FIBROMYALGIA: ABSTRACTS 2010
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 2010. The studies were selected from the extensive literature on fibromyalgia so as to cover a wide range of subjects in limited space.

Abstracts for 2011 will be posted quarterly during the year. Similar collections of abstracts produced annually from 1999 on can be found on the website of the National Fibromyalgia Partnership: www.fmpartnership.org.

The abstracts are arranged in alphabetical order by lead author.

Ablin JN, Buskila D

Emerging therapies for fibromyalgia: an update

IMPORTANCE OF THE FIELD: Fibromyalgia syndrome (FMS) is currently perceived by rheumatologists and pain physicians alike as representing the classic condition of central sensitization. This term has come to denote a condition in which chronic, widespread pain is attributed mainly to an increase in the processing and handling of pain by the CNS. Thus, effective treatment of the pain of FMS must be directed at the function of the CNS. Over recent years, the pharmacological industry has focused increasing attention on this syndrome, leading to the recent approval of three first medications specifically indicated in the treatment of FMS (i.e., pregabalin, duloxetine and milnacipran). Nonetheless, treatment of FMS remains challenging and in many cases incompletely successful. Issues with drug compliance and side effects, as well as limitations of intrinsic effectiveness, hamper the outcome in many cases. Thus, FMS continues to pose a significantly unmet medical need. AREAS COVERED IN THIS REVIEW: **In the current review, we attempt to update readers on novel developments in the FMS over the last 2 years.** We include a discussion of the various pharmacological classes of medications which appear to be of promising potential in this area, including sodium oxybate, dopamine agonists, naltrexone, novel anticonvulsive medications, synthetic cannabinoids, NMDA antagonists and others. WHAT THE READER WILL GAIN: Readers of this review will gain a glimpse into upcoming pharmacological directions in the management of FMS as well as attain an understanding of the mechanisms and pathophysiological pathways which are currently considered targets for drug development in FMS. TAKE HOME MESSAGE: Following the introduction of three medications specifically indicated in the management of FMS over the last 4 years, additional research is actively

leading towards the introduction of new drugs aimed at improving symptoms related to pain and sleep in FMS. Physicians involved in the treatment of FMS patients are required to keep up-to-date on these promising avenues of progress and to be ready to incorporate them into clinical use.

Expert Opin Emerg Drugs. 2010 Sep; 15(3):521–33

Amris K, Jespersen A, Bliddal H

Self-reported somatosensory symptoms of neuropathic pain in fibromyalgia and chronic widespread pain correlate with tender point count and pressure-pain thresholds

Widespread pain and pain hypersensitivity are the hallmark of fibromyalgia, a complex pain condition linked to central sensitization. In this study the painDETECT questionnaire (PDQ), validated to identify neuropathic pain and based on pain quality items, was applied in a cross-sectional sample of patients with chronic widespread pain (CWP). The aims of the study were to assess the patient-reported sensory neuropathic symptoms by PDQ and to correlate these with tender point (TP) count and pressure-pain thresholds. Eighty-one patients (75 F, 6 M) with CWP (ACR-criteria) filled in the PDQ. Manual TP examination was conducted according to ACR guidelines. Computerized cuff pressure algometry was used for the assessment of pressure-pain detection thresholds (PDT, unit: kPa) and pressure-pain tolerance thresholds (PTT, unit: kPa). Mean TP count was 14.32 (range: 2–18), mean PDQ score 22.75 (range: 5–37). Mean PDT was 8.8kPa (range: 2–36) and mean PTT 30.9kPa (range: 4–85). Deep-tissue hyperalgesia was the predominant somatosensory symptom reported in 83%, but other neuropathic symptoms were also frequent, e.g. burning 51% and prickling 47%. Statistically significant correlations were found between PDQ score and TP count: $r=0.35$ ($p<0.01$), and PDQ score and PDT: $r=0.45$ ($p<0.01$), and PTT: $r=0.43$ ($p<0.01$). The study indicates that pain in CWP has neuropathic features, and that the presence and number of tender points are associated with neuropathic pain symptoms. A high mean PDQ score was found to correlate with TP count and pressure-pain thresholds. **The PDQ may become a useful tool assisting in the identification of central sensitization in patients with CWP and in the future diagnostic assessment fibromyalgia**.

Pain. 2010 Sep 9. [Epub ahead of print]

Arnold LM, Clauw D, Wang F, Ahl J, Gaynor PJ, Wohlreich MM

Flexible dosed duloxetine in the treatment of fibromyalgia: A randomized, double-blind, placebo-controlled trial

OBJECTIVE: To investigate the efficacy of flexible dose duloxetine 60-120 mg/day on changes in fibromyalgia (FM) symptoms assessed by the Patient

Global Impression of Improvement (PGI-I) scale. METHODS: Outpatients ≥ 18 years of age who met American College of Rheumatology criteria for FM, and had ≥ 4 score on the Brief Pain Inventory (BPI) average pain item, were randomized to duloxetine (n = 263) or placebo (n = 267) for 24 week double-blind treatment (primary endpoint at Week 12). Key secondary measures included BPI average pain severity, patient-rated scales assessing mood, anxiety, pain, sleep, and stiffness, Clinical Global Impression of Severity (CGI-S), Multidimensional Fatigue Inventory, Cognitive and Physical Functioning Questionnaire, Beck Depression Inventory (BDI), Beck Anxiety Inventory, and Medical Outcome Study Short-Form Health Survey (SF-36). RESULTS: At Week 12, duloxetine-treated patients reported significantly greater global improvement with mean PGI-I scores of 2.8 compared to 3.4 in the placebo group ($p < 0.001$). Significantly more duloxetine-versus placebo-treated patients (57% vs 32%; $p < 0.001$) reported feeling "much" or "very much better" (PGI-I score ≤ 2). There was significantly greater improvement with duloxetine versus placebo treatment in BPI average pain severity, mood (including BDI total), anxiety (patient-rated only), stiffness, CGI-S, fatigue, all SF-36 domains (except role-physical and physical component summary), and being less bothered by pain or sleep difficulties. Treatment-emergent adverse events occurring significantly more frequently with duloxetine included: nausea, headache, constipation, dry mouth, dizziness, diarrhea, and hyperhidrosis. CONCLUSION**: Treatment with duloxetine 60, 90, and 120 mg/day was associated with feeling much better, pain reduction, being less bothered by sleep difficulties, and improvement in mood, stiffness, fatigue and functioning**. (Clinical trial registry NCT00673452)

J Rheumatol. 2010 Sep 15. [Epub ahead of print]

Cook DB, Stegner AJ, Ellingson LD

Exercise alters pain sensitivity in Gulf War veterans with chronic musculoskeletal pain

