FIBROMYALGIA: ABSTRACTS 2011
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 2011. The studies were selected from the extensive literature on fibromyalgia so as to cover a wide range of subjects in limited space.

The following studies were published in the period January through December, 2011, and others will be added to this selection at intervals 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 , Williams DA, Hudson JI, Martin SA, Clauw DJ, Crofford LJ, Wang F, Emir B, Lai C, Zablocki R, Mease PJ

Development of responder definitions for fibromyalgia clinical trials

OBJECTIVE: To develop responder definitions for fibromyalgia clinical trials using key symptom and functional domains. METHODS: 24 candidate responder definitions were developed by expert consensus and evaluated in 12 randomized, placebo-controlled fibromyalgia trials of 4 medications. For each definition, treatment effects of the medication compared with placebo were analyzed using the Cochran-Mantel-Haenszel test or Chi Square test. A meta-analysis of the pooled results for the 4 medications established risk ratios to determine the definitions that best favored medication over placebo. RESULTS: **Two definitions performed best in the analyses. Both definitions included ≥ 30% reduction in pain and ≥ 10% improvement in physical function. They differed in that one (FM30 short version) included ≥ 30% improvement in sleep or fatigue, and the other (FM30 long version) required ≥ 30% improvement in 2 of the following symptoms: sleep, fatigue, depression, anxiety, or cognition.** In the analysis of both versions, the response rate was ≥ 15% for each medication and significantly greater than placebo. The risk ratio favoring drug over placebo (95% CI) in the pooled analysis for the FM30 short version was 1.50 (1.24, 1.82), $P \leq 0.0001$; the FM30 long version was 1.60 (1.31, 1.96), $P \leq 0.00001$. CONCLUSION: Among the 24 responder definitions tested, 2 were identified as most sensitive in identifying response to treatment. The identification of responder definitions for fibromyalgia clinical trials that include assessments of key symptom and functional domains may improve the sensitivity of clinical trials to identify meaningful improvements, leading to improved management of fibromyalgia.

Arthritis Rheum. 2011 Sep 27. doi: 10.1002/art.33360. [Epub ahead of print]

Becker S, Schweinhardt P

Dysfunctional neurotransmitter systems in fibromyalgia, their role in central stress circuitry and pharmacological actions on these systems

Fibromyalgia is considered a stress-related disorder, and hypo- as well as hyperactive stress systems (sympathetic nervous system and hypothalamic-pituitary-adrenal axis) have been found. Some observations raise doubts on the view that alterations in these stress systems are solely responsible for fibromyalgia symptoms. **Cumulative evidence points at dysfunctional transmitter systems that may underlie the major symptoms of the condition. In addition, all transmitter systems found to be altered in fibromyalgia influence the body's stress systems.** Since both transmitter and stress systems change during chronic stress, it is conceivable that both systems change in parallel, interact, and contribute to the phenotype of fibromyalgia. As we outline in this paper, subgroups of patients might exhibit varying degrees and types of transmitter dysfunction, explaining differences in symptomatology and contributing to the heterogeneity of fibromyalgia. The finding that not all fibromyalgia patients respond to the same medications, targeting dysfunctional transmitter systems, further supports this hypothesis.

Pain Res Treat. 2012; 2012:741746. Epub 2011 Oct 2

Bennett RM, Goldenberg DL

Fibromyalgia, myofascial pain, tender points and trigger points: splitting or lumping?

Myofascial trigger points (MTPs) have long been a contentious issue in relation to fibromyalgia, and poorly defined pain complaints in general. Can MTPs be reproducibly identified? Do MTPs have valid objective findings, such as spontaneous electromyographic activity, muscle microdialysis evidence for an inflammatory milieu or visualization with newer ultrasound techniques? Is fibromyalgia a syndrome of multiple MTPs, or is focal muscle tenderness a manifestation of central sensitization? **These issues are discussed with relevance to a recent paper reporting that manual palpation of active MTPs elicits the spontaneous pain experienced by fibromyalgia patients.** [See Ge et al. and Giamberardino et al.]

Arthritis Res Ther. 2011 Jun 30; 13(3):117. [Epub ahead of print]

Ceko M, Bushnell MC, Gracely RH

Neurobiology underlying fibromyalgia symptoms

Fibromyalgia is characterized by chronic widespread pain, clinical symptoms that include cognitive and sleep disturbances, and other abnormalities such as increased sensitivity to painful stimuli, increased sensitivity to multiple sensory

modalities, and altered pain modulatory mechanisms. Here we relate experimental findings of fibromyalgia symptoms to anatomical and functional brain changes. Neuroimaging studies show augmented sensory processing in pain-related areas, which, together with gray matter decreases and neurochemical abnormalities in areas related to pain modulation, supports the psychophysical evidence of altered pain perception and inhibition. Gray matter decreases in areas related to emotional decision making and working memory suggest that cognitive disturbances could be related to brain alterations. Altered levels of neurotransmitters involved in sleep regulation link disordered sleep to neurochemical abnormalities. Thus, current evidence supports the view that **at least some fibromyalgia symptoms are associated with brain dysfunctions or alterations, giving the long-held "it is all in your head" view of the disorder a new meaning.**

Pain Res Treat. 2012; 2012:585419. Epub 2011 Oct 27

Choy E, Marshall D , Gabriel ZL, Mitchell SA, Gylee E, Dakin HA

A systematic review and mixed treatment comparison of the efficacy of pharmacological treatments for fibromyalgia

OBJECTIVES: To review the literature on pharmacological treatments for fibromyalgia. METHODS: Relative efficacy was estimated in terms of outcome measures highlighted by the Outcome Measures in Rheumatology Network using a Bayesian mixed treatment comparison (MTC) meta-analysis. Randomized controlled trials reporting treatments for fibromyalgia were identified by systematically reviewing electronic databases (Cochrane Library, Medline, EMBASE; accessed February 2008) and conducting manual bibliographic searches. RESULTS: Forty-five randomized controlled trials met the prespecified inclusion criteria for the systematic review. There were limited robust clinical data for some therapeutic classes (tricyclic antidepressants, analgesics, sedative hypnotics, monoamine oxidase inhibitors) and only 21 studies met the more stringent criteria for inclusion in the MTC. The majority of studies included in the MTC assessed the anticonvulsant pregabalin (n = 5) or the serotonin norepinephrine reuptake inhibitors (SNRIs) duloxetine (n = 3) and milnacipran (n = 3). Licensed doses of pregabalin and duloxetine were significantly ($P < 0.05$) more efficacious than placebo in terms of absolute reduction in pain, number of "responders" (≥30% reduction in pain), or change in Fibromyalgia Impact Questionnaire score (pregabalin 450 mg/d only). There was no significant difference between licensed doses of pregabalin and duloxetine for these outcomes. However licensed doses of pregabalin produced significantly greater improvements in sleep compared with milnacipran (as measured by Medical Outcomes Study Sleep Scale). CONCLUSIONS: **The current study confirms the therapeutic efficacy of pregabalin and the SNRIs, duloxetine and milnacipran, in the treatment of fibromyalgia. Given their different modes of action, combination therapy with pregabalin plus an SNRI should be investigated in future research.**

Semin Arthritis Rheum. 2011 Aug 23. [Epub ahead of print]

Crawford BK, Piault EC, Lai C, Bennett RM

Assessing fibromyalgia-related fatigue: content validity and psychometric performance of the Fatigue Visual Analog Scale in adult patients with fibromyalgia

