

FIBROMYALGIA: ABSTRACTS 2006 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 2006. The studies were selected from the extensive literature on fibromyalgia so as to cover a wide range of subjects in limited space.

The following studies were published in the period January through September, 2006, and others will be added to this selection at the end of 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.

Bazzichi L, Giannaccini G, Betti L, Italiani P, Fabbrini L, Defeo F, Giacomelli C, Giuliano T, Rossi A, Uccelli A, Giusti L, Mascia G, Lucacchini A, Bombardieri S

Peripheral benzodiazepine receptors on platelets of fibromyalgic patients

OBJECTIVE: The aim of the present study was to analyze if alterations of peripheral-type benzodiazepine receptor (PBR) characteristics occurred in platelet membranes of patients affected by primary fibromyalgia (FM). **DESIGN AND METHODS:** Platelets were obtained from 30 patients with FM. Evaluation of kinetic parameters of PBR was performed using [(3)H] PK11195 as specific radioligand compared with 16 healthy volunteers. **RESULTS:** The results showed a significant increase of PBR binding sites value in platelet membranes from FM patients (B(max) was 5366+/-188 fMol/mg vs. controls, 4193+/-341 fMol/mg, mean+/-SEM) (**p<0.01) but not for affinity value (K(d) was 4.90+/-0.39 nM vs. controls, 4.74+/-0.39 nM, mean+/-SEM) (p>0.05). Symptom severity scores (pain and tiredness) were positively correlated with B(max). **CONCLUSIONS: Our results showed an up-regulation of PBR in platelets of FM patients, and this seems to be related to the severity of fibromyalgic symptoms.**

Clin Biochem. 2006 Sep; 39(9):867-72. Epub 2006 Jul 13

Bennett R, Nelson D

Cognitive behavioral therapy for fibromyalgia

Cognitive behavioral therapy (CBT) techniques offer short-term, goal-oriented psychotherapy. In this respect, it differs from classical psychoanalysis in emphasizing changes in thought patterns and behaviors rather than providing 'deep insight'. Importantly, the beneficial effects of CBT can be achieved in 10-20 sessions, compared with the many years required for classical psychoanalysis. Although CBT is often done on a one-to-one basis, it also lends itself to a group therapeutic setting. CBT was initially used in the treatment of mood disorders, but its use has subsequently been expanded to include various other medical conditions, including chronic pain states. Over the past 18 years, several chronic pain treatment programs have used CBT techniques in the management of fibromyalgia. In this review, the results from 13 programs using CBT, alone or in combination with other treatment modalities, are analyzed. **In most studies, CBT provided worthwhile improvements in pain-related behavior, self-efficacy, coping strategies and overall physical function.** Sustained improvements in pain were most evident when individualized CBT was used to treat patients with juvenile fibromyalgia. The current data indicate that CBT, as a single treatment modality, does not offer any distinct advantage over well-planned group programs of education or exercise, or both. Its role in the management of fibromyalgia patients needs further research.

Nat Clin Pract Rheumatol. 2006 Aug; 2(8):416–24

Burckhardt CS

Multidisciplinary approaches for management of fibromyalgia

Multidisciplinary approaches to fibromyalgia syndrome (FMS) treatment are advocated for treating the complex symptoms and problems confronting many patients. **Exercise and cognitive-behavioral strategies together with patient education commonly comprise the multidisciplinary approach to treatment in clinical trials.** A review of the research literature suggests that **they are effective for decreasing pain and FMS impact and increasing self-efficacy and physical functioning.** Limitations of the current evidence base include a lack of studies that include medication treatment as part of the multidisciplinary approach as well as lack of attention to the diversity of patient psychosocial issues that may interfere with treatment effectiveness. The review recommends that further randomized clinical trials be carried out with subgroups of patients using standardized outcome measurements, adequate treatment length and sufficient length of follow-up to be able to observe and document changes in patient symptoms and behaviors over time.

Curr Pharm Des. 2006; 12(1):59–66

Elvin A, Siosteen AK, Nilsson A, Kosek E

Decreased muscle blood flow in fibromyalgia patients during standardised muscle exercise: a contrast media enhanced colour Doppler study