Since returning from the Persian Gulf, nearly 100,000 veterans of the first Gulf War (GVs) have reported numerous symptoms with no apparent medical explanation. **A primary complaint of these individuals is chronic musculoskeletal pain (CMP)**. CMP symptoms in GVs are similar to those reported by patients with fibromyalgia (FM), but have not received equivalent scientific attention. Exercise research in CMP patients suggests that acute exercise may exacerbate pain while chronic exercise can reduce pain and improve other symptoms. However, the influence of exercise on GVs with CMP is largely unexplored. This study examined the impact of an acute bout of exercise on pain sensitivity in GVs with CMP. Thirty-two GVs (CMP, n = 15; Control, n = 17) were recruited to complete a series of psychophysical assessments to determine pain sensitivity to heat and pressure stimuli before and after exercise. In response to heat-pain stimuli, GVs with CMP reported higher pain intensity and affect ratings than healthy GVs and exhibited a significant increase in ratings following exercise. GVs with CMP rated

exercise as more painful and effortful and were generally more sensitive to heat-pain stimuli than healthy GVs. These results are similar to what has been reported for acute exercise in patients with FM. PERSPECTIVE: Gulf War veterans with CMP perceive exercise as more painful and effortful than healthy GVs and experience increased pain sensitivity following exercise. **These results suggest that similar abnormalities in central nervous system processing of nociceptive information documented in FM may also be occurring in GVs with CMP**.

J Pain. 2010 Aug; 11(8):764–72. Epub 2010 Mar 23

Cordero MD, De Miguel M, Moreno Fernández AM, Carmona López IM, Garrido Maraver J, Cotán D, Gámez Izquierdo L, Bonal P, Campa F, Bullon P, Navas P, Sánchez Alcázar JA

Mitochondrial dysfunction and mitophagy activation in blood mononuclear cells of fibromyalgia patients: implications in the pathogenesis of the disease

INTRODUCTION: Fibromyalgia is a chronic pain syndrome with unknown etiology. Recent studies have shown some evidence demonstrating that oxidative stress may have a role in the pathophysiology of fibromyalgia. However, it is still not clear whether oxidative stress is the cause or the effect of the abnormalities documented in fibromyalgia. Furthermore, the role of mitochondria in the redox imbalance reported in fibromyalgia also is controversial. We undertook this study to investigate the role of mitochondrial dysfunction, oxidative stress, and mitophagy in fibromyalgia. METHODS: We studied 20 patients (2 male, 18 female patients) from the database of the Sevillian Fibromyalgia Association and 10 healthy controls. We evaluated mitochondrial function in blood mononuclear cells from fibromyalgia patients measuring, coenzyme Q10 levels with high-performance liquid chromatography (HPLC), and mitochondrial membrane potential with flow cytometry. Oxidative stress was determined by measuring mitochondrial superoxide production with MitoSOX and lipid peroxidation in blood mononuclear cells and plasma from fibromyalgia patients. Autophagy activation was evaluated by quantifying the fluorescence intensity of LysoTracker Red staining of blood mononuclear cells. Mitophagy was confirmed by measuring citrate synthase activity and electron microscopy examination of blood mononuclear cells. RESULTS: We found reduced levels of coenzyme Q10, decreased mitochondrial membrane potential, increased levels of mitochondrial superoxide in blood mononuclear cells, and increased levels of lipid peroxidation in both blood mononuclear cells and plasma from fibromyalgia patients. Mitochondrial dysfunction was also associated with increased expression of autophagic genes and the elimination of dysfunctional mitochondria with mitophagy. CONCLUSIONS: **These findings may support the role of oxidative stress and mitophagy in the pathophysiology of fibromyalgia.**

Arthritis Res Ther. 2010 Jan 28; 12(1):R17. [Epub ahead of print]

Fontaine KR, Conn L, Clauw DJ

Effects of lifestyle physical activity on perceived symptoms and physical function in adults with fibromyalgia: results of a randomized trial

INTRODUCTION: Although exercise is therapeutic for adults with fibromyalgia (FM), its symptoms often create obstacles that discourage exercise. We evaluated the effects of accumulating at least 30 minutes of self-selected lifestyle physical activity (LPA) on perceived physical function, pain, fatigue, body mass index, depression, tenderness, and the six-minute walk test in adults with FM. METHODS: Eighty-four minimally active adults with FM were randomized to either LPA or a FM education control (FME) group. LPA participants worked toward accumulating 30 minutes of self-selected moderate-intensity LPA, five to seven days per week, while the FME participants received information and support. RESULTS: Seventy-three of the 84 participants (87%) completed the 12-week trial. The LPA group increased their average daily steps by 54%. Compared to FME, the LPA group reported significantly less perceived functional deficits (P = .032) and less pain (P = .006). There were no differences between the groups on the six-minute walk test (P = .067), fatigue, depression, body mass index, or tenderness. CONCLUSIONS**: Accumulating 30 minutes of LPA throughout the day produces clinically relevant changes in perceived physical function and pain in previously minimally active adults with FM.**

Arthritis Res Ther. 2010 Mar 30;12(2):R55. [Epub ahead of print]

Gardner A, Boles RG

Beyond the serotonin hypothesis: Mitochondria, inflammation and neurodegeneration in major depression and affective spectrum disorders

For many years, a deficiency of monoamines including serotonin has been the prevailing hypothesis on depression, yet research has failed to confirm consistent relations between brain serotonin and depression. High degrees of overlapping comorbidities and common drug efficacies suggest that depression is one of a family of related conditions sometimes referred to as the "affective spectrum disorders", and variably including migraine, irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia and generalized anxiety disorder, among many others. **Herein, we present data from many different experimental modalities that strongly suggest components of mitochondrial dysfunction and inflammation in the pathogenesis of depression and other affective spectrum disorders.** The three concepts of monoamines, energy metabolism and inflammatory pathways are inter-related in many complex manners. For example, the

major categories of drugs used to treat depression have been demonstrated to exert effects on mitochondria and inflammation, as well as on monoamines. Furthermore, commonly used mitochondrial-targeted treatments exert effects on mitochondria and inflammation, and are increasingly being shown to demonstrate efficacy in the affective spectrum disorders. We propose that interactions among monoamines, mitochondrial dysfunction and inflammation can inspire explanatory, rather than mere descriptive, models of these disorders.

Prog Neuropsychopharmacol Biol Psychiatry. 2010 Aug 5. [Epub ahead of print]

Geisser ME, Clauw DJ, Strand V, Gendreau RM, Palmer R, Williams DA

Contributions of change in clinical status parameters to Patient Global Impression of Change (PGIC) scores among persons with fibromyalgia treated with milnacipran

Clinical trials on the treatment of pain syndromes have adopted Patient Global Impression of Change (PGIC) as a primary outcome. However, little is known about how change in clinical status influences these ratings. The present study examined relationships between changes in pain, depressed mood, physical functioning, vitality, sleep disturbance, cognitive complaints, and PGIC ratings among 1260 participants with fibromyalgia (FM) who completed one of two trials examining the safety and efficacy of milnacipran. Many of the relationships between change in clinical status and PGIC ratings were stronger among persons who rated themselves as improved (responders) versus those reporting no change or a worsening of their condition (non-responders). Among non-responders, simultaneous regression analysis revealed that greater degrees of depressed mood and pain, and poorer physical function were significantly associated with worse PGIC ratings. Among responders, improvements in pain were significantly associated with better PGIC ratings, along with improvements in vitality, sleep, physical function, and cognitive complaints. These findings underscore the complexity of global ratings in FM patients, and suggest the association between clinical status and PGIC ratings varies as a function of perceived treatment response**. Several domains were associated with PGIC ratings, highlighting the need to assess multiple outcomes in clinical trials of treatments for FM.**

Pain. 2010 May; 149 (2):373–8. Epub 2010 Mar 23

Geenen R, Bijlsma JW

Deviations in the endocrine system and brain of patients with fibromyalgia: cause or consequence of pain and associated features?