OBJECTIVES: To document 1) the content validity and 2) measure improvements in fatigue, using the Fatigue Visual Analogue Scale (VAS) assessment tool in patients with fibromyalgia. METHODS: The relevance and comprehensiveness of the Fatigue VAS were tested through a qualitative analysis of 20 subjects' verbatim transcripts from semi-structured qualitative interviews. Data from two randomised, controller trials in fibromyalgia (n=1121) were used to conduct correlation analyses with the Fatigue and Tiredness items from the Fibromyalgia Impact Questionnaire (FIQ) and the Short Form-36 Vitality scale. Known-groups and cross classification analyses were conducted to demonstrate the ability to measure improvement in fatigue using the Fatigue VAS. RESULTS: All subjects spontaneously reported that fatigue was an important symptom to capture in fibromyalgia. The Fatigue VAS was well understood by most subjects (n=18/20). High correlations (Pearson r>0.75) and good agreement (k>0.66) were found between the Fatigue VAS and the FIQ tiredness items no. 16 and 17 and SF-36™ Vitality scale. In both clinical trials there was a substantial separation of approximately 20 points on the mean change in the Fatigue VAS score between responders (>30% improvement in pain VAS) and non-responders. CONCLUSIONS: Previous studies have confirmed that fatigue is a major component of the fibromyalgia experience. **This current study reports that fibromyalgia patients spontaneously rated fatigue as a highly significant feature of their illness, and supports the use of the Fatigue VAS as a valid questionnaire in fibromyalgia clinical trials.**

Clin Exp Rheumatol. 2011 Jul 14. [Epub ahead of print]

Dharmshaktu P, Tayal V, Kalra BS

Efficacy of antidepressants as analgesics: A review

Persistent pain disorders are usually not adequately alleviated by nonsteroidal anti-inflammatory drugs or other simple analgesics. Use of antidepressants as adjuvant therapy for the control of persistent pain is currently being practiced in disorders such as fibromyalgia, neuropathic pain, rheumatoid conditions, low back pain, and headache. This review describes the various mechanisms of analgesic activity of antidepressants along with their efficacy and tolerability profiles. Meta-analyses and clinical studies of these agents were retrieved through the use of MEDLINE, Google scholar, and Cochrane databases. Antidepressants are effective in both neuropathic and non-neuropathic pain and have diverse mechanisms independent of their antidepressant effects. Tricyclic antidepressants (amitryptiline, nortryptiline, desipramine) are effective compounds in the treatment of neuropathic pain, fibromyalgia, low back pain, and headaches**. Studies are ongoing for the dual serotonin norepinephrine reuptake inhibitors (duloxetine,**

venlafaxine) in several persistent pain conditions and these may be recommended in neuropathic pain, migraines, and fibromyalgia. Evidence suggests that although the analgesic effects of selective serotonin reuptake inhibitors (fluoxetine, paroxetine, citalopram) are limited and inconsistent, yet they have a superior tolerability profile compared with tricyclic antidepressants.

J Clin Pharmacol. 2011 Mar 17. [Epub ahead of print]

Foerster BR, Petrou M, Edden RA, Schmidt-Wilcke T, Lowe SE, Clauw DJ, Harris RE

Reduced insular gamma-aminobutyric acid in fibromyalgia

OBJECTIVE: Recent scientific findings have reinvigorated interest in examining the role of γ-aminobutyric acid (GABA), the major inhibitory central nervous system neurotransmitter, in chronic pain conditions. Decreased inhibitory neurotransmission is a proposed mechanism in the pathophysiology of chronic pain syndromes such as fibromyalgia (FM). The purpose of this study was to test the hypothesis that decreased levels of insular and anterior cingulate GABA would be present in FM patients and the concentration of this neurotransmitter would be correlated with pressure pain thresholds. METHODS: Sixteen FM patients and 17 age- and sex-matched healthy controls underwent pressure pain testing and a 3 Tesla proton magnetic resonance spectroscopy session in which the right anterior insula, right posterior insula, anterior cingulate and occipital cortex were examined at rest. RESULTS: Compared with healthy controls, FM patients had significantly lower levels of GABA in the right anterior insula (mean±SD 1.17±0.24 arbitrary institutional units versus 1.42±0.32 arbitrary institutional units; p=0.016). There was a trend towards increased GABA levels in the anterior cingulate of FM patients versus healthy controls (p=0.06). No significant differences between groups were detected in the posterior insula or occipital cortex (p>0.05 for all comparisons). Within the right posterior insula, higher levels of GABA were positively correlated with pressure pain thresholds for the FM patients (rho=0.63; p=0.02). CONCLUSION: **Diminished inhibitory neurotransmission resulting from lower concentrations of GABA within the right anterior insula may play a role in the pathophysiology of FM and other central pain syndromes.**

Arthritis Rheum. 2011 Sep 13. doi: 10.1002/art.33339. [Epub ahead ofprint]

Ge HY, Wang Y, Fernández-de-Las-Peñas C, Graven-Nielsen T, Danneskiold-Samsøe B, Arendt-Nielsen L

Reproduction of overall spontaneous pain pattern by manual stimulation of active myofascial trigger points in fibromyalgia patients

INTRODUCTION: It has previously been reported that local and referred pain from active myofascial trigger points (MTPs) in the neck and shoulder region contribute to fibromyalgia (FM) pain and that the pain pattern induced from active MTPs can reproduce parts of the spontaneous clinical FM pain pattern. The current study investigated whether the overall FM pain pattern can be reproduced by local and referred pain from active MTPs located in different muscles. METHODS: A spontaneous pain pattern in FM was recorded in 30 FM patients, and 30 healthy subjects served as controls. Local and referred pain patterns induced from active (patients) and latent (controls) MTPs were recorded following manual stimulation. The existence of MTPs was confirmed by intramuscular electromyographical registration of spontaneous electrical activity. RESULTS: Local and referred pain areas induced from key active MTPs in FM were larger than pain areas from latent MTPs in healthy controls ($P < 0.001$), but were similar to the overall spontaneous FM pain area in FM ($P > 0.05$). The induced pain area was positively associated with current spontaneous pain intensity in FM ($P < 0.01$). The locations of key active MTPs in FM patients were found to have latent MTPs in healthy subjects. The muscles containing key active MTPs in FM are often observed in the muscles of extensor digitorum, trapezius, infraspinatus in the upper part of the body and of quadratus lumborum, gluteus medius in the lower part of the body. CONCLUSIONS: The overall spontaneous FM pain pattern can be reproduced by mechanical stimulation of active MTPs located in different muscles, suggesting that fibromyalgia pain is largely composed of pain arising from muscle pain and spasm. **Targeting active MTPs and related perpetuating factors may be an important strategy in FM pain control.**

Arthritis Res Ther. 2011 Mar 22; 13(2):R48. [Epub ahead of print]

Giamberardino MA, Affaitati G, Fabrizio A, Costantini R

Effects of treatment of myofascial trigger points on the pain of fibromyalgia

Myofascial pain syndromes (MPSs) from trigger points (TrPs) and fibromyalgia syndrome (FMS) are common musculoskeletal pain conditions that frequently coexist in the same patients. In recent decades, it has become evident that these entities greatly influence each other's clinical expression. FMS is mainly rooted in the central nervous system, while TrPs have a peripheral origin. However**,** the **nociceptive impulses from TrPs may have significant impact on symptoms of FMS, probably by enhancing the level of central sensitization typical of this condition.** Several attempts have been made to assess the effects of treatment of co-occurring TrPs in FMS. We report the outcomes of these studies showing that local extinction of TrPs in patients with fibromyalgia produces significant relief of FMS pain. Though further studies are needed, these findings suggest that assessment and treatment of concurrent TrPs in FMS should be systematically performed before any specific fibromyalgia therapy is undertaken.