The aim of the study was to investigate if contrast enhanced ultrasound (US) imaging of muscular blood flow during and following exercise could detect alterations in vascularity in fibromyalgia (FM) patients. Ten FM patients and 10 matched controls were examined with US during standardised static and directly following static and dynamic muscular contractions of the infraspinatus muscle. Doppler ultrasound evaluation was performed before and after the administration of ultrasound contrast media. The FM patients had lower magnitude of muscle vascularity following dynamic ($p<0.001$) and during ($p<0.002$) static exercise compared to controls. The immediate flow response to muscular activity was not only of a lower magnitude, but also of a shorter duration in FM patients following dynamic exercise ($p<0.001$) and during static exercise ($p<0.01$). There were no statistically significant group differences in blood flow intensity or duration following static contraction. In conclusion, contrast enhanced US was found useful to study real-time muscle blood flow changes during and following standardised, low-intensity exercise in FM patients and healthy controls. **Our results support the suggestion that muscle ischemia can contribute to pain in FM, possibly by maintaining the central nervous changes such as central sensitisation/disinhibition. US with contrast can be a new valuable approach to assess muscle perfusion in pain patients during standardised exercise.**

Eur J Pain. 2006 Feb; 10(2):137–44

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

The association between experimental and clinical pain measures among persons with fibromyalgia and chronic fatigue syndrome

Evoked or experimental pain is often used as a model for the study of clinical pain, yet there are little data regarding the relationship between the two. In addition, there are few data regarding the types of stimuli and stimulus intensities that are most closely related to clinical pain. In this study, 36 subjects with fibromyalgia (FM), chronic fatigue syndrome (CFS), or both syndromes were administered measures of clinical pain and underwent a dolorimetry evaluation. Subjects also underwent experimental pain testing utilizing heat and pressure stimulation. Stimulation levels evoking low, moderate and high sensory intensity, and comparable levels of unpleasantness, were determined for both types of stimuli using random staircase methods. Clinical pain was assessed using visual analogue ratings and the short form of the McGill Pain Questionnaire (MPQ).

ratings of heat pain sensation were not significantly associated with clinical pain ratings, with the exception of unpleasantness ratings at high stimulus intensities. Pain threshold and tolerance as assessed by dolorimetry were significantly associated with average measures of clinical pain. Both intensity and unpleasantness ratings of pressure delivered using random staircase methods were significantly associated with clinical pain at low, moderate and high levels, and the strength of the association was greater at increasingly noxious stimulus intensities. **These findings suggest that random pressure stimulation as an experimental pain model in these populations more closely reflects the clinical pain for these conditions.** These findings merit consideration when designing experimental studies of clinical pain associated with FM and CFS.

Eur J Pain. 2006 Mar 16; [Epub ahead of print]

Gusi N, Tomas-Carus P, Hakkinen A, Hakkinen K, Ortega-Alonso A

Exercise in waist-high warm water decreases pain and improves health-related quality of life and strength in the lower extremities in women with fibromyalgia

OBJECTIVE: To evaluate the short- and long-term efficacy of exercise therapy in a warm, waist-high pool in women with fibromyalgia. METHODS: Thirty-four women (mean +/- SD tender points 17 +/- 1) were randomly assigned to either an exercise group (n = 17) to perform 3 weekly sessions of training including aerobic, proprioceptive, and strengthening exercises during 12 weeks, or to a control group (n = 17). Maximal unilateral isokinetic strength was measured in the knee extensors and flexors in concentric and eccentric actions at 60 degrees /second and 210 degrees /second, and in the shoulder abductors and adductors in concentric contractions. Health-related quality of life (HRQOL) was assessed using the EQ-5D questionnaire; pain was assessed on a visual analog scale. All were measured at baseline, posttreatment, and after 6 months. RESULTS: The strength of the knee extensors in concentric actions increased by 20% in both limbs after the training period, and these improvements were maintained after the de-training period in the exercise group. The strength of other muscle actions measured did not change. HRQOL improved by 93% (P = 0.007) and pain was reduced by 29% (P = 0.012) in the exercise group during the training, but pain returned close to the pretraining level during the subsequent de-training. However, there were no changes in the control group during the entire period. CONCLUSION: **The therapy relieved pain and improved HRQOL and muscle strength in the lower limbs at low velocity in patients with initial low muscle strength and high number of tender points.** Most of these improvements were maintained long term.

Arthritis Rheum. 2006 Feb 15; 55(1):66-73

Harris RE, Gracely RH, McLean SA, Williams DA,
Giesecke T, Petzke F, Sen A, Clauw DJ

