and norepinephrine transporters; however, there is a difference in their affinities and selectivity for these transporters. Although duloxetine has affinity for both receptors, it is somewhat more selective for the serotonin transporter. In contrast, milnacipran is somewhat more selective for norepinephrine than serotonin reuptake inhibition. Pharmacologic agents that specifically target serotonin and norepinephrine reuptake may prove to be valuable tools in the treatment of fibromyalgia. (c) 2009 Elsevier Inc.

Am J Med. 2009 Dec; 122(12 Suppl):S44–55

Reichling DB, Levine JD

Critical role of nociceptor plasticity in chronic pain

The transition from acute to chronic pain states might be the most important challenge in research to improve clinical treatment of debilitating pain. **We describe a recently identified mechanism of neuronal plasticity in primary afferent nociceptive nerve fibers (nociceptors) by which an acute inflammatory insult or environmental stressor can trigger long-lasting hypersensitivity of nociceptors to inflammatory cytokines.** This phenomenon, “hyperalgesic priming,” depends on the epsilon isoform of protein kinase C (PKC- ϵ) and a switch in intracellular signaling pathways that mediate cytokine-induced nociceptor hyperexcitability. We discuss the impact of this discovery on our understanding of, and ultimately our ability to treat, a variety of enigmatic and debilitating pain conditions, including those associated with repetitive injury, and generalized pain conditions, such as fibromyalgia.

Trends Neurosci. 2009 Sep 23

Russell IJ, Perkins AT, Michalek JE; Oxybate SXB-26
Fibromyalgia Syndrome Study Group

Collaborators (43): Bennett RM, Price M, Barron A, Evans T, Diab I, Lacombe J, Habros JS, Yatabe H, Holman AJ, Meyers R, Kivitz A, Morrison D, Kopp E, Downs J, Mease P, Granner D, Neiman A, Fanguy D, Nordstrom D, Sturgeon RB, Pappas J, Wilkinson J, Patkar A, Tarter K, Russell J, Haynes W, Seiden D, Rosen F, Sheldon EA, Alabaci M, Silverman SL, Joseph C, Smith NL,

Francisco T, Wallace D, Arnold I, Willis LG, Craddock A, Winfield JB, Bradshaw P, Daughtridge A, Wood P, Warren L

Sodium oxybate relieves pain and improves function in fibromyalgia syndrome: a randomized, double-blind, placebo-controlled, multicenter clinical trial

OBJECTIVE: To evaluate the safety and efficacy of sodium oxybate for management of the symptoms of fibromyalgia syndrome (FMS). **METHODS:** Patients with FMS (according to the American College of Rheumatology 1990 criteria) were randomized, after discontinuing their prestudy medications for FMS, to receive 4.5 gm or 6 gm of sodium oxybate or matching placebo once per night for 8 weeks. The primary outcome variable (POV) was a composite score for changes from baseline in 3 coprimary self-report measures: patient's pain rating (in daily electronic diaries) on a visual analog scale (PVAS), the Fibromyalgia Impact Questionnaire (FIQ) score, and the Patient Global Impression of Change (PGI-C). A beneficial response rate for the POV composite score was defined as $\geq 20\%$ improvement in the PVAS and FIQ scores plus a rating of "much better" or "very much better" on the PGI-C. Secondary measures included subjective sleep outcomes (on the Jenkins Scale for Sleep) and quality-of-life measures. The analyses were based on an intent-to-treat (ITT) population. **RESULTS:** The ITT population included 188 patients with FMS, 78% of whom completed the trial. Significant benefit was observed with both dosages of sodium oxybate, according to changes in the POV and subjective sleep quality. Improvements in the PVAS score were significantly correlated with sleep outcomes. Sodium oxybate was well tolerated overall; dose-related nausea ($\leq 28\%$ of patients) and dizziness ($\leq 18\%$ of patients) tended to resolve with continued therapy. **CONCLUSION:** **Sodium oxybate therapy was well tolerated and significantly improved the symptoms of FMS.** Further study of sodium oxybate as a novel therapeutic option for FMS is warranted.