The brain and endocrine system are crucial interfaces responding to pathological and psychological processes. This review discusses whether endocrine deviations

and structural and functional changes in the brain are a cause or consequence of fibromyalgia. Studies in patients with fibromyalgia virtually uniformly observed subtle alterations in hypothalamic pituitary adrenal functioning, hyporeactive autonomic nervous system responsiveness to stressors, and structural and functional changes in the brain. Our model proposes that predisposing factors, such as genetic vulnerability and trauma, have led to an alteration of the nociceptive system including several neuroendocrine changes. The resulting pain and associated symptoms, such as sleep disturbance, low fitness, fatigue, stress, and distress, are a cause of new neuroendocrine changes. **The model predicts that favorable neuroendocrine changes are to be expected after successful pharmacological or non-pharmacological interventions that target pain and associated symptoms.**

Ann N Y Acad Sci. 2010 Apr; 1193(1):98–110

Häuser W, Petzke F, Sommer C

Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome

Duloxetine (DLX), milnacipran (MLN), and pregabalin (PGB) are the only drugs licensed by the US Food and Drug Administration (FDA) for fibromyalgia syndrome (FMS). Evidence on the comparative benefits and harms is still accruing. The authors searched MEDLINE, SCOPUS, Cochrane Central Register of Controlled Trials, and sought unpublished data from the databases of FDA, US National Institutes for Health, and Industry through May 2009 for randomized controlled trials. Outcomes of interest were symptom reduction (pain, fatigue, sleep disturbance, depressed mood, reduced health-related quality of life), and adverse events. 17 studies with 7,739 patients met the inclusion criteria. The 3 drugs were superior to placebo except DLX for fatigue, MLN for sleep disturbance, and PGB for depressed mood. Adjusted indirect comparisons indicated no significant differences for 30% pain relief and dropout rates due to adverse events between the 3 drugs. Significant differences in average symptom reduction were found: DLX and PGB were superior to MLN in reduction of pain and sleep disturbances. DLX was superior to MLN and PGB in reducing depressed mood. MLN and PGB were superior to DLX in reducing fatigue. The risk of headache and nausea with DLX and MLN was higher compared with PGB. The risk of diarrhea was higher with DLX compared to MLN and PGB. There is evidence for the short-term (up to 6 months) efficacy of DLX, MLN, and PGB. Differences with regard to the occurrence of the key symptoms of FMS and to drug-specific adverse events may be relevant for the choice of medication. PERSPECTIVE**: This article presents comparative data on the efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome.** The results can help clinicians in choosing medication since the 3 drugs have different effects on the key symptoms of fibromyalgia syndrome and differences in side effects, contraindications, and warnings.

J Pain. 2010 Jun; 11(6):505–21. Epub 2010 Apr 24

Hayes SM, Myhal GC, Thornton JF, Camerlain M, Jamison C, Cytryn KN, Murray S

Fibromyalgia and the therapeutic relationship: Where uncertainty meets attitude

BACKGROUND: Fibromyalgia remains underdiagnosed and suboptimally treated even though it affects an estimated 3.3% of Canadians. The present study examines knowledge and attitudinal challenges affecting optimal care. METHODS: A mixed-methods approach was employed. Discussion groups, semistructured interviews and a quantitative online survey (five-point scale) were conducted (June 2007 to January 2008). Participants included 189 general practitioners (GPs) and 139 specialists (anesthesiologists, neurologists, physiatrists, psychiatrists and rheumatologists) distributed across Canada. Participants included 18 patients to enrich the scope of the findings. RESULTS: GPs reported insufficient knowledge and skill in diagnosing fibromyalgia, with not all believing it to be a diagnosable condition (mean 3.74⁄5). Twenty-three per cent of GPs and 12% of specialists characterized fibromyalgia patients as malingerers. They further reported a lack of knowledge and skill in treating fibromyalgia (mean 2.73⁄5), including the pain, sleep disorders and mood disorders related to the condition (mean 3.32⁄5). Specialists shared these challenges, although to a lesser degree —"We are not trained to treat distress and suffering" (specialist). Attitudinal issues centred around frustration (mean 3.91⁄5) and negative profiling of fibromyalgia patients (mean 3.06⁄5 and 1.99⁄5). CONCLUSIONS: Findings revealed the presence of GP attitudinal and confidence challenges in caring for fibromyalgia patients. **As care of fibromyalgia patients moves to general practices, these fundamental competencies must be addressed to assure that all patients receive the quality of care necessary to manage their disease and to empower physicians to be more professionally effective.** As stated by one patient, "Why are we being penalized for having this disability?"

Pain Res Manag. 2010 Nov-Dec; 15(6):385–91

Howard KJ, Mayer TG, Neblett R, Perez Y, Cohen H, Gatchel RJ

Fibromyalgia syndrome in chronic disabling occupational musculoskeletal disorders: prevalence, risk factors, and posttreatment outcomes

OBJECTIVE: To identify the prevalence, risk factors, and treatment outcomes of patients with chronic disabling occupational musculoskeletal disorders (CDOMD)

who met criteria for fibromyalgia. METHODS: This was a prospective prognostic study of a consecutive cohort of CDOMD patients (n = 449) admitted for treatment. Patients were assessed for chronic widespread pain and fibromyalgia. The measures included demographic, injury-related and occupational information, psychosocial measures, and 1-year work status follow-up. RESULTS: The CDOMD patients with fibromyalgia reported higher-level psychosocial distress. **Women with fibromyalgia were 9.6 times less likely to return to work 1-year posttreatment and, of those who did, were 4.3 times less likely to retain work.** CONCLUSIONS: Of this cohort, 23.2% patients met criteria for fibromyalgia. Patients with fibromyalgia were found to show greater psychosocial distress and significantly poorer rates of work return and work retention 1-year postrehabilitation.