Comparison of clinical and evoked pain measures in fibromyalgia

Evoked pain measures such as tender point count and dolorimetry are often used to determine tenderness in studies of fibromyalgia (FM). However, these measures frequently do not improve in clinical trials and are known to be influenced by factors other than pain such as distress and expectancy. The purpose of this investigation was to determine whether evoked pain paradigms that present pressure stimuli in a random fashion (eg, Multiple Random Staircase [MRS]) would track with clinical pain improvement in patients with FM better than traditional measures. Sixty-five subjects enrolled in a randomized clinical trial of acupuncture were observed longitudinally. Clinical pain was measured on a 101-point numerical rating scale (NRS) and the Short Form McGill Pain Questionnaire (SF-MPQ), whereas evoked pressure sensitivity was assessed via manual tender point count, dolorimetry, and MRS methods. Improvements in clinical pain and evoked pain were assessed irrespective of group assignment. Improvement was seen in clinical pain during the course of the trial as measured by both NRS ($P = .032$) and SF-MPQ ($P = .001$). The MRS was the only evoked pain measure to improve correspondingly with treatment (MRS, $P = .001$; tender point count and dolorimeter, $P > .05$). MRS change scores were correlated with changes in NRS pain ratings ($P = .003$); however, this association was not stronger than tender point or dolorimetry correlations with clinical pain improvement ($P > .05$). Pain sensitivity as assessed by random paradigms was associated with improvements in clinical FM pain. Sophisticated pain testing paradigms might be responsive to change in clinical trials. **PERSPECTIVE: Trials in fibromyalgia often use both clinical and experimental methods of pain assessment; however, these two outcomes are often poorly correlated.** We explore the relationship between changes in clinical and experimental pain within FM patients. Pressure pain testing that applies stimuli in a random order is associated with improvements in clinical pain, but this association was not stronger than other experimental techniques.

J Pain. 2006 Jul; 7(7):521–7

Hayden RJ, Louis DS, Doro C

Fibromyalgia and myofascial pain syndromes and the workers' compensation environment: an update

Fibromyalgia and myofascial pain syndromes are terms used to describe a constellation of complaints ranging from generalized aches to specific tender trigger points often accompanied by fatigue, depression, and sleep disturbances. In the past 5 years, research has been directed primarily at determining the pathophysiology of fibromyalgia and myofascial pain syndromes and the treatment of

patients' comorbidities to alleviate their symptomatology. **Controversy exists as to whether fibromyalgia and myofascial pain syndromes represent a specific pathology or are merely terms to describe clinical conditions** that provide patients with the reassurance that their symptoms are real and help clinicians with therapeutic direction. In the occupational health setting, this uncertainty can lead to significant difficulty in determining short- and long-term disability and assigning culpability to an individual's work environment.

Clin Occup Environ Med. 2006; 5(2):455–69, x–xi

Katz RS, Wolfe F, Michaud K

Fibromyalgia diagnosis: a comparison of clinical, survey, and American College of Rheumatology criteria

OBJECTIVE: The American College of Rheumatology (ACR) criteria for fibromyalgia are the de facto criteria used for research. However, ACR criteria are not generally utilized by nonrheumatologists, and rheumatologists may diagnose fibromyalgia in patients who do not satisfy the ACR criteria. We undertook this study to determine concordance between ACR criteria and clinician diagnosis and between proposed survey criteria and clinician diagnosis. **METHODS:** Consecutive patients in a clinical practice setting were evaluated by tender point examination, survey criteria for fibromyalgia (Regional Pain Scale score $>$ or $=$ 8 and fatigue score $>$ or $=$ 6), and clinical diagnosis. **RESULTS: Among the 206 patients, the clinician diagnosed fibromyalgia in 49.0%, while 29.1% satisfied ACR criteria and 40.3% satisfied survey criteria.** Clinical and survey criteria were concordant in 74.8% of cases (kappa = 0.49 [95% confidence interval 0.36, 0.60]). Clinical criteria and ACR criteria were concordant in 75.2% of cases (kappa = 0.50 [95% confidence interval 0.35, 0.59]), and survey criteria and ACR criteria were concordant in 72.3% (kappa = 0.40 [95% confidence interval 0.25, 0.51]). The ACR tender point criterion ($>$ or $=$ 11) was not a factor in clinical and survey criteria. However, the tender point count was useful in clinical diagnosis. **CONCLUSION:** Clinical diagnosis and ACR and survey criteria are moderately concordant (72–75%) and address a common pool of symptoms and physical findings. Because there is no gold standard for fibromyalgia diagnosis and because fibromyalgia is often viewed as a trait diagnosis, all methods of diagnosis have utility. **The survey method has the advantage that it does not require physical examination.**

Arthritis Rheum. 2006 Jan; 54(1):169–76

Jackson JL, O'Malley PG, Kroenke K

Antidepressants and cognitive-behavioral therapy for symptom syndromes

Somatic symptoms are common in primary care and clinicians often prescribe antidepressants as adjunctive therapy. There are many possible reasons why this may work, including treating comorbid depression or anxiety, inhibition of ascending pain pathways, inhibition of prefrontal cortical areas that are responsible for "attention" to noxious stimuli, and the direct effects of the medications on the syndrome. There are good theoretical reasons why antidepressants with balanced norepinephrine and serotonin effects may be more effective than those that act predominantly on one pathway, though head-to-head comparisons are lacking. For the 11 painful syndromes review in this article, cognitive-behavioral therapy is most consistently demonstrated to be effective, with various antidepressants having more or less randomized controlled data supporting or refuting effectiveness. **This article reviews the randomized controlled trial data for the use of antidepressant and cognitive-behavior therapy for 11 somatic syndromes: irritable bowel syndrome, chronic back pain, headache, fibromyalgia, chronic fatigue syndrome, tinnitus, menopausal symptoms, chronic facial pain, noncardiac chest pain, interstitial cystitis, and chronic pelvic pain.** For some syndromes, the data for or against treatment effectiveness is relatively robust, for many, however, the data, one way or the other is scanty.