Arthritis Rheum. 2009 Jan; 60(1):299–309

Russell IJ, Crofford LJ, Leon T, Cappelleri JC, Bushmakin AG, Whalen E, Barrett JA, Sadosky A

The effects of pregabalin on sleep disturbance symptoms among individuals with fibromyalgia syndrome

OBJECTIVES: Sleep disturbances are common in patients with fibromyalgia (FM). The objective of this analysis was to evaluate the effects of pregabalin on sleep in patients with FM. **METHODS:** Analyses were based on two randomized, double-blind, placebo-controlled trials of pregabalin (300mg, 450mg, and 600mg daily) in adult FM patients. Sleep outcomes included the Medical Outcomes Study (MOS) Sleep Scale and a daily diary assessment of sleep quality. Treatment effects were evaluated using analysis of covariance. Clinically important differences (CID) in the Sleep Quality Diary and MOS Sleep Disturbance scores

were estimated using mixed-effects models of changes in scores as a function of patients' global impressions of change. Mediation modeling was used to quantify the direct treatment effects on sleep in contrast to indirect influence of the treatment on sleep via pain. RESULTS: A total of 748 and 745 patients were randomized in the respective studies. Patients were predominantly Caucasian females, average age 48–50 years, on average had FM for 9–10 years, and experienced moderate to severe baseline pain. Pregabalin significantly improved the Sleep Quality Diary ($P < 0.001$), MOS Sleep Disturbance ($P < 0.01$), MOS Quantity of Sleep ($P < 0.003$), and MOS Sleep Problems Index scores ($P < 0.02$) relative to placebo. Treatment effects for the 450mg and 600mg groups exceeded the estimated CID thresholds of 0.83 and 7.9 for the Sleep Quality Diary and MOS Sleep Disturbance scores, respectively. Mediation models indicated that 43–80% of the benefits on sleep (versus placebo) were direct effects of pregabalin, with the remainder resulting from an indirect effect of treatment via pain relief. CONCLUSIONS: **These data demonstrate improvement in FM-related sleep dysfunction with pregabalin therapy. The majority of this benefit was a direct effect of pregabalin on the patients' insomnia, while the remainder occurred through the drug's analgesic activity.**

Sleep Med. 2009 Jun; 10(6):604–10

Schafranski MD, Malucelli T, Machado F, Takeshi H, Kaiber F, Schmidt C, Harth F

Intravenous lidocaine for fibromyalgia syndrome: an open trial

Fibromyalgia is a disorder characterized by chronic widespread pain. In this study, we investigated the effect of intravenous infusions of lidocaine in pain and quality of life of patients with fibromyalgia. Twenty-three consecutive patients were included in the study, which consisted of five sequential intravenous 2% lidocaine infusions with rising dosages (2–5 mg/kg, days 1–5). Fibromyalgia Impact Questionnaire (FIQ), Health Assessment Questionnaire, and a visual analog scale (VAS) for pain were applied before the first lidocaine infusion, immediately after the fifth infusion and 30 days after the fifth infusion. A significant improvement was observed in the FIQ scores after the fifth infusion (73.52 ± 16.56 vs 63.29 ± 21.21, $p = 0.02$), which was maintained after 30 days (73.52 ± 16.56 vs 63.85 ± 24.59, $p = 0.04$). Similar results were seen concerning the VAS: 8.19 ± 1.76 vs 6.84 ± 2.44, $p = 0.01$ and 8.19 ± 1.76 vs 7.17 ± 2.35, $p = 0.05$, respectively. **Intravenous lidocaine infusions are safe and effective in the management of fibromyalgia.**

Clin Rheumatol. 2009 Mar 5

Schneider M, Vernon H, Ko G, Lawson G, Perera J

Chiropractic management of fibromyalgia syndrome: a systematic review of the literature