J Occup Environ Med. 2010 Dec; 52(12):1186–91

Hsu MC, Schubiner H, Lumley MA, Stracks JS, Clauw DJ, Williams DA

Sustained pain reduction through affective self-awareness in fibromyalgia: a randomized controlled trial

BACKGROUND AND OBJECTIVE: Affect and how it is regulated plays a role in pain perception, maintenance of pain, and its resolution. This randomized, controlled trial evaluated an innovative affective self-awareness (ASA) intervention, which was designed to reduce pain and improve functioning in individuals with fibromyalgia. PARTICIPANTS AND METHODS: Forty-five women with fibromyalgia were randomized to a manualized ASA intervention (n = 24) or wait-list control (n = 21). The intervention began with a one-time physician consultation, followed by 3 weekly, 2-h group sessions based upon a mind-body model of pain. Sessions focused on structured written emotional disclosure and emotional awareness exercises. Outcomes in both conditions were measured by a blinded assessor at baseline, post-intervention, and 6-month follow-up. MEASURES: The primary outcome was pain severity (Brief Pain Inventory); secondary outcomes included tender-point threshold and physical function (SF-36 Physical Component Summary). Intent-to-treat analyses compared groups on outcomes using analysis of covariance and on the proportion of patients achieving >/=30% and >/=50% pain reduction at 6 months. RESULTS: Adjusting for baseline scores, the intervention group had significantly lower pain severity ($p < 0.001$), higher self-reported physical function ($p < 0.001$), and higher tender-point threshold ($p = 0.02$) at 6 months compared to the control group. From baseline to 6 months, 45.8% of the ASA intervention group had >/=30% reduction in pain severity, compared to none of the controls ($p < 0.001$). CONCLUSIONS: **The affective self-awareness intervention improved pain, tenderness, and self-reported physical function for at least 6 months in women with fibromyalgia compared to wait-list controls.** This study suggests the value of interventions targeting emotional processes

in fibromyalgia, although further studies should evaluate the efficacy of this intervention relative to active controls.

J Gen Intern Med. 2010 Oct; 25(10):1064–70. Epub 2010 Jun 8

Kadetoff D, Kosek E

Evidence of reduced sympatho-adrenal and hypothalamic-pituitary activity during static muscular work in patients with fibromyalgia

OBJECTIVE: To assess activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenocortical axis during static exercise in patients with fibromyalgia. PATIENTS AND METHODS: Sixteen patients with fibromyalgia and 16 healthy controls performed a static knee extension until exhaustion. Plasma catecholamines, adrenocorticotropic hormone and cortisol, as well as blood pressure and heart rate, were assessed before, during and following contraction. Plasma C reactive protein was analysed at baseline. RESULTS: Blood pressure and heart rate increased during contraction ($p < 0.001$) and decreased following contraction ($p < 0.001$) in both groups alike. Compared with baseline, plasma catecholamines increased during contraction in both groups ($p < 0.001$), but patients with fibromyalgia had lower levels of plasma adrenaline ($p < 0.04$) and noradrenaline ($p < 0.08$) at all times. Adrenocorticotropic hormone increased at exhaustion in controls ($p < 0.001$), but not in patients with fibromyalgia, who also had lower adrenocorticotropic hormone at exhaustion ($p < 0.02$) compared with controls. There were no group differences, or changes over time in plasma cortisol. High sensitivity C reactive protein was higher in patients with fibromyalgia compared with controls ($p < 0.02$). CONCLUSION: **Patients with fibromyalgia exhibited a hypoactive sympatho-adrenal system as well as a hypo-reactive hypothalamic-pituitary axis during static exercise.**

J Rehabil Med. 2010 Sep; 42(8):765–72

Kashikar-Zuck S, Johnston M, Ting TV, Graham BT, Lynch-Jordan AM, Verkamp E, Passo M, Schikler KN, Hashkes PJ, Spalding S, Banez G, Richards MM, Powers SW, Arnold LM, Lovell D

Relationship between school absenteeism and depressive symptoms among adolescents with juvenile fibromyalgia

OBJECTIVE: To describe school absences in adolescents with Juvenile Primary Fibromyalgia Syndrome (JPFS) and examine the relationship between school absenteeism, pain, psychiatric symptoms, and maternal pain history. METHODS: Adolescents with JPFS (N = 102; mean age 14.96 years) completed measures of pain and depressive symptoms, and completed a psychiatric interview. Parents provided information about the adolescents' school absences, type of schooling,

and parental pain history. School attendance reports were obtained directly from schools. RESULTS: Over 12% of adolescents with JPFS were homeschooled. Those enrolled in regular school missed 2.9 days per month on average, with one-third of participants missing more than 3 days per month. Pain and maternal pain history were not related to school absenteeism. However, depressive symptoms were significantly associated with school absences. CONCLUSION: **Many adolescents with JPFS experience difficulties with regular school attendance**. Long-term risks associated with school absenteeism and the importance of addressing psychological factors are discussed.

J Pediatr Psychol. 2010 Oct;35(9): 996–1004. Epub 2010 Apr 1

Kool MB, van Middendorp H, Lumley MA, Schenk Y, Jacobs JW, Bijlsma JW, Geenen R

Lack of understanding in fibromyalgia and rheumatoid arthritis: the Illness Invalidation Inventory (3*I)

BACKGROUND: Patients with rheumatic diseases may face "discounting" (denying and patronising) or "lack of understanding" because of having symptoms without external clinical signs, but instruments to assess such invalidation experiences are lacking. OBJECTIVES: To develop and evaluate the Illness Invalidation Inventory (3*I), to compare invalidation experiences of two groups of patients who differ in visual signs and laboratory findings—rheumatoid arthritis (RA) and fibromyalgia—and to examine the association of invalidation with health status. METHODS: A questionnaire (eight items with respect to five sources: spouse, family, medical professionals, work environment and social services) was constructed. It was completed by 142 patients with RA and 167 patients with fibromyalgia. RESULTS: Principal axis factoring with oblimin rotation yielded two factors with high internal consistency (alpha>0.70): "discounting" (five items) and "lack of understanding" (three items). Patients with fibromyalgia experienced significantly more discounting and lack of understanding from their family, medical professionals, colleagues and social services than did patients with RA. Both patient groups experienced more invalidation from social services, colleagues and family than from medical professionals and spouses. More discounting and lack of understanding correlated with poorer mental well-being and social functioning in both patient groups. Discounting correlated with more physical disability and pain in patients with RA. CONCLUSIONS: **The 3*I is a brief, reliable instrument for assessing patients' perceptions of invalidation from different sources, which differ between patient groups and are associated with health status.** Future validation research should clarify the clinical impact of invalidation on treatment adherence and outcome.