CNS Spectr. 2006 Mar; 11(3):212–22

Lawson K

Emerging pharmacological therapies for fibromyalgia

Fibromyalgia is a chronic pain disorder for which pathophysiological mechanisms are difficult to identify and current drug therapies demonstrate limited effectiveness and significant tolerability. To date, no drugs have been officially approved for the indication of fibromyalgia, and randomized, controlled clinical trials with fibromyalgia patients are taking place to identify potential therapeutic approaches. Although **emerging therapies, such as the antidepressants duloxetine and milnacipran and the antiepileptic pregabalin, offer certain efficacy,** randomized controlled trials are generally difficult due to factors such as a lack of understanding of the pathophysiology and a heterogeneous fibromyalgia patient population. For a significant advance in the drug treatment of fibromyalgia, novel clues are still awaited that may offer an effective therapeutic approach.

Curr Opin Investig Drugs. 2006 Jul; 7(7):631–6

Leavitt F, Katz RS

Distraction as a key determinant of impaired memory in patients with fibromyalgia

OBJECTIVE: Patients with fibromyalgia (FM) frequently complain of poor memory, severe enough to affect job performance and to lead to disability. Yet common practices in neurocognitive examinations often fail to document cognitive abnormalities that match the severity of their memory complaints. Often, neuropsychologists gauge memory competence with measures free of distraction and produce high rates of normality on neurocognitive examination. We hypothesized that neurocognitive tests encoded with a source of stimulus competition that interferes with the processing and/or absorption of information would be better than others in gauging FM memory competence. **METHODS:** Thirty-five patients with FM and 35 controls, matched for age and sex, and presenting with complaints of memory loss, completed cognitive measures with and without stimulus competition. **RESULTS:** Eleven (31.4%) patients with FM showed impairment on at least one measure of memory encoded free of stimulus competition. By comparison, 30 (85.7%) showed impairment on at least one measure encoded with a source of stimulus competition. The Auditory Consonant Trigram detected impairment in 29 (82.6%) cases, and was by far the most sensitive measure. FM patients lost information at a 58% rate following a 9 second distraction. This loss was disproportionate to the loss shown by both age matched controls with memory problems (40%) and to normative values (20%) based on individuals free of memory problems. **CONCLUSION:** The findings validate the perception of failing memory in patients with FM and are the first psychometric based evidence to our knowledge of short-term memory problems in FM linked to interference from a source of distraction. **Adding a source of distraction caused the majority of FM patients to retain new information poorly, and may be integral to an understanding of FM memory problems.** Much needs to be learned about why new information is disproportionately lost by FM populations when a source of distraction enters the experiential field.

J Rheumatol. 2006 Jan; 33(1):127–32

Leo RJ, Brooks VL

Clinical potential of milnacipran, a serotonin and norepinephrine reuptake inhibitor, in pain

Milnacipran is a serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor currently available for use as an antidepressant in several countries. Phase III clinical trials are currently underway to assess its potential role in the treatment of fibromyalgia syndrome, and in pursuit of US Food and Drug Administration approval for this indication. Evidence has accumulated suggesting that in animal models, milnacipran may exert pain-mitigating influences involving NE- and 5-

HT-related processes at supraspinal, spinal and peripheral levels of pain transmission. **Preliminary evidence suggests that milnacipran may be useful in mitigating pain and fatigue associated with fibromyalgia.** However, its role in addressing comorbidities associated with fibromyalgia, including visceral pain and migraine, has yet to be investigated.

Curr Opin Investig Drugs. 2006 Jul; 7(7):637–42

Littlejohn GO, Guymer EK

Fibromyalgia syndrome: which antidepressant drug should we choose?