OBJECTIVE: Fibromyalgia syndrome (FMS) is one of the most commonly diagnosed nonarticular soft tissue conditions in all fields of musculoskeletal medicine, including chiropractic. The purpose of this study was to perform a comprehensive review of the literature for the most commonly used treatment procedures in chiropractic for FMS and to provide evidence ratings for these procedures. The emphasis of this literature review was on conservative and nonpharmaceutical therapies. **METHODS:** The Scientific Commission of the Council on Chiropractic Guidelines and Practice Parameters (CCGPP) was charged with developing literature syntheses, organized by anatomical region, to evaluate and report on the evidence base for chiropractic care. This article is the outcome of this charge. As part of the CCGPP process, preliminary drafts of these articles were posted on the CCGPP Web site www.ccgpp.org (2006–8) to allow for an open process and the broadest possible mechanism for stakeholder input. Online comprehensive literature searches were performed of the following databases: Cochrane Database of Systematic Reviews; National Guidelines Clearinghouse; Cochrane Central Register of Controlled Trials; Manual, Alternative, and Natural Therapy Index System; Index to Chiropractic Literature, Cumulative Index to Nursing and Allied Health Literature; Allied and Complementary Medicine; and PubMed up to June 2006. **RESULTS:** Our search yielded the following results: 8 systematic reviews, 3 meta-analyses, 5 published guidelines, and 1 consensus document. Our direct search of the databases for additional randomized trials did not find any chiropractic randomized clinical trials that were not already included in one or more of the systematic reviews/guidelines. The review of the Manual, Alternative, and Natural Therapy Index System and Index to Chiropractic Literature databases yielded an additional 38 articles regarding various nonpharmacologic therapies such as chiropractic, acupuncture, nutritional/herbal supplements, massage, etc. Review of these articles resulted in the following recommendations regarding nonpharmaceutical treatments of FMS. **Strong evidence supports aerobic exercise and cognitive behavioral therapy. Moderate evidence supports massage, muscle strength training, acupuncture, and spa therapy (balneotherapy). Limited evidence supports spinal manipulation, movement/body awareness, vitamins, herbs, and dietary modification.** **CONCLUSIONS:** Several non-pharmacologic treatments and manual-type therapies have acceptable evidentiary support in the treatment of FMS.

J Manipulative Physiol Ther. 2009 Jan; 32(1):25–40

Solano C, Martinez A, Becerril L, Vargas A, Figueroa J, Navarro C, Ramos-Remus C, Martinez-Lavin M

Autonomic dysfunction in fibromyalgia assessed by the Composite Autonomic Symptoms Scale (COMPASS)

BACKGROUND: It has been suggested that autonomic nervous system dysfunction may explain all of fibromyalgia (FM) multisystem features. Such proposal is based mostly on the results of diverse heart rate variability analyses. The Composite Autonomic Symptom Scale (COMPASS) is a different validated method to recognize dysautonomia. **OBJECTIVES:** The main objective of our study was to investigate symptoms of autonomic dysfunction in FM patients by means of COMPASS. A secondary objective was to define whether there is a correlation between COMPASS and Fibromyalgia Impact Questionnaire (FIQ) scores in FM patients. **METHODS:** Design, analytical cross-sectional study. Our study population included 3 different groups of women: 30 patients with FM, 30 patients with rheumatoid arthritis, and 30 women who considered themselves healthy. All participants filled out COMPASS and FIQ questionnaires. **RESULTS:** FM patients had significantly higher values in all COMPASS domains. COMPASS total score (54.6 +/- 20.9; mean +/- standard deviation) clearly differentiated FM patients from the other 2 groups (21.6 +/- 16.5 and 9.5 +/- 10.2, respectively). $P < 0.0001$. The majority of FM patients gave affirmative answers to questions related to orthostatic, digestive, sleep, sudomotor, or mucosal dysfunction. There was a significant correlation between COMPASS and FIQ scores (Spearman $r = 0.5$, $P < 0.005$). **CONCLUSIONS:** Patients with FM have multiple nonpain symptoms related to different expressions of autonomic dysfunction. **There is a correlation between a questionnaire that measures FM severity (FIQ) and an autonomic dysfunction questionnaire (COMPASS). Such correlation suggests that autonomic dysfunction is inherent to FM.**