Ann Rheum Dis. 2010 May 24. [Epub ahead of print]

Lee YC, Chen PP

A review of SSRIs and SNRIs in neuropathic pain

IMPORTANCE OF THE FIELD: Selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) are becoming increasingly used in the treatment of neuropathic pain and fibromyalgia. However, they are not without adverse effects and their efficacy has not been clear because of conflicting evidence. Areas covered in this review: We have examined the current evidence on the efficacy of SSRIs and SNRIs in the treatment of neuropathic pain and fibromyalgia. Relevant randomized, placebo-controlled studies were identified through a MEDLINE search of English-language literature from January 1990 to December 2009. WHAT THE READER WILL GAIN: The evidence for efficacy of SSRIs in the treatment neuropathic pain is moderate at best. However, SNRIs [such as] venlafaxine and duloxetine have been shown to be effective in the treatment of painful diabetic neuropathy and polyneuropathy. With fibromyalgia, both SSRIs (fluoxetine and paroxetine) and SNRIs (duloxetine and milnacipran) have been shown to improve pain relief, function and quality of life. TAKE HOME MESSAGE: SSRIs and SNRIs may be considered in the treatment of neuropathic pain if treatment with tricyclic antidepressants and anticonvulsants fails, or if there are contraindications to these drugs. **There is also sufficient evidence to indicate that SNRIs are effective in the treatment of fibromyalgia and may be considered early in the treatment of fibromyalgia.**

Expert Opin Pharmacother. 2010 Jul 19. [Epub ahead of print]

Liptan GL

Fascia: A missing link in our understanding of the pathology of fibromyalgia

Significant evidence exists for central sensitization in fibromyalgia, however the cause of this process in fibromyalgia—and how it relates to other known abnormalities in fibromyalgia—remains unclear. Central sensitization occurs when persistent nociceptive input leads to increased excitability in the dorsal horn neurons of the spinal cord. In this hyperexcited state, spinal cord neurons produce an enhanced responsiveness to noxious stimulation, and even to formerly innocuous stimulation. No definite evidence of muscle pathology in fibromyalgia has been found. However, there is some evidence for dysfunction of the intramuscular connective tissue, or fascia, in fibromyalgia. This paper proposes that inflammation of the fascia is the source of peripheral nociceptive input that leads to central sensitization in fibromyalgia. The fascial dysfunction is proposed to be due to inadequate growth hormone production and HPA axis dysfunction in fibromyalgia. Fascia is richly innervated, and the major cell of the fascia, the fibroblast, has been shown to secrete pro-inflammatory cytokines, particularly IL-6, in response to strain. **Recent biopsy studies using immuno-histochemical staining techniques have found increased levels of collagen and inflammatory**

mediators in the connective tissue surrounding the muscle cells in fibromyalgia patients. The inflammation of the fascia is similar to that described in conditions such as plantar fasciitis and lateral epicondylitis, and may be better described as a dysfunctional healing response. This may explain why NSAIDs and oral steroids have not been found effective in fibromyalgia. **Inflammation and dysfunction of the fascia may lead to central sensitization in fibromyalgia.** If this hypothesis is confirmed, it could significantly expand treatment options to include manual therapies directed at the fascia such as Rolfing and myofascial release, and direct further research on the peripheral pathology in fibromyalgia to the fascia.

J Bodyw Mov Ther. 2010 Jan;14(1):3–12

Mannerkorpi K, Nordeman L, Cider A, Jonsson G

Does moderate-to-high intensity Nordic walking improve functional capacity and pain in fibromyalgia? A prospective randomized controlled trial

INTRODUCTION: The objective of this study was to investigate the effects of moderate-to-high intensity Nordic walking (NW) on functional capacity and pain in fibromyalgia (FM). METHODS: A total of 67 women with FM were recruited to the study and randomized either to moderate-to-high intensity Nordic Walking (n = 34, age 48 ± 7.8 years) or to a control group engaging in supervised low-intensity walking (LIW, n = 33, age 50 ± 7.6 years). Primary outcomes were the six-minute walk test (6MWT) and the Fibromyalgia Impact Questionnaire Pain scale (FIQ Pain). Secondary outcomes were: exercise heart rate in a submaximal ergometer bicycle test, the FIQ Physical (activity limitations) and the FIQ total score. RESULTS: A total of 58 patients completed the post-test. Significantly greater improvement in the 6MWT was found in the NW group (P = 0.009), as compared with the LIW group. No between-group difference was found for the FIQ Pain (P = 0.626). A significantly larger decrease in exercise heart rate (P = 0.020) and significantly improved scores on the FIQ Physical (P = 0.027) were found in the NW group as compared with the LIW group. No between-group difference was found for the change in the FIQ total. The effect sizes were moderate for the above mentioned outcomes. CONCLUSIONS: **Moderate-to-high intensity aerobic exercise by means of Nordic walking twice a week for 15 weeks was found to be a feasible mode of exercise, resulting in improved functional capacity and a decreased level of activity limitations**. Pain severity did not change over time during the exercise period.

Arthritis Res Ther. 2010; 12(5):R189. Epub 2010 Oct 13

Moldofsky H, Inhaber NH, Guinta DR, Alvarez-Horine SB

Effects of sodium oxybate on sleep physiology and sleep/wake-related symptoms in patients with fibromyalgia syndrome: a double-blind, randomized, placebo-controlled study

OBJECTIVE: To determine the effects of sodium oxybate (SXB) on sleep physiology and sleep/wake-related symptoms in patients with fibromyalgia syndrome (FM). METHODS: Of 304 patients with FM (American College of Rheumatology tender point criteria) in the screened study population, 209 underwent polysomnography, 195 were randomized, and 151 completed this 8-week, double-blind, placebo-controlled study of SXB 4.5 g and 6 g/night. We evaluated changes in objective sleep measures and subjective symptoms, including daytime sleepiness [Epworth Sleepiness Scale (ESS)], fatigue visual analog scale (FVAS), sleep [Jenkins Scale for Sleep (JSS)], and daytime functioning [Functional Outcome of Sleep Questionnaire (FOSQ), SF-36 Vitality domain, and Fibromyalgia Impact Questionnaire (FIQ) general and morning tiredness]. RESULTS: Pretreatment screening revealed an elevated incidence of maximum alpha EEG-intrusion > 24 min/hour of sleep (66%), periodic limb movements of sleep (20.1% ≥ 5/hour), and moderate to severe obstructive sleep apnea disorder (15.3% apnea-hypopnea index ≥ 15/hour). Compared with placebo, both doses of SXB achieved statistically significant improvements in ESS, morning FVAS, JSS, FOSQ, SF-36 Vitality, and FIQ general and morning tiredness; both doses also demonstrated decreased rapid eye movement (REM) sleep (all $p \leq 0.040$). SXB 6 g/night improved afternoon, evening and overall FVAS, reduced wakefulness after sleep onset, and increased Stage 2, slow-wave, and total non-REM sleep (all $p \leq 0.032$) versus placebo. Moderate correlations (≥ 0.40) were noted between changes in subjective sleep and pain measures. Adverse events occurring significantly more frequently with SXB than placebo were nausea, pain in extremity, nervous system disorders, dizziness, restlessness, and renal/urinary disorders (including urinary incontinence). CONCLUSION: **This large cohort of patients with FM demonstrated that SXB treatment improved EEG sleep physiology and sleep-related FM symptoms.**

J Rheumatol. 2010 Oct; 37(10):2156–66. Epub 2010 Aug 3

Moore RA, Straube S, Paine J, Phillips CJ, Derry S, McQuay HJ

Fibromyalgia: moderate and substantial pain intensity reduction predicts improvement in other outcomes and substantial quality of life gain