Fibromyalgia syndrome [FM] has core clinical features of widespread pain and widespread abnormal tenderness. The specific cause of the altered neuro-physiology that underpins these clinical manifestations remains unclear. However, increased sensitisation of neural networks that relates to pain, as well as interacting mechanoreceptors, appear important targets for modulation by pharmacological agents. Further, many FM patients have emotional distress and some are depressed. **Antidepressant agents have therapeutic benefits in FM.** If depression is present antidepressant drugs will provide typical benefits to mood but not always to other key outcome measures, such as pain or tenderness. Selective serotonin receptor reuptake blockers are not as effective for overall FM improvement as drugs that block both serotonin and norepinephrine in a relatively balanced way. Thus tricyclic antidepressants will improve many important FM outcomes but are effective in only about 40 percent of individuals. **Newer agents of this class, such as duloxetine and milnacipran, show improvement in key FM outcomes in about 60 percent of patients.** Longer term studies will indicate the durability of these responses and the overall tolerance of the drugs. Any drug therapy will need to be integrated with appropriate education, exercise and attention to psychological modulatory factors to achieve best results.

Curr Pharm Des. 2006; 12(1):3–9

Lucas HJ, Brauch CM, Settas L, Theoharides TC

Fibromyalgia—new concepts of pathogenesis and treatment

Fibromyalgia (FMS) is a debilitating disorder characterized by chronic diffuse muscle pain, fatigue, sleep disturbance, depression and skin sensitivity. There are no genetic or biochemical markers and patients often present with other comorbid diseases, such as migraines, interstitial cystitis and irritable bowel syndrome. Diagnosis includes the presence of 11/18 trigger points, but many patients with early symptoms might not fit this definition. Pathogenesis is still unknown, but there has been evidence of increased corticotropin-releasing hormone (CRH) and

substance P (SP) in the CSF of FMS patients, as well as increased SP, IL-6 and IL-8 in their serum. Increased numbers of activated mast cells were also noted in skin biopsies. **The hypothesis is put forward that FMS is a neuro-immuno-endocrine disorder where increased release of CRH and SP from neurons in specific muscle sites triggers local mast cells to release proinflammatory and neurosensitizing molecules.** There is no curative treatment although low doses of tricyclic antidepressants and the serotonin-3 receptor antagonist tropisetron, are helpful. Recent nutraceutical formulations containing the natural anti-inflammatory and mast cell inhibitory flavonoid quercetin hold promise since they can be used together with other treatment modalities.

Int J Immunopathol Pharmacol. 2006 Jan–Mar; 19(1):5–10

Mahaney PE, Vu AT, McComas CC, Zhang P, Nogle LM, Watts WL, Sarkahian A, Leventhal L, Sullivan NR, Uveges AJ, Trybulski EJ

Synthesis and activity of a new class of dual acting norepinephrine and serotonin reuptake inhibitors: 3-(1H-indol-1-yl)-3-arylpropan-1-amines

Compounds with a combination of norepinephrine and serotonin reuptake inhibition have been approved in the US and Europe for a number of indications, including major depressive disorder and pain disorders such as diabetic neuropathy and fibromyalgia. Efforts to design selective norepinephrine reuptake inhibitors based on SAR from the aryloxypropanamine series of monoamine reuptake inhibitors have led to the **identification of a potent new class of dual acting norepinephrine and serotonin reuptake inhibitors**, namely the 3-(1H-indol-1-yl)-3-arylpropan-1-amines.

Bioorg Med Chem. 2006 Sep 12; [Epub ahead of print]

Mannerkorpi K, Svantesson U, Broberg C

Relationships between performance-based tests and patients' ratings of activity limitations, self-efficacy, and pain in fibromyalgia.

OBJECTIVE: To investigate the relationship between performance-based tests, ratings of activity limitations, self-efficacy, and pain in fibromyalgia. DESIGN: Descriptive. SETTING: University hospital. PARTICIPANTS: Sixty-nine women with fibromyalgia (mean age, 45+/-7.8y). INTERVENTIONS: Not applicable. MAIN OUTCOME MEASURES: The patients completed 4 performance-based tests focusing on muscle power function and 3 unloaded arm movements. The patients rated their activity limitations by means of the subscales of physical function (PF) and pain on the Fibromyalgia Impact Questionnaire (FIQ), the Medical Outcomes

Study 36-Item Short-Form Health Survey (SF-36), and the Arthritis Self-Efficacy Scale (ASES). Spearman correlation coefficient (ρ) and multivariate regression analysis were conducted. RESULTS: The highest correlations were found between the 6-minute walk test (6MWT) (ρ range, $-.48$ to $.68$) and the activity limitations and between hand grip strength (ρ range, $-.34$ to $.57$) and the activity limitations. The regression analysis indicated that hand grip strength explained 25% of the variation in the SF-36 PF scale. The 6MWT plus endurance of the shoulder muscles explained 24% of the variation in the FIQ PF scale and the 6MWT plus active abduction of the shoulder explained 48% of the variation in the ASES function scale. Correlations between the performance-based tests and the activity limitations tended to be higher than those between performance and pain. CONCLUSIONS: The majority of the performance-based tests and the patients' subjective ratings of activity limitations showed significant relationships. **The 6MWT and hand grip strength, reflecting activity limitations in the SF-36, FIQ, and ASES, are recommended for use in clinical research and in the clinical examination when planning treatment for patients with fibromyalgia.**

Arch Phys Med Rehabil. 2006 Feb; 87(2):259–64

Marinus J, Van Hilten JJ

Clinical expression profiles of complex regional pain syndrome, fibromyalgia and a-specific repetitive strain injury: more common denominators than pain?