Curr Pain Headache Rep. 2011 May 5. [Epub ahead of print]

Hamnes B, Hauge MI, Kjeken I, Hagen KB

'I have come here to learn how to cope with my illness, not to be cured': A qualitative study of patient expectations prior to a one-week self-management programme

BACKGROUND: Self-management programmes (SMPs) have been developed to help patients with chronic rheumatic diseases to manage their health problems. Patients' expectations prior to treatment are important determinants of outcomes, and should therefore be identified, to ensure that interventions meet the participants' needs. The aim of the present study was to determine participant expectations with respect to a one-week inpatient SMP for those with fibromyalgia (FM) and rheumatoid arthritis (RA). METHODS: A qualitative study consisting of semi-structured interviews was used to explore the expectations of eight participants with FM and eight with RA. The data were analysed using thematic analysis. RESULTS: **The findings show that the participants expected the SMP to be a turning point towards a better future and to empower them to assume more responsibility for their own health and self-care.** They also expected the SMP to facilitate acceptance, help them to gain new knowledge and be a forum in which to share their experience. Participants who were employed assumed that participation in the SMP would help to ensure that they would continue in their jobs. CONCLUSIONS: This qualitative study indicated that identifying expectations prior to an SMP provides important information which has implications for the programme's implementation. Additional themes, such as acceptance of the illness and management of work, should also be included in the programmes and they should focus more on sharing experience.

Musculoskeletal Care. 2011 Jul 20. doi: 10.1002/msc.212. [Epub ahead of print]

Henry DE, Chiodo AE, Yang W

Central nervous system reorganization in a variety of chronic pain states: a review

Chronic pain can develop from numerous conditions and is one of the most widespread and disabling health problems today. Unfortunately, the pathophysiology of chronic pain in most of these conditions, along with consistently effective treatments, remain elusive. However, recent advances in neuroimaging and neurophysiology are rapidly expanding our understanding of these pain syndromes. **It is now clear that substantial functional and structural changes, or plasticity, in the central nervous system (CNS) are associated with many chronic pain syndromes.** A group of cortical and subcortical brain regions, often referred to as the "pain matrix," often show abnormalities on functional imaging studies in persons with chronic pain, even with different pain locations and etiologies. Changes in the motor and sensory homunculus are also seen. Some of these CNS changes return to a normal state with resolution of the pain. It is

hoped that this knowledge will lead to more effective treatments or even new preventative measures. The purpose of this article is to review recent advances in the understanding of the CNS changes associated with chronic pain in a number of clinical entities encountered in the field of physical medicine and rehabilitation. These clinical entities include nonspecific low back pain, fibromyalgia, complex regional pain syndrome, postamputation phantom pain, and chronic pain after spinal cord injury.

PM R. 2011 Dec; 3(12):1116–25

Jones GT, Nicholl BI, McBeth J, Davies KA, Morriss RK, Dickens C, Macfarlane GJ

Role of road traffic accidents and other traumatic events in the onset of chronic widespread pain: Results from a population-based prospective study

OBJECTIVE: To determine the relationship between physically traumatic events and the onset of chronic widespread pain (CWP). METHODS: This was a case-control study nested within a large prospective cohort. CWP was determined, by questionnaire, as per the American College of Rheumatology fibromyalgia classification criteria. Data were also collected on psychological health, health behavior, and sleep problems. Participants without CWP were then followed up at 4 years, and (new-onset) CWP was determined in the same manner. At followup, participants were also asked to report whether they had experienced any of a series of physically traumatic events between baseline and followup. RESULTS: A total of 2,069 individuals (46.6%) participated at followup, and 241 of these individuals (11.6%) reported CWP. More than one-third of the study population reported at least one physically traumatic event; although these individuals were more likely to develop CWP, this relationship was completely attenuated after adjustment for confounding (odds ratio 1.01, 95% confidence interval 0.73–1.40). However, **there was some evidence to suggest that involvement in a road traffic accident, specifically, may confer an increase in the risk of CWP onset.** CONCLUSION: This study provides support for the "at risk" phenotype hypothesis, where individuals characterized by poorer health and psychological variables may be predisposed to develop CWP following a traumatic trigger. However, although this has been seen with road traffic accidents, it is not the case with other events. Future research should examine what is peculiar about an accident, or about one's reaction to it, that confers this increase in the risk of CWP onset.

Arthritis Care Res (Hoboken). 2011 May; 63(5):696–701.

Jones KD, King LA, Mist SD, Bennett RM, Horak FB

Postural control deficits in people with fibromyalgia: a pilot study

INTRODUCTION: Postural instability and falls are increasingly recognized problems in patients with fibromyalgia (FM). The purpose of this study was to determine whether FM patients, compared to age-matched healthy controls (HCs), have differences in dynamic posturography, including sensory, motor, and limits of stability. We further sought to determine whether postural instability is associated with strength, proprioception and lower-extremity myofascial trigger points (MTPs); FM symptoms and physical function; dyscognition; balance confidence; and medication use. Last, we evaluated self-reported of falls over the past six months. METHODS: In this cross-sectional study, we compared middle-aged FM patients and age-matched HCs who underwent computerized dynamic posturography testing and completed the Fibromyalgia Impact Questionnaire-Revised (FIQR) and balance and fall questionnaires. All subjects underwent a neurological and musculoskeletal examination. Descriptive statistics were used to characterize the sample and explore the relationships between variables. The relationships between subjective, clinical and objective variables were evaluated by correlation and regression analyses. RESULTS: Twenty-five FM patients and twenty-seven HCs (combined mean age ± standard deviation (SD): 48.6 ± 9.7 years) completed testing. FM patients scored statistically lower on composite sensory organization tests (primary outcome; $P < 0.010$), as well as with regard to vestibular, visual and somatosensory ratio scores on dynamic posturography. Balance confidence was significantly different between groups, with FM patients reporting less confidence than HCs (mean ± SD: 81.24 ± 19.52 vs. 98.52 ± 2.45; $P < 0.001$). Interestingly, 76% to 84% of FM patients had gastrocnemius and/or anterior tibialis MTPs. Postural stability was best predicted by dyscognition, FIQR score and body mass index. **Regarding falls, 3 (11%) of 27 HCs had fallen only once during the past 6 months, whereas 18 (72%) of 25 FM patients had fallen at least once. Fifteen FM patients (60%) reported falling at least three times in the past six months.** CONCLUSIONS: In this study, we report that middle-aged FM patients have consistent objective sensory deficits on dynamic posturography, despite having a normal clinical neurological examination. Further study is needed to determine prospective fall rates and the significance of lower-extremity MTPs. The development of interventions to improve balance and reduce falls in FM patients may need to combine balance training with exercise and cognitive training.

Arthritis Res Ther. 2011 Aug 2; 13(4):R127. [Epub ahead of print]

Kindler LL, Bennett RM, Jones KD

Central sensitivity syndromes: mounting pathophysiologic evidence to link fibromyalgia with other common chronic pain disorders

The aim of this study was to review emerging data from the fields of nursing, rheumatology, dentistry, gastroenterology, gynecology, neurology, and orthopedics that support or dispute pathophysiologic similarities in pain syndromes studied by each specialty**. A literature search was performed through PubMed and Ovid using the terms fibromyalgia, temporomandibular joint disorder, irritable bowel syndrome, irritable bladder/interstitial cystitis, headache, chronic low back pain, chronic neck pain, functional syndromes, and somatization.** Each term was linked with pathophysiology and/or central sensitization. This paper presents a review of relevant articles with a specific goal of identifying pathophysiologic findings related to nociceptive processing. The extant literature presents considerable overlap in the pathophysiology of these diagnoses. Given the psychosomatic lens through which many of these disorders are viewed, demonstration of evidence-based links supporting shared pathophysiology between these disorders could provide direction to clinicians and researchers working to treat these diagnoses**. "Central sensitivity syndromes" denotes an emerging nomenclature that could be embraced by researchers investigating each of these disorders.** Moreover, a shared paradigm would be useful in promoting cross-fertilization between researchers. Scientists and clinicians could most effectively forward the understanding and treatment of fibromyalgia and other common chronic pain disorders through an appreciation of their shared pathophysiology.