Chronic pain is associated with a range of other problems, including disturbed sleep, depression, anxiety, fatigue, reduced quality of life, and an inability to work or socialise. We investigated whether good symptom control of pain (using definitions of moderate and substantial benefit) is associated with improvement in other symptoms. Individual patient data from four randomised trials in fibro-

myalgia (2575 patients) lasting 8–14weeks were used to calculate percentage pain reduction for each completing patient (1858), divided into one of five groups according to pain reduction, irrespective of treatment: substantial benefit – 50% pain reduction; moderate – 30% to <50%; minimal – 15% to <30%; marginal – 0% to <15%; worse – <0% (increased pain intensity). We then calculated change from baseline to end of trial for measures of fatigue, function, sleep, depression, anxiety, ability to work, general health status, and quality-adjusted life year (QALY) gain over a 12-month period. Substantial and moderate pain intensity reductions were associated with statistically significant reduction from baseline by end of trial in all measures, with values by trial end at or approaching normative values. Substantial pain intensity reduction resulted in 0.11 QALYs gained, and moderate pain intensity reduction in 0.07 QALYs gained over a 12-month period. **Substantial and moderate pain intensity reduction predicts broad beneficial outcomes and improved quality of life that do not occur without pain relief. Pain intensity reduction is a simple and effective predictor of which patients should continue treatment, and which should discontinue and try an alternative therapy**.

Pain. 2010 May; 149(2):380–4. Epub 2010 Mar 26

Motley CP, Maxwell ML

Fibromyalgia: helping your patient while maintaining your sanity

In caring for the patient with fibromyalgia, the primary care provider benefits from an understanding of fibromyalgia as a distinct entity. **Evidence-based diagnostic criteria for fibromyalgia can be used in all individuals who present with multiple site pain, fatigue, and poor sleep.** Planning therapy for individuals with fibromyalgia often involves using both pharmacologic and nonpharmacologic treatment in the primary care setting.

Prim Care. 2010 Dec; 37(4):743–55, vi

Napadow V, Lacount L, Park K, As-Sanie S, Clauw DJ, Harris RE

Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity

OBJECTIVE:: Fibromyalgia (FM) is considered to be the prototypical central chronic pain syndrome and is associated with widespread pain that fluctuates spontaneously. Multiple studies have demonstrated altered brain activity in these patients. Our objective was to investigate the degree of connectivity between multiple brain networks in FM, as well as how activity in these networks correlates with spontaneous pain. METHODS: Resting functional magnetic

resonance imaging (fMRI) data in FM patients (n=18) and age-matched healthy controls (HC, n=18) were analyzed using dual regression independent component analysis (ICA)—a data driven approach used to identify independent brain networks. We evaluated intrinsic, or resting, connectivity in multiple brain networks: the default mode network (DMN), the executive attention network (EAN), and the medial visual network (MVN), with the MVN serving as a negative control. Spontaneous pain levels were also covaried with intrinsic connectivity. RESULTS: We found that FM patients had greater connectivity within the DMN and right EAN (rEAN; $p<0.05$, corrected), and greater connectivity between the DMN and the insular cortex—a brain region known to process evoked pain. Furthermore, greater spontaneous pain at the time of the scan correlated with greater intrinsic connectivity between the insula and both the DMN and rEAN ($p<0.05$, corrected). CONCLUSION: Our findings indicate that **resting brain activity within multiple networks is associated with spontaneous clinical pain in FM**. These findings may also have broader implications for how subjective experiences such as pain arise from a complex interplay amongst multiple brain networks.

Arthritis Rheum. 2010 Aug; 62(8):2545–55

Riva R, Mork PJ, Westgaard RH, Rø M, Lundberg U

Fibromyalgia syndrome is associated with hypocortisolism

BACKGROUND: Fibromyalgia syndrome (FMS) is a disease of unknown pathogenesis characterized by chronic musculoskeletal pain. FMS has been also associated with altered endocrinological responses, but findings are inconsistent. PURPOSE: The aim of the present study was to investigate free salivary cortisol levels in FMS patients compared with healthy controls with a particular focus on the cortisol awakening response (CAR). The saliva samples were collected in a controlled hospital-hotel setting, in which the participants' compliance was high and a number of potential confounders were analyzed. METHOD: Twenty-nine chronic female FMS patients and 29 age-matched healthy female controls were recruited. Salivary cortisol samples were investigated eight times: in the afternoon when participants arrived at the hospital, after stress provocation (to be reported separately), in the evening, before they went to sleep, upon awakening, 30 and 60 min later, and during the afternoon of the second day. Questionnaires measuring pain levels, sleeping problems, perceived stress, and personality were administered to the participants. Other psychophysiological measurements were used to assess sleep quality and heart rate. RESULTS: Patients with FMS had significantly lower cortisol levels during the day, most pronounced in the morning (CAR). The potential confounders analyzed did not influence the results. As expected, FMS patients reported more pain, stress, sleeping problems, anxiety, and depression. CONCLUSION: **The results lend support to the hypothesis of a dysfunction in**

the hypothalamus-pituitary-adrenal axis in FMS patients, with generally lower cortisol values, most pronounced upon awakening (CAR).

Int J Behav Med. 2010 Sep; 17(3):223–33. Epub 2010 May 11

Robinson ME, Craggs JG, Price DD, Perlstein WM, Staud R

Gray matter volumes of pain-related brain areas are decreased in fibromyalgia syndrome

Fibromyalgia (FM) is a chronic, widespread musculoskeletal pain disorder that is very prevalent in the general population (approximately 5%). Accumulating evidence suggests that FM is associated with central pain processing abnormalities, ie, central sensitization. Several previous studies of chronic pain patients, including FM, have shown gray matter atrophy of brain areas associated with sensory and affective pain processing. These findings, however, have not been confirmed in all FM studies. In this study, we investigated gray matter volumes of brain areas associated with pain-related areas of FM patients identified by functional brain imaging. Using voxel-based morphometric (VBM) analysis of magnetic resonance brain images, we compared 19 pain-related brain areas of 14 female FM patients and 11 healthy controls (NC). We found that FM patients had significantly less gray matter volumes than NC in 3 of these brain regions, including the anterior and mid-cingulate, as well as mid-insular cortices. Importantly, FM patients demonstrated neither global gray matter atrophy nor gray matter changes associated with depression, as shown in some studies. Using a more stringent analysis than other VBM studies, we provide evidence for decreased gray matter volumes in a number of pain-related brain areas in FM. **Although the mechanisms for these gray matter changes are presently unclear, they may contribute to some of the core features of this chronic disorder including affective disturbances and chronic widespread pain.** PERSPECTIVE: Increasing evidence supports the association of chronic pain with accelerated gray matter atrophy in pain disorders like low back pain, IBS, and FM syndrome. However, cause-effect relationships between chronic pain and decreased gray matter volumes have not been established yet and will require future prospective studies.