PURPOSE: To systematically evaluate and compare the clinical manifestations, disease course, risk factors and demographic characteristics of Complex Regional Pain Syndrome type 1 (CRPS), fibromyalgia (FM) and a-specific Repetitive Strain Injury (RSI). METHOD: A literature search was performed using terms related to the aforementioned topics and diseases. Only original clinical studies that included at least 20 subjects were eligible. RESULTS: Fifty-nine studies on CRPS, 73 on FM and 7 on a-specific RSI were identified. The diseases show similarities in age distribution, male-female ratio, pain characteristics and sensory signs and symptoms. Motor, autonomic and trophic changes are frequently reported in CRPS, but only occasionally in FM and RSI. Systemic symptoms are found in patients with CRPS and FM, and in a subgroup of patients with RSI. In all three disorders, symptoms usually start locally, but may spread to other body regions later, which, in the case of FM, is a prerequisite for diagnosis. Disease onset is always, usually, or occasionally of traumatic origin in RSI, CRPS and FM, respectively. Anxiety and depression are more frequent in patients compared to controls, but probably not very different from patients with other pain conditions or chronic diseases. CONCLUSIONS: **Apart from some obvious differences between CRPS, FM and RSI, the similarities are conspicuous. The common features of CRPS, FM and a-specific RSI may suggest that a common pathway is involved**, but until patients with these types of symptoms are assessed with a

uniform assessment procedure, a thorough comparison cannot be made. A systematic evaluation of patients with a suspected diagnosis of CRPS, FM or RSI, may lead to a better appreciation of the differences and similarities in these diseases and help to unravel the underlying mechanisms.

Disabil Rehabil. 2006 Mar 30; 28(6):351–62

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

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

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

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

McLean SA, Williams DA, Stein PK, Harris RE, Lyden AK, Whalen G, Park KM, Liberzon I, Sen A, Gracely RH, Baraniuk JN, Clauw DJ

Cerebrospinal fluid corticotropin-releasing factor concentration is associated with pain but not fatigue symptoms in patients with fibromyalgia

Previous studies have identified stress system dysregulation in fibromyalgia (FM) patients; such dysregulation may be involved in the generation and/or mainten-

ance of pain and other symptoms. Corticotropin-releasing factor (CRF) is the principal known central nervous system mediator of the stress response; however, to date no studies have examined cerebrospinal fluid (CSF) CRF levels in patients with FM. The relationship between CSF CRF level, heart rate variability (HRV), and pain, fatigue, and depressive symptoms was examined in patients with FM. Among participants (n=26), CSF CRF levels were associated with sensory pain symptoms ($r=0.574$, $p=0.003$) and affective pain symptoms ($r=0.497$, $p=0.011$), but not fatigue symptoms. **Increased HRV was also strongly associated with increased CSF CRF and FM pain.** In multivariate analyses adjusting for age, sex, and depressive symptoms, the association between CSF CRF and sensory pain symptoms ($t=2.54$, $p=0.027$) persisted. Women with FM who reported a history of physical or sexual abuse had lower CSF CRF levels than women who did not report such a history. **CSF CRF levels are associated with both pain symptoms and variation in autonomic function in FM.** Differences in CSF CRF levels among women with and without a self-reported history of physical or sexual abuse suggest that subgroups of FM patients may exist with different neurobiological characteristics. Further studies are needed to better understand the nature of the association between CSF CRF and pain symptoms in FM.

Neuropsychopharmacology. 2006 Aug 23; [Epub ahead of print]

McNally JD, Matheson DA, Bakowsky VS

The epidemiology of self-reported fibromyalgia in Canada

Fibromyalgia (FM) is a poorly understood condition characterized by chronic diffuse musculoskeletal pain. This study describes the self-reported epidemiology of FM in Canada using data collected from the Canadian Community Health Survey, Cycle 1.1 (2000). FM prevalence rates with corresponding 95 percent confidence intervals were calculated. The Canadian prevalence rate was 1.1 percent with a female-to-male ratio of six to one. In women, rates increased with age up to 65 years, declining thereafter. Data collected on age-at-diagnosis is presented and demonstrates a surprising number of newly diagnosed FM cases among people in their 20s and 30s, signifying that FM is a problem for people of all ages. The association with FM and a number of sub-populations was also investigated. With respect to geography and environment, **the FM prevalence rate in women was shown to be approximately two percent in all Canadian regions except Quebec, where it was 1.1 percent.** Further analysis by language suggested that geographical and cultural differences might best explain this observation. Finally, an association with a number of behavioral and socioeconomic determinants of health, including weight, is presented.