Pain Manag Nurs. 2011 Mar;12(1):15-24. [Epub 2009 Dec 2]

Lee JH, Cho KI, Kim SM, Lee HG, Kim TI

Arterial stiffness in female patients with fibromyalgia and its relationship to chronic emotional and physical stress

BACKGROUND AND OBJECTIVES: In patients with fibromyalgia (FM) syndrome, stress and pain may chronically enhance sympathetic activity, altering cardiovascular responses and inducing the arterial wall-stiffening process. We investigated arterial stiffness in FM patients using pulse wave velocity (PWV) and analyzed whether arterial stiffness was affected by the clinical parameters of FM. SUBJECTS AND METHODS: This study included 108 female FM patients (51.5±8.9 years) without any known cardiovascular diseases and 76 healthy female controls (50.1±8.9 years). FM patients underwent a manual tender point survey for tender point counts, and completed the visual analogue scale (VAS) of pain and fibromyalgia impact questionnaire (FIQ), which were composed of a physical and feel score. Brachial-ankle pulse-wave velocity (baPWV) was measured with an automated device. The study participants were subdivided into 2 groups based on the sum of the FIQ score (group A: FIQ ≥50, group B: <50). RESULTS: Patients with FM had significantly higher baPWV than the controls, and significant increase were noted in baPWV values of group A compared with those of group B. BaPWV showed a significant positive correlation (correlation coefficient=6.83, p=0.022) with severity of disease assessed by FIQ. CONCLUSION: **The patients with FM showed significantly increased arterial**

stiffness, suggesting a pathophysiologic link between FM and endothelial dysfunction. This study provides a basis for clarifying the mechanism by which chronic pain syndrome is associated with an increased risk of vascular stiffness.

Korean Circ J. 2011 Oct; 41(10):596–602. Epub 2011 Oct 31

Lee YC, Nassikas NJ, Clauw DJ

The role of the central nervous system in the generation and maintenance of chronic pain in rheumatoid arthritis, osteoarthritis and fibromyalgia

Pain is a key component of most rheumatologic diseases. In fibromyalgia, the importance of central nervous system pain mechanisms (for example, loss of descending analgesic activity and central sensitization) is well documented. A few studies have also noted alterations in central pain processing in osteoarthritis, and some data, including the observation of widespread pain sensitivity, suggest that central pain-processing defects may alter the pain response in rheumatoid arthritis patients**. When central pain is identified, different classes of analgesics (for example, serotonin-norepinephrine reuptake inhibitors, α2δ ligands) may be more effective than drugs that treat peripheral or nociceptive pain (for example, nonsteroidal anti-inflammatory drugs and opioids).**

Arthritis Res Ther. 2011 Apr 28; 13(2):211 [Epub ahead of print]

Lynch ME, Campbell F

Cannabinoids for treatment of chronic non-cancer pain: a systematic review of randomized trials

Effective therapeutic options for patients living with chronic pain are limited. The pain relieving effect of cannabinoids remains unclear. A systematic review of randomized controlled trials (RCTs) examining cannabinoids in the treatment of chronic non-cancer pain was conducted according to the PRISMA statement update on the QUORUM guidelines for reporting systematic reviews that evaluate health care interventions. Cannabinoids studied included smoked cannabis, oromucosal extracts of cannabis based medicine, nabilone, dronabinol and a novel THC analogue. Chronic non-cancer pain conditions included neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain. Overall the quality of trials was excellent. **Fifteen of the eighteen trials that met the inclusion criteria demonstrated a significant analgesic effect of cannabinoid as compared with placebo and several reported significant improvements in sleep.** There were no serious adverse effects. Adverse effects most commonly reported were generally well tolerated, mild to moderate in severity and led to withdrawal from the studies in only a few cases. Overall there is evidence that cannabinoids are safe and modestly effective in neuropathic pain with preliminary

evidence of efficacy in fibromyalgia and rheumatoid arthritis. The context of the need for additional treatments for chronic pain is reviewed. Further large studies of longer duration examining specific cannabinoids in homogeneous populations are required.

Br J Clin Pharmacol. 2011 Nov; 72(5):735–44.
doi:10.1111/j.1365–125.2011.03970.x.

Lyon P, Cohen M, Quintner J

An evolutionary stress-response hypothesis for chronic widespread pain (fibromyalgia syndrome)

OBJECTIVE. The study aimed to seek a unifying biological basis for the phenomena encompassed in fibromyalgia syndrome (chronic widespread pain and associated morbidities). SETTING. While much progress has been made in the last decade in understanding chronic widespread pain, its pathogenesis remains stubbornly obscure and its treatment difficult. Two themes are gaining currency in the field: that chronic widespread pain is the result of central sensitization of nociception, and that chronic pain is somehow related to activation of a global stress response. DESIGN. In this article we merge these two ideas within the perspective of evolutionary biology to generate a hypothesis about the critical molecular pathway involved in chronic stress response activation, namely substance P and its preferred receptor, neurokinin-1 (NK-1R), which has many empirically testable implications. CONCLUSION. Drawing on diverse findings in neurobiology, immunology, physiology, and comparative biology, **we suggest that the form of central sensitization that leads to the profound phenomenological features of chronic widespread pain is part of a whole-organism stress respons**e, which is evolutionarily conserved, following a general pattern found in the simplest living systems.

Pain Med. 2011 Jun 21. [Epub ahead of print]

Mease PJ, Spaeth M, Clauw DJ, Arnold LM, Bradley LA, Russell I Jon, Kajdasz DK, Walker DJ, Chappell AS

Estimation of minimum clinically important difference for pain in fibromyalgia

OBJECTIVE: To estimate the minimum clinically important difference (MCID) for several pain measures obtained from the Brief Pain Inventory (BPI) for patients with fibromyalgia. METHODS: Data were pooled across 12-week treatment periods from 4 randomized, double-blind, placebo-controlled studies designed to evaluate the safety and efficacy of duloxetine for the treatment of fibromyalgia. Each study enrolled subjects with American College of Rheumatology-defined fibromyalgia who presented with moderate to severe pain. The MCIDs for the BPI

average pain item score and the BPI severity score (the mean of the BPI pain scale values: right now, average, least, and worst), were estimated by anchoring against the Patient Global Impression of Improvement (PGI-I) scale. RESULTS: The anchor-based MCIDs for the BPI average pain item and severity scores were 2.1 and 2.2 points, respectively. These MCIDs correspond to 32.3% and 34.2% reductions from baseline in scores. CONCLUSION: In these analyses, the MCIDs for several pain measures obtained from the BPI were similar, approximately 2 points and corresponded to a 30%–35% improvement from baseline at endpoint. **These findings may be beneficial for use in designing clinical trials in which the BPI is used to evaluate improvements in pain severity**.