J Pain. 2010 Dec 9. [Epub ahead of print]

Salinsky M, Storzbach D, Munoz S

Cognitive effects of pregabalin in healthy volunteers: a double-blind, placebo-controlled trial

BACKGROUND: Antiepileptic drugs (AEDs) can be associated with neurotoxic side effects including cognitive dysfunction, a problem of considerable importance given the usual long-term course of treatment. Pregabalin is a relatively new

AED widely used for the treatment of seizures and some types of chronic pain including fibromyalgia. We measured the cognitive effects of 12 weeks of pregabalin in healthy volunteers. METHODS: Thirty-two healthy volunteers were randomized in a double-blind parallel study to receive pregabalin or placebo (1:1). Pregabalin was titrated over 8 weeks to 600 mg/d. At baseline, and after 12 weeks of treatment, all subjects underwent cognitive testing. Test-retest changes in all cognitive and subjective measures were Z scored against test-retest regressions previously developed from 90 healthy volunteers. Z scores from the placebo and pregabalin groups were compared using Wilcoxon tests. RESULTS: Thirty subjects completed the study (94%). Three of 6 target cognitive measures (Digit Symbol, Stroop, Controlled Oral Word Association) revealed significant test-retest differences between the pregabalin and placebo groups, all showing negative effects with pregabalin ($p < 0.05$). These cognitive effects were paralleled by complaints on the Portland Neurotoxicity Scale, a subjective measure of neurotoxicity ($p < 0.01$). CONCLUSION: At conventional doses and titration, pregabalin induced mild negative cognitive effects and neurotoxicity complaints in healthy volunteers. These effects are one factor to be considered in the selection and monitoring of chronic AED therapy. Class of Evidence: **This study provides Class I evidence that pregabalin 300 mg BID negatively impacts cognition on some tasks in healthy volunteers.**

Neurology. 2010 Mar 2; 74(9):755–61

Schmidt-Wilcke T, Clauw DJ

Pharmacotherapy in fibromyalgia (FM)—implications for the underlying pathophysiology

Although chronic pain states are highly prevalent, the underlying neurobiological mechanisms involved in causing pain are incompletely understood. This is especially true for the so-called chronic functional pain syndromes and pain syndromes of unknown origin, such as fibromyalgia (FM), in which no structural correlates of pain experience, in terms of a nociceptive source, can clearly be defined. In addition to limited therapeutic options and often unsatisfactory treatment, such patients often struggle with socio-medical acceptance of their pain condition. As FM has become more widely recognized, options available for treatment have grown along with our understanding of the neurobiological mechanisms underlying chronic pain experience and concomitant symptoms. **The current review aims to provide an overview of existing pharmacotherapies for FM, and their implications for the underlying pathophysiology.** Further, we discuss some of the potential targets that have been recently identified that may hold promise for the development of novel treatments.

Pharmacol Ther. 2010 Sep; 127(3):283–94. Epub 2010 Apr 11

Silverman SL, Harnett J, Zlateva G, Mardekian

Identifying fibromyalgia-associated symptoms and conditions from a clinical perspective: a step toward evaluating healthcare resource utilization in fibromyalgia

OBJECTIVE: The study aims to determine, from the physician's perspective, the conditions and symptoms most relevant to the diagnosis of fibromyalgia (FM) for identifying International Classification of Diseases-diagnosis codes and prescription medications to evaluate FM-related healthcare resource utilization. METHODS: A questionnaire was administered using an online physician network (SERMO™) from which responses of 102 physicians were evaluated: anesthesiologists (n = 6), neurologists (n = 18), primary care physicians (n = 16), pain specialists (n = 16), psychiatrists (n = 15), and rheumatologists (n = 31). Physicians scored the relative importance to a diagnosis of FM (0 = least relevant/important, 10 = most relevant/important) of 24 conditions and symptoms derived from a list provided by the National Data Bank for Rheumatic Diseases. Conditions and symptoms with mean scores ≥ 5 were considered the most relevant. Other survey questions included treatment goals, assessment of disease severity, medication use, and characterization of the physicians' experience and clinical practice. RESULTS: Ten conditions and symptoms (mean score) were reported as most relevant: Muscle pain (8.7), Fatigue/tiredness (8.5), Insomnia (8.0), Depression (7.8), Thinking/remembering (6.7), Nervousness (6.0), Muscle weakness (5.9), Headache (5.7), Irritable bowel syndrome (5.5), and Pain/cramps in abdomen (5.1). Treatment goals, severity assessment, and use of medications were generally similar across physician specialties. CONCLUSIONS: **This survey identified 10 conditions and symptoms that physician respondents considered most relevant to a diagnosis of FM.** Further evaluation to determine how these conditions and symptoms contribute to FM–associated healthcare resource utilization is warranted.

Pain Pract. 2010 Nov-Dec; 10(6):520–9

Solberg Nes L, Carlson CR, Crofford LJ, Leeuw RD, Segerstrom SC

Self-regulatory deficits in fibromyalgia and temporomandibular disorders

Chronic pain conditions such as fibromyalgia (FM) and temporomandibular disorders (TMDs) are accompanied by complex interactions of cognitive, emotional, and physiological disturbances. Such conditions are complicated and draining to live with, and successful adaptation may depend on ability to self-regulate. **Self-regulation involves capacity to exercise control and guide or alter reactions and behavior, abilities essential for human adjustment.** Research indicates that self-regulatory strength is a limited source that can be depleted or fatigued, however, and the current study aimed to show that patients

with FM and TMD are vulnerable to self-regulatory fatigue as a consequence of their condition. Patients (N=50) and pain-free matched controls (N=50) were exposed to an experimental self-regulation task followed by a persistence task. Patients displayed significantly less capacity to persist on the subsequent task compared with controls. In fact, patients exposed to low self-regulatory effort displayed similar low persistence to patients and controls exposed to high self-regulatory effort, indicating that patients with chronic pain conditions may be suffering from chronic self-regulatory fatigue. Baseline heart rate variability, blood glucose, and cortisol predicted persistence, more so for controls than for patients, and more so in the low vs. high self-regulation condition. Impact of chronic pain conditions on self-regulatory effort was mediated by pain, but not by any other factors. The current study suggests that **patients with chronic pain conditions likely suffer from chronic self-regulatory fatigue**, and underlines the importance of taking self-regulatory capacity into account when aiming to understand and treat these complex conditions.

Pain. 2010 Oct; 151(1):37–44. Epub 2010 Jun 18

Staud R, Robinson ME, Weyl EE, Price DD

Pain variability in fibromyalgia is related to activity and rest: role of peripheral tissue impulse input

Because fibromyalgia (FM) patients frequently report activity-dependent deep tissue pains, impulse input from painful body regions may be relevant for their musculoskeletal complaints. In addition, peripheral impulse input may induce and maintain thermal and mechanical hyperalgesia of FM patients. If so, activity and rest may alternately enhance and diminish intensity of FM pain. However, the effects of exercise on pain are ambiguous in studies of FM. Whereas exercise-only studies demonstrated increased pain and hyperalgesia during and after physical activity, some exercise studies that included rest periods resulted in decreased FM pain and increased function. To further clarify these effects, we examined the effects of alternating exercise with rest on clinical pain and thermal/mechanical hyperalgesia of 34 FM patients and 36 age-matched healthy controls (NC). Using an ergometer, all subjects performed arm exercise to exhaustion twice alternating with 15-minute rest periods. Although strenuous muscle activity was reported as painful by most FM subjects, overall clinical pain consistently decreased during the rest periods. Additionally, FM subjects' pain sensitivity to mechanical pressure decreased after each exercise and rest session. CONCLUSION: Alternating strenuous exercise with brief rest periods not only decreased overall clinical pain of FM subjects but also their mechanical hyperalgesia. No prolonged worsening of overall FM pain and hyperalgesia occurred despite vigorous muscle activity. **Our findings contribute further evidence that FM pain and hyperalgesia are at least partially maintained by muscle impulse input, and that some types of exercises may be beneficial for FM.** PERSPECTIVE: FM is a pain-

amplification syndrome that depends at least in part on peripheral tissue impulse input. Whereas muscle activity increased overall pain, short rest periods produced analgesic effects.