Chronic Dis Can. 2006; 27(1):9–16

Menzies V, Taylor AG, Bourguignon C

Effects of guided imagery on outcomes of pain, functional status, and self-efficacy in persons diagnosed with fibromyalgia

OBJECTIVES: (1) To investigate the effects of a 6-week intervention of guided imagery on pain level, functional status, and self-efficacy in persons with fibromyalgia (FM); and (2) to explore the dose-response effect of imagery use on outcomes. DESIGN: Longitudinal, prospective, two-group, randomized, controlled clinical trial. SETTING AND SUBJECTS: The sample included 48 persons with FM recruited from physicians' offices and clinics in the mid-Atlantic region. INTERVENTION: Participants randomized to Guided Imagery (GI) plus Usual Care intervention group received a set of three audiotaped guided imagery scripts and were instructed to use at least one tape daily for 6 weeks and report weekly frequency of use (dosage). Participants assigned to the Usual Care alone group submitted weekly report forms on usual care. MEASURES: All participants completed the Short-Form McGill Pain Questionnaire (SF-MPQ), Arthritis Self-Efficacy Scale (ASES), and Fibromyalgia Impact Questionnaire (FIQ), at baseline, 6, and 10 weeks, and submitted frequency of use report forms. RESULTS: FIQ scores decreased over time in the GI group compared to the Usual Care group ($p = 0.03$). Ratings of self-efficacy for managing pain ($p = 0.03$) and other symptoms of FM also increased significantly over time ($p < 0.01$) in the GI group compared to the Usual Care group. Pain as measured by the SF-MPQ did not change over time or by group. Imagery dosage was not significant. CONCLUSIONS: **This study demonstrated the effectiveness of guided imagery in improving functional status and sense of self-efficacy for managing pain and other symptoms of FM. However, participants' reports of pain did not change.** Further studies investigating the effects of mind-body interventions as adjunctive self-care modalities are warranted in the fibromyalgia patient population.

J Altern Complement Med. 2006 Jan–Feb; 12(1):23–30

Pamuk ON, Cakir N

The frequency of thyroid antibodies in fibromyalgia patients and their relationship with symptoms

We determined the frequency of thyroid autoantibodies in fibromyalgia (FM) patients and the relationship between FM symptoms and these antibodies. Euthyroid 128 FM patients, 64 rheumatoid arthritis (RA) patients, and 64 healthy control subjects were included in the study. The sociodemographic features and the clinical features of FM patients were determined. By using a visual analog scale, patients were questioned about the severity of FM-related symptoms. All patients were administered with Duke-Anxiety Depression (Duke-AD) scale, the physical function items of the fibromyalgia impact questionnaire scale. Thyroid

autoimmunity was defined as the presence of detectable antithyroglobulin (TgAb) and/or antithyroid peroxidase (TPOAb) antibodies by the immunometric methods. Patients with a connective tissue disorder, hypo- or hyperthyroidism, and patients who had psychiatric treatment within the last 6 months were not included into the study. The frequencies of thyroid autoimmunity in FM (34.4%) and RA (29.7%) patients were significantly higher than controls (18.8%) ($p < 0.05$). Twenty-six (20.3%) FM patients had positive TgAb and 31 (24.2%) had positive TPOAb. When patients with thyroid autoimmunity were compared to others, it was seen that the mean age, the percentage of postmenopausal patients, the frequency of dryness of the mouth, and the percentage of patients with a previous psychiatric treatment were higher in this group ($p < 0.05$). **FM patients had thyroid autoimmunity similar to the frequency in RA and higher than controls.** Age and postmenopausal status seemed to be associated with thyroid autoimmunity in FM patients. The presence of thyroid autoimmunity had no relationship with the depression scores of FM patients.