Arthritis Care Res (Hoboken). 2011 Feb 10

Mhalla A, Baudic S, Ciampi de Andrade D, Gautron M, Perrot S, Teixeira MJ, Attal N, Bouhassira D

Long-term maintenance of the analgesic effects of transcranial magnetic stimulation in fibromyalgia

We assessed for the first time the long-term maintenance of repetitive transcranial magnetic stimulation (rTMS)-induced analgesia in patients with chronic widespread pain due to fibromyalgia. Forty consecutive patients were randomly assigned, in a double-blind fashion, to 2 groups: one receiving active rTMS (n=20) and the other, sham stimulation (n=20), applied to the left primary motor cortex. The stimulation protocol consisted of 14 sessions: an "induction phase" of 5 daily sessions followed by a “maintenance phase” of 3 sessions a week apart, 3 sessions a fortnight apart, and 3 sessions a month apart. The primary outcome was average pain intensity over the last 24 hours, measured before each stimulation from day 1 to week 21 and at week 25 (1 month after the last stimulation). Other outcomes measured included quality of life, mood and anxiety, and several parameters of motor cortical excitability. Thirty patients completed the study (14 in the sham stimulation group and 16 in the active stimulation group). Active rTMS significantly reduced pain intensity from day 5 to week 25. These analgesic effects were associated with a long-term improvement in items related to quality of life (including fatigue, morning tiredness, general activity, walking, and sleep) and were directly correlated with changes in intracortical inhibition. In conclusion, these results suggest that TMS may be a valuable and safe new therapeutic option in patients with fibromyalgia.

Pain. 2011 Jul; 152(7):1478–85. Epub 2011 Mar 11

Miro E, Lupianez J, Hita E, Martinez MP, Sanchez AI, Buela-Casal G

Attentional deficits in fibromyalgia and its relationships with pain, emotional distress and sleep dysfunction complaints

Cognitive complaints are common among subjects with fibromyalgia (FM). Yet, few studies have been able to document these deficits with cognitive tasks. A main limitation of existing studies is that attention has been broadly defined and the tasks used to measure attention are not designed to cover all the main components of the attentional system. Research on attention has identified three primary functions of attention, known as alerting, orienting and executive functioning. This study used the attentional network test-interactions task to explore whether and which of the three attentional networks are altered in FM. **Results showed that FM patients have impaired executive control (greater interference), reduced vigilance (slower overall reaction time) and greater alertness (higher reduction in errors after a warning cue).** Vigilance and alertness showed several relations with depression, anxiety and sleep quality. Sleep dysfunction was a significant predictor for alertness, whereas there were no significant predictors for vigilance. These findings highlight that the treatment of sleep difficulties in FM patients may help with some of their cognitive complaints.

Psychol Health. 2011 Mar 3:1–16. [Epub ahead of print]

Moldofsky H , Harris HW, Archambault WT, Kwong T, Lederman S

Effects of bedtime very low dose cyclobenzaprine on symptoms and sleep physiology in patients with fibromyalgia: A double-blind randomized placebo-controlled study

OBJECTIVE: To determine the effects of bedtime very low dose (VLD) cyclobenzaprine (CBP) on symptoms and sleep physiology of patients with fibromyalgia (FM), unrefreshing sleep, and the α-nonREM sleep electroencephalographic (EEG) anomaly at screening. METHODS: Of 37 patients with FM in the screened population, 36 were randomized and treated in this 8-week, double-blind, placebo-controlled, dose-escalating study of VLD CBP 1-4 mg at bedtime. We evaluated changes in subjective symptoms including pain, tenderness, fatigue, mood [Hospital Anxiety and Depression Scale (HAD)], and objective EEG sleep physiology (at screening, baseline, and Weeks 2, 4, and 8). RESULTS: In the VLD CBP-treated group (n = 18) over 8 weeks, musculoskeletal pain and fatigue decreased, tenderness improved; total HAD score and the HAD depression subscore decreased; patient-rated and clinician-rated fatigue improved. In the placebo-treated group (n = 18), none of these outcome measures changed significantly. Compared to placebo at 8 weeks, VLD CBP significantly improved pain, tenderness, and the HAD Depression subscore. Analysis of cyclic alternating pattern (CAP) sleep EEG revealed that significantly more subjects in the VLD CBP group than the placebo group had increased nights of restorative sleep in which CAP(A2+A3)/CAP(A1+A2+A3) = CAP(A2+A3(Norm)) ≤ 33%. For VLD CBP-treated subjects, the increase in nights with CAP(A2+A3(Norm)) ≤ 33% was correlated to improvements in fatigue, total HAD score, and HAD depression score. CONCLUSION: **Bedtime VLD CBP treatment improved core FM symptoms.** Nights with CAP(A2+A3(Norm)) ≤ 33% may provide a biomarker for assessing

treatment effects on nonrestorative sleep and associated fatigue and mood symptoms in persons with FM.

J Rheumatol. 2011 Sep 1. [Epub ahead of print]

Moldofsky H, Patcai J

Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study

BACKGROUND: The long term adverse effects of Severe Acute Respiratory Syndrome (SARS), a viral disease, are poorly understood. METHODS: Sleep physiology, somatic and mood symptoms of 22 Toronto subjects, 21 of whom were healthcare workers, (19 females, 3 males, mean age 46.29 yrs.+/- 11.02) who remained unable to return to their former occupation (mean 19.8 months, range: 13 to 36 months following SARS) were compared to 7 healthy female subjects. Because of their clinical similarities to patients with fibromyalgia syndrome (FMS) these post-SARS subjects were similarly compared to 21 drug free female patients, (mean age 42.4 +/- 11.8 yrs.) who fulfilled criteria for fibromyalgia. RESULTS: Chronic post-SARS is characterized by persistent fatigue, diffuse myalgia, weakness, depression, and nonrestorative sleep with associated REM-related apneas/hypopneas, an elevated sleep EEG cyclical alternating pattern, and alpha EEG sleep anomaly. Post-SARS patients had symptoms of pre- and post-sleep fatigue and post-sleep sleepiness that were similar to the symptoms of patients with FMS, and similar to symptoms of patients with chronic fatigue syndrome. Both post-SARS and FMS groups had sleep instability as indicated by the high sleep EEG cyclical alternating pattern rate. The post-SARS group had a lower rating of the alpha EEG sleep anomaly as compared to the FMS patients. The post-SARS group also reported less pre-sleep and post-sleep musculoskeletal pain symptoms. CONCLUSIONS: **The clinical and sleep features of chronic post-SARS form a syndrome of chronic fatigue, pain, weakness, depression and sleep disturbance, which overlaps with the clinical and sleep features of FMS and chronic fatigue syndrome.**

BMC Neurol. 2011 Mar 24; 11(1):37 [Epub ahead of print]

Nijs J, Paul van Wilgen C, Van Oosterwijck J, van Ittersum M, Meeus M

How to explain central sensitization to patients with 'unexplained' chronic musculoskeletal pain: practice guidelines

Central sensitization provides an evidence-based explanation for many cases of 'unexplained' chronic musculoskeletal pain. Prior to commencing rehabilitation in such cases, it is crucial to change maladaptive illness perceptions, to alter maladaptive pain cognitions and to reconceptualise pain. This can be accomplished

by patient education about central sensitization and its role in chronic pain, a strategy known as pain physiology education. Pain physiology education is indicated when: 1) the clinical picture is characterized and dominated by central sensitization; and 2) maladaptive illness perceptions are present. Both are prerequisites for commencing pain physiology education. **Face-to-face sessions of pain physiology education, in conjunction with written educational material, are effective for changing pain cognitions and improving health status in patients with various chronic musculoskeletal pain disorders.** These include patients with chronic low back pain, chronic whiplash, fibromyalgia and chronic fatigue syndrome. After biopsychosocial assessment, pain physiology education comprises first a face-to-face session explaining basic pain physiology and contrasting acute nociception versus chronic pain (Session 1). Written information about pain physiology should be provided as homework in between sessions 1 and 2. The second session can be used to correct misunderstandings, and to facilitate the transition from knowledge to adaptive pain coping during daily life. Pain physiology education is a continuous process initiated during the educational sessions and continued within both the active treatment and during the longer term rehabilitation program. Note: "The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity" as described by Wolfe et al, in Arthritis Care & Research, Vol. 62, No. 5, May 2010, pp. 600-610 have been approved by the American College of Rheumatology (ACR) Board of Directors as Provisional. This signifies that the criteria have been quantitively validated using patient data, but have not undergone validation based on an external data set.