J Clin Rheumatol. 2009 Jun; 15(4):172–6

Stahl SM

Fibromyalgia—pathways and neurotransmitters

Fibromyalgia is a syndrome of widespread chronic pain associated with sleep disorders, depressed mood, cognitive impairment and fatigue. Its etiology and pharmacopathology are poorly understood but it is thought to result from a dysfunction of central pain processing mechanisms leading to generalised pain sensitisation. Pain perception is the result of a bidirectional process of ascending and descending pathways. Nociceptive input from peripheral afferent neurons is sent via the dorsal horn of the spinal cord to the higher brain centres involved in pain perception. Some descending inhibitory projections to the spinal cord attenuate the nociceptive effects. Numerous neurotransmitters including serotonin, dopamine, noradrenaline and substance P are involved in these processes. In other neuronal pathways in the brain, the same neurotransmitters are involved in mood

control, sleep regulation and cognitive function, providing a neurochemical substrate for the wide range of symptoms seen in fibromyalgia. **Attenuation of neuronal hyperactivity through ligands acting at the alpha2-delta subunits of voltage-dependent calcium channels and increased inhibitory activity of the descending pathways by inhibition of serotonin and noradrenaline reuptake are two mechanisms that are currently exploited by new medication for the treatment of fibromyalgia.** Copyright (c) 2009 John Wiley & Sons, Ltd.

Hum Psychopharmacol. 2009 Jun; 24 Suppl 1:S11–7

Staud R

Chronic widespread pain and fibromyalgia: two sides of the same coin?

Chronic widespread pain (CWP) is very prevalent in the general population (5%-10%) and is characterized by pain in all four body quadrants, the neck, and back. CWP differs from localized pain not only in its distribution but also in the way it affects lives. Multiple pain sites are associated with higher pain intensity, longer pain duration, and greater disability. Anxiety and depression are more common in CWP patients than among those with localized pain and pain-free controls. Fibromyalgia (FM) has been classified as CWP of more than a 3-month duration, with mechanical hyperalgesia at $>$ or $=$ 11 tender-point sites. FM has been found in 2% to 4% of community subjects and represents the extreme of CWP. **This article compares pain characteristics, quality of life, consequences for daily living, and psychosocial status between FM patients and individuals with CWP.** Available evidence shows that FM is associated with more severe symptoms and consequences for daily life and higher pain severity compared with CWP.

Curr Rheumatol Rep. 2009 Dec; 11(6):433–6

Staud R, Nagel S, Robinson ME, Price DD

Enhanced central pain processing of fibromyalgia patients is maintained by muscle afferent input: A randomized, double-blind, placebo-controlled study

Fibromyalgia (FM) syndrome is characterized by pain and widespread hyperalgesia to mechanical, thermal, and electrical stimuli. Despite convincing evidence for central sensitization of nociceptive pain pathways, the role of peripheral tissue impulse input in the initiation and maintenance of FM is unclear. Therefore this randomized, double-blind, placebo-controlled trial of 22 female normal controls (NCs) and 28 female FM subjects tested the effects of trapezius muscle (TrapM) tender point injections with 1% lidocaine on local pain thresholds as well as on remote heat hyperalgesia at the forearm. Prior to muscle injections