Clin Rheumatol. 2006 Mar 16; [Epub ahead of print]

Schug SA

Combination analgesia in 2005—a rational approach: focus on paracetamol-tramadol

A multimodal (or balanced) approach to anaesthesia is a familiar concept that offers important benefits in the management of both acute and chronic pain. Rational combinations of analgesic agents with different mechanisms of action can achieve improved efficacy and/or tolerability and safety compared with equianalgesic doses of the individual drugs. Combining different agents also enhances efficacy in complex pain states that involve multiple causes. Combinations of paracetamol plus a weak opioid agent are widely used. One such combination, paracetamol plus tramadol, exploits the well-established complementary pharmacokinetics and mechanisms of action of these two drugs. This combination has demonstrated genuine synergy in animal studies and also combines paracetamol's rapid onset of efficacy with tramadol's prolonged analgesic effect. Numerous studies have confirmed the efficacy and tolerability of paracetamol plus tramadol in both acute and chronic pain. As a single-dose treatment for acute post-operative pain, this combination delivers rapid and sustained pain relief that is greater than either agent alone. There is also extensive evidence for efficacy in the long-term management of chronic pain conditions, including osteoarthritis, low back pain and fibromyalgia. **In the setting of chronic pain, paracetamol plus tramadol has shown sustained efficacy, safety and tolerability for up to 2 years without the development of tolerance.** The efficacy of this combination has been demonstrated as well in respect to reduction of pain intensity and, more importantly, with regard to improvement of function and quality of life and the reduction of disability. Comparative trials have shown

that paracetamol plus tramadol has comparable efficacy to paracetamol plus codeine, but with reduced somnolence and constipation compared with the codeine combination. The paracetamol plus tramadol combination is also free of organ toxicity associated with selective and non-selective non-steroidal anti-inflammatory drugs. Hence, paracetamol plus tramadol offers an effective and well-tolerated alternative to anti-inflammatory drugs or other paracetamol plus weak opioid combinations.

Clin Rheumatol. 2006 Jul; 25 Suppl 7:16–21. Epub 2006 Jun 2

Staud R

Are tender point injections beneficial? The role of tonic nociception in fibromyalgia

Characteristic symptoms of fibromyalgia syndrome (FM) include widespread pain, fatigue, sleep abnormalities, and distress. FM patients show psychophysical evidence for mechanical, thermal, and electrical hyperalgesia. To fulfill FM criteria, the mechanical hyperalgesia needs to be widespread and present in at least 11 out of 18 well-defined body areas (tender points). Peripheral and central abnormalities of nociception have been described in FM and these changes may be relevant for the increased pain experienced by these patients. **Important nociceptor systems in the skin and muscle seem to undergo profound changes in FM patients by yet unknown mechanisms.** These changes may result from the release of algescic substances after muscle or other soft tissue injury. These pain mediators can sensitize important nociceptor systems, including the transient receptor potential channel, vanilloid subfamily member 1 (TRPV1), acid sensing ion channel (ASIC) receptors, and purino-receptors (P2X3). Subsequently, tissue mediators of inflammation and nerve growth factors can excite these receptors and cause substantial changes in pain sensitivity. FM pain is widespread and does not seem to be restricted to tender points (TP). It frequently comprises multiple areas of deep tissue pain (trigger points) with adjacent much larger areas of referred pain. Analgesia of areas of extensive nociceptive input has been found to provide often long lasting local as well as general pain relief. Thus **interventions aimed at reducing local FM pain seem to be effective but need to focus less on tender points but more on trigger points (TrP) and other body areas of heightened pain and inflammation.**

Curr Pharm Des. 2006; 12(1):23–7

Staud R

Biology and therapy of fibromyalgia: pain in fibromyalgia syndrome

Fibromyalgia (FM) pain is frequent in the general population but its pathogenesis is only poorly understood. Many recent studies have emphasized the role of central nervous system pain processing abnormalities in FM, including central sensitization and inadequate pain inhibition. However, increasing evidence points towards peripheral tissues as relevant contributors of painful impulse input that might either initiate or maintain central sensitization, or both. It is well known that **persistent or intense nociception can lead to neuroplastic changes in the spinal cord and brain, resulting in central sensitization and pain.** This mechanism represents a hallmark of FM and many other chronic pain syndromes, including irritable bowel syndrome, temporomandibular disorder, migraine, and low back pain. Importantly, after central sensitization has been established only minimal nociceptive input is required for the maintenance of the chronic pain state. Additional factors, including pain related negative affect and poor sleep have been shown to significantly contribute to clinical FM pain. Better understanding of these mechanisms and their relationship to central sensitization and clinical pain will provide new approaches for the prevention and treatment of FM and other chronic pain syndromes.

Arthritis Res Ther. 2006; 8(3):208. Epub 2006 Apr 24

Wallace DJ

Is there a role for cytokine based therapies in fibromyalgia?

Cytokines are glycoproteins that serve as chemical messengers between cells. They assist in the regulation of cell growth and repair and also have immune modulating properties. Cytokines play a role in diverse clinical processes and phenomena such as fatigue, fever, sleep, pain, stress and aching. **A review of the fibromyalgia literature and related studies suggest that IL-1, IL-6 and IL-8 are dysregulated in the syndrome.** Therapies directed against these cytokines may be of potential importance in the management of fibromyalgia.

Curr Pharm Des. 2006; 12(1):17–22