Man Ther. 2011 Oct;16(5):413–8. Epub 2011 May 31

Paul-Savoie E, Potvin S, Daigle K, Normand E, Corbin JF, Gagnon R, Marchand S

A deficit in peripheral serotonin levels in major depressive disorder but not in chronic widespread pain

OBJECTIVES: It has been proposed that serotonin dysfunctions underlie the pathophysiology of various mood disorders (including major depressive disorder, MDD) and chronic pain conditions characterized by deficient pain inhibition, such as fibromyalgia (FM). There are reliable data showing that serotonin disturbances are involved in the pathophysiology of MDD. However, in the case of FM, results published so far are less consistent. Therefore, the current cross-sectional study sought to measure plasma serotonin levels in FM patients, MDD patients, and healthy controls (HC). METHODS: Twenty-nine FM patients, 17 MDD patients, and 57 HC were recruited who did not differ in terms of age, sex, and the presence or absence of a regular menstrual cycle. Plasma samples were analysed with mass spectrometry. RESULTS: Serotonin levels were decreased in MDD patients, relative to FM patients and HC. Post hoc analyses showed that serotonin levels

were decreased in FM patients taking antidepressants, relative to HC, but not in drug-free FM patients. Moreover, serotonin levels were negatively correlated with mood symptoms across groups. DISCUSSION: Our results further confirm that MDD is associated with decreased serotonin levels, but that serotonin levels are not altered in FM per se, and suggest that 5-Hydroxytryptamine is related to mood symptoms in these patient groups. Our results also suggest that the taking of antidepressants is a major confound to consider when studying serotonin functioning in FM. **The long-term use of antidepressants in** FM **may lead to serotonin depletion. Conversely, serotonin depletion may be before the taking of antidepressants in** FM**.**

Clin J Pain. 2011 Mar 16.[Epub ahead of print]

Robinson JP, Theodore BR, Wilson HD, Waldo PG, Turk DC

Determination of fibromyalgia syndrome after whiplash injuries: Methodologic issues

Problems in diagnosing fibromyalgia syndrome (FM) among motor vehicle collision (MVC) patients with whiplash (WL) include the following: the predominance of tender points (TPs) in the neck/shoulder girdle region; the 3-month duration of widespread pain criterion; and, the stability of diagnosis. The present study examined the prevalence of FM in a cohort (N=326) patients with persistent neck pain 3 months after WL injury who were enrolled in a treatment program. Physical examinations were performed at baseline and at the end of treatment. Results indicated that WL patients had a greater proportion of neck/ shoulder girdle TPs, relative to distal TPs. Compared with a matched cohort of treatment-seeking FM patients, WL patients indicated fewer distal TPs (mean=7.3 TPs vs mean=5.6 TPs, P<001), but were equivalent on neck/shoulder girdle TPs (mean=9.0 TPs vs 9.2 TPs, NS). Baseline prevalence of FM for the WL cohort based on ACR criteria was 14% (95% CI=10%-18%), adjusted TP criterion discounting for neck/shoulder tenderness indicated a prevalence of FM of 8% (95% CI=5%–11%). Finally, 63% of patients meeting American College of Rheumatology FM criteria at baseline did not meet this criterion at post-treatment (~6 months after an MVC). In conclusion, present criteria used in determining FM may result in spuriously inflated rates of diagnosis among WL patients because of persistent localized tenderness after an MVC. Furthermore, **the transient nature of FM "symptoms" among WL patients should be taken into account before making a final diagnosis.** The present criteria used in determining fibromyalgia may result in spuriously inflated rates of diagnosis among whiplash patients because of persistent localized tenderness after motor vehicle collisions.

Pain. 2011 Jun; 152(6):1311–6. Epub 2011 Mar 17

Schmidt-Wilcke T, Clauw DJ

Fibromyalgia: from pathophysiology to therapy

Individuals with fibromyalgia generally experience chronic widespread pain, which can be accompanied by further symptoms including fatigue, sleep disturbances, cognitive dysfunction, anxiety and depressive episodes. As the recognition and diagnosis of fibromyalgia has improved, the availability of therapeutic options for patients has increased. Furthermore, research into the neurobiological mechanisms that contribute to the chronic pain and concomitant symptoms experienced by patients with fibromyalgia has advanced our understanding of this debilitating disorder. In this Review, we aim to provide an overview of existing pathophysiological concepts. The roles of biological and psychological stress, genetic factors, and pain and sensory processing in the pathophysiology of fibromyalgia and related conditions are discussed. In addition, **pharmacological treatments, including monoamine modulators, calcium channel modulators and γ-aminobutyric acid modulators, as well as non-pharmacological treatment options are considered.**

Nat Rev Rheumatol. 2011 Jul 19; 7(9):518–27. doi:10.1038/nrrheum.2011.98

Siler AC, Gardner H, Yanit K, Cushman T, McDonagh M

Systematic review of the comparative effectiveness of antiepileptic drugs for fibromyalgia

Fibromyalgia is a difficult-to-treat chronic pain syndrome that affects 2% of the US population. Pregabalin is an antiepileptic recently FDA approved for fibromyalgia treatment. Other antiepileptics have been suggested for treatment. This systematic review examines the relative benefits and harms of antiepileptic drugs in the treatment of fibromyalgia. A literature search was conducted and 8 studies matched criteria (7 studies of pregabalin, 1 of gabapentin). Both drugs reduced mean pain scores more than placebo at a modest rate (pregabalin, 38% to 50%; gabapentin, 51%). In a 6-month trial of pregabalin responders, 32% continued to have response at 6 months, with a mean time to loss of response of 34 days. Compared to placebo, the drugs had similarly high rates of adverse events and withdrawals. Without a head-to-head trial it is not possible to conclude if one antiepileptic is more effective or harmful than the other, although limited evidence suggests potential differences. Future studies must directly compare the drugs, include a more broadly defined population, examine long-term benefits and harms, and include cointerventions. We conclude that **pregabalin and gabapentin are modestly effective for the treatment of fibromyalgia but that their long-term safety and efficacy remain unknown.** PERSPECTIVE: This systematic review evaluates the benefits and harms of using the antiepileptic drugs gabapentin and pregabalin for the treatment of fibromyalgia. Conclusions from this paper can help clinicians to more effectively treat the pain associated with fibromyalgia.

J Pain. 2011 Apr; 12(4):407–15.[Epub 2010 Dec 13]

Sperber AD, Akiva S, Leshno M, Halpern Z, Buskila D

Validation of new symptom-based fibromyalgia criteria for irritable bowel syndrome co-morbidity studies

BACKGROUND/AIMS: There is significant co-morbidity between irritable bowel syndrome (IBS) and fibromyalgia syndrome (FMS). However, FMS is diagnosed by physical examination, which limits the conduct of co-morbidity studies in a large population-based study. The purpose of this study was to determine the diagnostic validity of a new symptom-based criteria in patients with FMS and/or IBS using the American College of Rheumatology (ACR) criteria as a gold standard. METHODS: The study participants consisted of women with FMS (n = 30), IBS (n = 27) and controls (n = 28). A new symptom-based diagnostic criteria for FMS comprised a regional pain scale and a visual analogue scale for fatigue. All subjects underwent a physical examination for FMS (ACR criteria) and structured questionnaires of regional pain scale and visual analogue scale for fatigue. A fibromyalgia intensity score was calculated and thresholds of tenderness were determined by a dolorimeter. RESULTS: The number of participants diagnosed with FMS in the entire study population (n = 85) was 31 by the new criteria. Compared to the ACR, the sensitivity of the new criteria was 82.9%, specificity 96.0%, positive predictive value 93.5% and negative predictive value 88.9%. In addition, the new criteria were useful for the diagnosis of FMS among the subjects with IBS. A fibromyalgia intensity score was significantly correlated with the threshold of tenderness ($r = -0.62$, $P < 0.001$). CONCLUSIONS: **The new symptom-based diagnostic criteria for the diagnosis of FMS can be used in large-scale clinical and epidemiological co-morbidity studies, in which physical examination is unfeasible. Gastroenterologists investigating the effects of co-morbid FMS in IBS patients can use these new criteria with confidence.**