shoulder pain was standardized by tonic mechanical muscle stimulation, resulting in local pain ratings of 4.0+/-0.5 VAS units. Tonic muscle stimulation was interrupted for the TrapM injections but was continued afterwards at the same level. NC as well as FM subjects experienced significant increases of TrapM pressure pain thresholds from lidocaine injections but not from placebo injections ($p < 0.001$). Additionally, heat hyperalgesia of FM participants was significantly reduced at areas remote from the injection site (forearm) by lidocaine but not by placebo ($p = 0.02$). Neither lidocaine nor saline injections significantly affected clinical FM pain ratings, a result most likely due to the very low dose of lidocaine (50mg) used in this trial. Conclusion: Lidocaine injections increased local pain thresholds and decreased remote secondary heat hyperalgesia in FM patients, emphasizing **the important role of peripheral impulse input in maintaining central sensitization in this chronic pain syndrome**; similar to other persistent pain conditions such as irritable bowel syndrome and complex regional pain syndrome.

Pain. 2009 Jun 18

Tandeter H, Grynbaum M, Zuili I, Shany S, Shvartzman P

Serum 25-OH vitamin D levels in patients with fibromyalgia

BACKGROUND: The association between low levels of 25-hydroxyvitamin D and non-specific musculoskeletal pain, including fibromyalgia syndrome, is controversial. Several studies have reported a “positive association” and two others found “no association.” **OBJECTIVES:** To test levels of 25OHD in patients with fibromyalgia syndrome and in matched controls. **METHODS:** The study population comprised 68 premenopausal women with a diagnosis of fibromyalgia and 82 age-matched premenopausal women without. The former were identified from the computerized medical databases of five primary care urban clinics in the south of Israel, and the control subjects were attending the participating clinics for regular periodic blood tests. For each patient, the matched control interview and blood test were performed within a week or two from the patient's interview and blood test, thus controlling for expected seasonal variations. **RESULTS:** Serum 25OHD was measured using different cutoff levels and compared between the groups (< 30 ng/ml, < 20 ng/ml and < 15 ng/ml). No statistically significant differences were found between the groups regardless of the cutoff level used. A logistic regression model for predicting women with 25OHD levels > 20 ng/ml showed that all the variables examined in both groups (age, country of birth, education) were not statistically significant. We found the expected seasonal variations of 25OHD levels, though these were not statistically significant. **CONCLUSIONS:** **We found no association between fibromyalgia and low 25OHD levels as previously suggested in other studies.**

Isr Med Assoc J. 2009 Jun;11(6):339–42

Togo F, Natelson BH, Adler GK, Ottenweller JE, Goldenberg DL, Struzik ZR, Yamamoto Y

Plasma cytokine fluctuations over time in healthy controls and patients with fibromyalgia

We examined the pattern of cytokine secretion across the 24-hr day for women with widespread pain and tenderness having the diagnosis of fibromyalgia (FM) and matched healthy controls. Subjects were given time to habituate to being in a clinical research laboratory environment and then were sampled for cytokines without their being disturbed for a 24-hr period including an 8-hr sleep period. Cytokine levels were uniformly low but characterized by bursts of secretion. Bursting occurred either in singlets or in doublets with a range from 88 to 131 mins between doublet bursts. There was an element of synchronization of these bursts with most occurring at the beginning of sampling. FM patients showed a shift to increased IL-10 in the nighttime compared to controls. The relation between this anti-inflammatory cytokine to the pro-inflammatory cytokines studied also differed between groups: FM patients showed an increased ratio of IL-10 burst amplitude to that of pro-inflammatory cytokines IL-1beta, IL-8, and TNF-alpha. We interpret this to indicate a skew away from the normal balance favoring pro-inflammatory cytokines in controls toward one favoring an anti-inflammatory response in FM. **These changes toward anti-inflammatory predominance in FM may explain the common complaint of disturbed sleep because these cytokines are known to disrupt sleep.**

Exp Biol Med (Maywood). 2009 Feb; 234(2):232–40

Watson NF, Buchwald D, Goldberg J, Noonan C, Ellenbogen RG

Neurologic signs and symptoms in fibromyalgia

OBJECTIVE: To determine the type and frequency of neurologic signs and symptoms in individuals with fibromyalgia (FM). **METHODS:** Persons with FM (n = 166) and pain-free controls (n = 66) underwent systematic neurologic examination by a neurologist blinded to disease status. Neurologic symptoms lasting at least 3 months were assessed with a standard questionnaire. We used logistic regression to evaluate the association of neurologic symptoms and examination findings with FM status. Within the FM group we examined the correlation between self-reported symptoms and physical examination findings. **RESULTS:** Age- and sex-adjusted estimates revealed that compared with the control group, the FM group had significantly more neurologic abnormalities in multiple categories, including greater dysfunction in cranial nerves IX and X (42% versus 8%) and more sensory (65% versus 25%), motor (33% versus 3%), and gait (28% versus 7%) abnormalities. Similarly, the FM group had significantly more neurologic symptoms than the control group in 27 of 29 categories, with the greatest differences observed for photophobia (70% versus 6%), poor balance (63% versus 4%), and weakness (58% versus 2%) and tingling (54% versus 4%)

in the arms or legs. Poor balance or coordination, tingling or weakness in the arms or legs, and numbness in any part of the body correlated with appropriate neurologic examination findings in the FM group. **CONCLUSION:** This blinded, controlled study demonstrated neurologic physical examination findings in persons with FM. **The FM group had more neurologic symptoms than did the controls, with moderate correlation between symptoms and signs.** These findings have implications for the medical evaluation of patients with FM.

Arthritis Rheum. 2009 Sep; 60(9):2839–44

Wilke WS

New developments in the diagnosis of fibromyalgia syndrome: say goodbye to tender points?

The Symptom Intensity Scale score can be used to identify and quantify fibromyalgia syndrome from information supplied by a simple questionnaire. In this paper, the author describes how this test was developed and argues in favor of its use in clinical practice in diagnosing fibromyalgia syndrome.

Cleve Clin J Med. 2009 Jun; 76(6):345–52

Wood PB, Glabus MF, Simpson R, Patterson JC 2nd

Changes in gray matter density in fibromyalgia: correlation with dopamine metabolism

Fibromyalgia (FM) has been associated with alterations in brain morphometry and abnormal dopaminergic neurotransmission. Evidence from preclinical models has demonstrated that dopamine plays a role in promoting neuronal integrity. We therefore sought to confirm previous findings of reduced gray matter density in subjects with FM and to determine whether variations in dopamine metabolism might affect gray matter density. Voxel-based morphometry was used to evaluate anatomical magnetic resonance imaging data from 30 female FM subjects in comparison with 20 age- and gender-matched healthy control subjects. In addition, data from a subset of subjects from both groups who had previously participated in our positron emission tomography study using radiolabeled DOPA (n = 14; 6 FM subjects and 8 control subjects) was used to determine whether correlation might exist between gray matter density and dopamine metabolism. We found a significant reduction in gray matter density within the bilateral parahippocampal gyri, right posterior cingulate cortex, and left anterior cingulate cortex. In addition, a positive correlation was demonstrated between an index of dopamine metabolism from the ventral tegmental area, wherein cell bodies of corticostriatal projection neurons originate, and gray matter density, specifically in the bilateral parahippocampal gyri and left pregenual cortex. The current results confirm our previous findings that FM is associated with altered brain morphometry. Alterations in dopamine metabolism might contribute to the associated

changes in gray matter density. PERSPECTIVE: Fibromyalgia is associated with reductions in gray matter density within brain regions ostensibly involved in phenomena related to the disorder, including enhanced pain perception, cognitive dysfunction, and abnormal stress reactivity. **Given mounting evidence of abnormal dopaminergic neurotransmission associated with the disorder, the strong correlation between dopamine metabolism and gray matter density provides insight as to the pathophysiology that might contribute to these changes.**

J Pain. 2009 Jun; 10(6):609–18