J Neurogastroenterol Motil. 2011 Jan; 17(1):67–72. [Epub 2011 Jan 26]

Staud R

Sodium oxybate for the treatment of fibromyalgia

INTRODUCTION: Gamma-hydroxybutyrate (GHB) is a short-chain fatty acid that is synthesized within the CNS, mostly from its parent compound gamma amino butyric acid (GABA). GHB acts as a neuromodulator/neurotransmitter to affect neuronal activity of other neurotransmitters and so stimulate the release of growth hormone. Its sodium salt (sodium oxybate: SXB) was approved by the Food and Drug Administration (FDA) for the treatment of narcolepsy. SXB has shown to improve disrupted sleep and increase NR3 (slow-wave restorative) sleep in patients with narcolepsy. It is rapidly absorbed and has a plasma half-life of 30–60 min, necessitating twice-nightly dosing. Most of the observed effects of SXB result from binding to GABA-B receptors. AREAS COVERED: Several randomized, controlled trials demonstrated significantly improved fibromyalgia (FM) symptoms with SXB. As seen in narcolepsy trials, SXB improved sleep of FM

patients, increased slow-wave sleep duration as well as delta power, and reduced frequent night-time awakenings. Furthermore, FM pain and fatigue was consistently reduced with nightly SXB over time. Commonly reported adverse events included headache, nausea, dizziness and somnolence. Despite its proven efficacy, SXB did not receive FDA approval for the management of FM in 2010, mostly because of concerns about abuse. EXPERT OPINION: **Insomnia, fatigue and pain are important clinical FM symptoms that showed moderate improvements with SXB in several large, well-designed clinical trials.** Because of the limited efficacy of currently available FM drugs additional treatment options are needed. In particular, drugs like SXB—which belong to a different drug class than other Food and Drug Administration (FDA)-approved FM medications such as pregabalin, duloxetine and milnacipran—would provide a much-needed addition to presently available treatment options. However, the FDA has set the bar high for future SXB re-submissions, with requirements of superior efficacy and improved risk mitigation strategies. **At this time, no future FDA submission of SXB for the fibromyalgia indication is planned.**

Expert Opin Pharmacother. 2011 Jun 16 [Epub ahead of print]

Vierck CJ

A mechanism-based approach to prevention of and therapy for fibromyalgia

Fibromyalgia syndrome (FMS) is characterized by pain referred to deep tissues. Diagnosis and treatment of FMS are complicated by a variable coexistence with regional pain, fatigue, sleep disruption, difficulty with mentation, and depression. The widespread, deep pain of FMS can be a consequence of chronic psychological stress with autonomic dysregulation. **Stress acts centrally to facilitate pain and acts peripherally, via sympathetic vasoconstriction, to establish painful muscular ischemia.** FMS pain, with or without a coexistent regional pain condition, is stressful, setting up a vicious circle of reciprocal interaction. Also, stress interacts reciprocally with systems of control over depression, mentation, and sleep, establishing FMS as a multiple-system disorder. Thus, stress and the ischemic pain it generates are fundamental to the multiple disorders of FMS, and a therapeutic procedure that attenuates stress and peripheral vasoconstriction should be highly beneficial for FMS. Physical exercise has been shown to counteract peripheral vasoconstriction and to attenuate stress, depression, and fatigue and improve mentation and sleep quality. Thus, **exercise can interrupt the reciprocal interactions between psychological stress and each of the multiple-system disorders of FMS.** The large literature supporting these conclusions indicates that exercise should be considered strongly as a first-line approach to FMS therapy.

Pain Res Treat. 2012; 2012:951354. Epub 2011 Oct 2

Walitt B, Fitzcharles MA, Hassett AL, Katz RS, Häuser W, Wolfe F

The longitudinal outcome of fibromyalgia: a study of 1555 patients

OBJECTIVE: To describe the diagnosis status and outcome of patients diagnosed with fibromyalgia (FM) by US rheumatologists. METHODS: We assessed 1555 patients with FM with detailed outcome questionnaires during 11,006 semiannual observations for up to 11 years. At entry, all patients satisfied American College of Rheumatology preliminary 2010 FM criteria modified for survey research. We determined diagnosis status, rates of improvement, responder subgroups, and standardized mean differences (effect sizes) between start and study completion scores of global well-being, pain, sleep problems, and health related quality of life. (QOL) RESULTS: The 5-year improvement rates were pain 0.4 (95% CI 0.2, 0.5), fatigue 0.4 (95% CI 0.2, 0.05), and global 0.0 (95% CI -0.1, 0.1). The standardized mean differences were patient global 0.03 (95% CI -0.02, 0.08), pain 0.22 (95% CI 0.16, 0.28), sleep problems 0.20 (95% CI 0.14, 0.25), physical component summary of the Short-form 36 (SF-36) 0.11 (95% CI -0.14, -0.07), and SF-36 mental component summary 0.03 (95% CI -0.07, 0.02). Patients switched between criteria-positive and criteria-negative states, with 716 patients (44.0%) failing to meet criteria at least once during 4228.5 patient-years (7448 observations). About 10% of patients had substantial improvement and about 15% had moderate improvement of pain. Overall, FM severity worsened in 35.9% and pain in 38.6%. CONCLUSION: Although we found no average clinically meaningful improvement in symptom severity overall, 25% had at least moderate improvement of pain over time. **The result that emerged from this longitudinal study was one of generally continuing high levels of self-reported symptoms and distress for most patients, but a slight trend toward improvement.**

J Rheumatol. 2011 Oct; 38(10):2238– 46. Epub 2011 Jul 15

Wang F, Ruberg SJ, Gaynor PJ, Heinloth AN, Arnold LM

Early improvement in pain predicts pain response at endpoint in patients with fibromyalgia

An unanswered, but clinically important question is whether there are early indicators that a patient might respond to duloxetine treatment for fibromyalgia pain. To address this question, pooled data from 4 double-blind, placebo-controlled trials in duloxetine-treated patients (N = 797) with primary fibromyalgia as defined by the American College for Rheumatology were analyzed. Classification and Regression Tree (CART) analysis was used to determine what level of early pain improvement as measured by the 24-hour average pain severity question on the Brief Pain Inventory (BPI) best predicted later response. The predictor variables tested were 10, 15, 20, 25, and 30% decrease in BPI 24-hour average pain from baseline to Week 1 and Week 2. The results of the CART analysis

showed that for patients with ≥15% improvement in pain at Week 1 and ≥30% improvement at Week 2, the probability of response at 3 months was 75%. For patients with <15% improvement at both Week 1 and Week 2, the probability of not responding at 3 months was 86%. Quantifiable early improvement in pain during the first 2 weeks of treatment with duloxetine was highly predictive of response or nonresponse after 3 months of treatment. PERSPECTIVE: This article presents early indicators that can highly predict later pain response or non-response in fibromyalgia patients treated with duloxetine. **The results may aid clinicians to predict the likelihood of response at 3 months within the first 2 weeks of treatment.**

J Pain. 2011 Oct;12(10):1088–94. Epub 2011 Jul 18

Winkelmann A, Perrot S, Schaefer C, Ryan K, Chandran A, Sadosky A, Zlateva G

Impact of fibromyalgia severity on health economic costs: results from a European cross-sectional study

BACKGROUND: Fibromyalgia (FM) is a chronic disorder characterized by persistent and widespread pain, often accompanied with fatigue, sleep disturbance and other symptoms. FM affects a population mostly of a productive age and is thus associated with significant lost productivity and disability, in addition to healthcare costs for medications and physician office visits. While other studies have examined FM costs in Europe, few, if any, have examined cost by FM severity level. OBJECTIVE: The objective of this study was to examine health resource utilization (HRU) and costs associated with FM in routine clinical practice in France and Germany across disease severity levels. METHODS: A total of 299 patients with FM, previously diagnosed by a rheumatologist, were recruited from physician offices in France and Germany during routine visits. Subjects completed questions about their pain, health-related quality of life, treatment satisfaction, productivity and FM-related out-of-pocket expenses; site staff recorded clinical, treatment and HRU information for the previous 3 months based on a review of medical records. FM severity was defined using subjects' Fibromyalgia Impact Questionnaire (FIQ) total scores. Annual costs from a societal perspective were calculated in €, year 2008 values, and included direct costs (e.g. physician office visits, medications, out-of-pocket expenses) and indirect costs (e.g. missed days of work and lost productivity). The mean annual costs were calculated based on 3-month data. RESULTS: Subjects were reported to have a mean (SD) of 2.9 (1.9) physician office visits in France and 4.9 (3.2) visits in Germany over the past 3 months, corresponding to an average of 11.6 and 19.6 visits a year, respectively. A total of 91% of subjects were receiving prescription medication for their FM. French subjects reported a lower use of anti-inflammatories (39% of subjects) and a higher use of other analgesics (59% of subjects) than German subjects (67% and 34%, respectively). Subjects in full- or part-time employment reported missing a mean (SD) of 2.7 (6.0) days of work due to FM in France and 2.1 (3.8) days in Germany over the last 4 weeks (cor-

responding to 32.4 and 25.2 days of work missed due to FM per year in France and Germany, respectively). In France, total costs were €7900 (direct €910, indirect €6990). In Germany, total costs were €7256 (direct €1765, indirect €5491). A trend of higher total costs was seen as FM severity increased; however, the results were significant (p = 0.003) only for Germany. CONCLUSIONS: FM **imposes a significant economic burden on society. Consistent with other studies,** FM **subjects were found to have substantial costs, over 75% of which were driven by indirect costs from lost productivity. These costs increased as** FM **severity increased, resulting in a more than 200% difference in cost between mild and severe** FM. Overall FM costs were similar between France and Germany; although lost productivity accounted for a higher proportion of costs in France.

Appl Health Econ Health Policy. 2011 Mar 1; 9(2):125–36

Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RS, Mease P, Russell AS, Russell IJ, Winfield JB

Fibromyalgia criteria and severity scales for clinical and epidemiological studies: A modification of the ACR preliminary diagnostic criteria for fibromyalgia

OBJECTIVE: To develop a fibromyalgia (FM) survey questionnaire for epidemiologic and clinical studies using a modification of the 2010 American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia (ACR 2010). We also created a new FM symptom scale to further characterize FM severity. METHODS: The ACR 2010 consists of 2 scales, the Widespread Pain Index (WPI) and the Symptom Severity (SS) scale. We modified these ACR 2010 criteria by eliminating the physician's estimate of the extent of somatic symptoms and substituting the sum of 3 specific self-reported symptoms. We also created a 0–31 FM Symptom scale (FS) by adding the WPI to the modified SS scale. We administered the questionnaire to 729 patients previously diagnosed with FM, 845 with osteoarthritis (OA) or with other noninflammatory rheumatic conditions, 439 with systemic lupus erythematosus (SLE), and 5210 with rheumatoid arthritis (RA). RESULTS: The modified ACR 2010 criteria were satisfied by 60% with a prior diagnosis of FM, 21.1% with RA, 16.8% with OA, and 36.7% with SLE. The criteria properly identified diagnostic groups based on FM severity variables. An FS score $\geq$ 13 best separated criteria+ and criteria- patients, classifying 93.0% correctly, with a sensitivity of 96.6% and a specificity of 91.8% in the study population. CONCLUSION: **A modification to the ACR 2010 criteria will allow their use in epidemiologic and clinical studies without the requirement for an examiner.** The criteria are simple to use and administer, but they are not to be used for self-diagnosis. **The FS may have wide utility beyond the bounds of** FM**, including substitution for widespread pain in epidemiological studies.**

J Rheumatol. 2011 Feb 1. [Epub ahead of print]

Note: "The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity" as described by Wolfe et al, in *Arthritis Care & Research*, Vol. 62, No. 5, May 2010, pp. 600–10 have been approved by the American College of Rheumatology (ACR) Board of Directors as Provisional. This signifies that the criteria have been quantitively validated using patient data, but have not undergone validation based on an external data set.

Wolfe F, Hassett AL, Walitt B, Michaud K

Mortality in fibromyalgia: a study of 8,186 patients over thirty-five years

OBJECTIVE: To determine if mortality is increased among patients diagnosed as having fibromyalgia. METHODS: We studied 8,186 fibromyalgia patients seen between 1974 and 2009 in 3 settings: all fibromyalgia patients in a clinical practice, patients participating in the US National Data Bank for Rheumatic Diseases (NDB), and patients invited to participate in the NDB who refused participation. Internal controls included 10,087 patients with osteoarthritis. Deaths were determined by multiple source communication, and all patients were also screened in the US National Death Index (NDI). We calculated standardized mortality ratios (SMRs) based on age- and sex-stratified US population data, after adjustment for NDI nonresponse. RESULTS: There were 539 deaths, and the overall SMR was 0.90 (95% confidence interval [95% CI] 0.61–1.26). Among 1,665 clinic patients, the SMR was 0.92 (95% CI 0.81–1.05). Sensitivity analyses varying the rate of NDI nonidentification did not alter the nonassociation. Adjusted for age and sex, the hazard ratio for fibromyalgia compared with osteoarthritis was 1.05 (95% CI 0.94–1.17). The standardized mortality odds ratio (OR) compared with the US general population was increased for suicide (OR 3.31, 95% CI 2.15–5.11) and for accidental deaths (OR 1.45, 95% CI 1.02–2.06), but not for malignancy. CONCLUSION**: Mortality does not appear to be increased in patients diagnosed with fibromyalgia, but the risk of death from suicide and accidents was increased.**

Arthritis Care Res (Hoboken). 2011 Jan; 63(1):94–101. [Epub 2010 Jul 26]

Yunus MB

The prevalence of fibromyalgia in other chronic pain conditions

Central sensitivity syndromes (CSS) include fibromyalgia syndrome (FMS), irritable bowel syndrome, temporomandibular disorder, restless legs syndrome, chronic fatigue syndrome, and other similar chronic painful conditions that are based on central sensitization (CS). CSS are mutually associated. In this paper, prevalence of FMS among other members of CSS has been described. **An important recent recognition is an increased prevalence of FMS in other**

chronic pain conditions with structural pathology, for example, rheumatoid arthritis, systemic lupus, ankylosing spondylitis, osteoarthritis, diabetes mellitus, and inflammatory bowel disease. Diagnosis and proper management of FMS among these diseases are of crucial importance so that unwarranted use of such medications as corticosteroids can be avoided, since FMS often occurs when RA or SLE is relatively mild.

Pain Res Treat. 2012; 2012:584573. Epub 2011 Nov 17