J Pain. 2010 May 6. [Epub ahead of print]

Staud R

Pharmacological treatment of fibromyalgia syndrome: new developments

Fibromyalgia is a chronic pain disorder characterized by widespread pain, stiffness, insomnia, fatigue and distress. Several randomized controlled trials (RCTs) have shown moderate effectiveness of pharmacological therapies for fibromyalgia pain. Evidence from these trials suggests that pharmacological therapy can not only improve pain but also fatigue, function and well-being in patients with fibromyalgia. Duloxetine and milnacipran, two highly selective serotonin-norepinephrine (noradrenaline) reuptake inhibitors, and the alpha(2) delta agonist pregabalin have been approved by the US FDA for the treatment of fibromyalgia symptoms. **In general, about half of all treated patients seem to experience a 30% reduction of symptoms, suggesting that many patients with fibromyalgia will require additional therapies**. Thus, other forms of treatment, including exercise, cognitive behavioural therapies and self-management strategies, may be necessary to achieve satisfactory treatment outcomes. Despite promising results of pilot trials, RCTs with dopamine receptor agonists and sodium channel antagonists have so far been disappointing for patients with fibromyalgia. However, new pharmacological approaches for the treatment of fibromyalgia pain and insomnia using sodium oxybate appear to be promising.

Drugs. 2010; 70(1):1–14

Straube S, Derry S, Moore RA, McQuay HJ

Pregabalin in fibromyalgia: meta-analysis of efficacy and safety from company clinical trial reports

OBJECTIVES: Meta-analysis of pregabalin trials in FM using company trial reports, which provide more detailed information about trials than published papers. FM is a common condition with a significant impact on quality of life. METHODS: Reports of five high-quality randomized trials (3808 patients) of pregabalin in FM were obtained from Pfizer. Four trials (2754 patients) were of classical trial design and one was an enriched enrolment randomized withdrawal design. Outcomes for meta-analysis from the four trials with classical design were pooled in an intention-to-treat analysis. RESULTS: Significant benefit of pregabalin over placebo was seen for a variety of outcomes including mean pain and

sleep scores, the proportion of patients achieving at least 50% pain relief and most of the individual domains of short-form 36. **Only a minority of patients achieve moderate or substantial pain relief. The proportions of patients with any adverse event, somnolence or dizziness were also significantly greater with pregabalin than with placebo**. There was no difference with regard to serious adverse events. A dose-response relationship was apparent for at least 50% pain relief and for adverse event outcomes. CONCLUSIONS: Pregabalin is effective in treating FM and is relatively safe. The size of therapeutic effect is similar to that with other recent interventions such as duloxetine and the combination of tramadol and paracetamol. Enriched enrolment randomized withdrawal design gives similar results to classical trial designs in FM.

Rheumatology (Oxford). 2010 Apr; 49(4):706–15. Epub 2010 Jan 7

Usui C, Hatta K, Doi N, Nakanishi A, Nakamura H, Nishioka K, Arai H

Brain perfusion in fibromyalgia patients and its differences between responders and poor responders to gabapentin

INTRODUCTION: The aim of the present study was to determine the brain areas associated with fibromyalgia, and whether pretreatment regional cerebral blood flow (rCBF) can predict response to gabapentin treatment. METHODS: A total of 29 women with fibromyalgia and 10 healthy women (without pain) matched for age were finally enrolled in the study. Technetium-99m ethyl cysteinate dimer single photon emission computed tomography ((99m)Tc-ECD SPECT) was performed in the fibromyalgia patients and controls. A voxel-by-voxel group analysis was performed using Statistic Parametric Mapping 5 (SPM5). After treatment with gabapentin, 16 patients were considered "responders," with decrease in pain of greater than 50% as evaluated by visual analogue scale (VAS). The remaining 13 patients were considered "poor responders." RESULTS: We observed rCBF abnormalities, compared to control subjects, in fibromyalgia including hypoperfusion in the left culmen and hyperperfusion in the right precentral gyrus, right posterior cingulate, right superior occipital gyrus, right cuneus, left inferior parietal lobule, right middle temporal gyrus, left postcentral gyrus, and left superior parietal lobule. Compared to responders, poor responders exhibited hyperperfusion in the right middle temporal gyrus, left middle frontal gyrus, left superior frontal gyrus, right postcentral gyrus, right precuneus, right cingulate, left middle occipital gyrus, and left declive. The right middle temporal gyrus, left superior frontal gyrus, right precuneus, left middle occipital gyrus, and left declive exhibited high positive likelihood ratios. CONCLUSIONS: **The present study revealed brain regions with significant hyperperfusion associated with the default-mode network, in addition to abnormalities in the sensory dimension of pain processing and affective-attentional areas in fibromyalgia patients. Furthermore, hyperperfusion in these areas was strongly predictive of poor response to gabapentin.**

Arthritis Res Ther. 2010; 12(2):R64. Epub 2010 Apr 7

Ware MA, Fitzcharles MA, Joseph L, Shir Y

The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial

BACKGROUND: Sleep disorders affect many patients with chronic pain conditions. Cannabis has been reported by several patient populations to help sleep. We evaluated the safety and efficacy of nabilone, a synthetic cannabinoid, on sleep disturbance in fibromyalgia (FM), a disease characterized by widespread chronic pain and insomnia. METHODS: We conducted a randomized, double-blind, active-control, equivalency crossover trial to compare nabilone (0.5–1.0 mg before bedtime) to amitriptyline (10–20 mg before bedtime) in patients with FM with chronic insomnia. Subjects received each drug for 2 wk with a 2-wk washout period. The primary outcome was sleep quality, measured by the Insomnia Severity Index and the Leeds Sleep Evaluation Questionnaire. Secondary outcomes included pain, mood, quality of life, and adverse events (AEs). RESULTS: Thirty-one subjects were enrolled and 29 completed the trial (26 women, mean age 49.5 yr). Although sleep was improved by both amitriptyline and nabilone, nabilone was superior to amitriptyline (Insomnia Severity Index difference = 3.2; 95% confidence interval = 1.2–5.3). Nabilone was marginally better on the restfulness (Leeds Sleep Evaluation Questionnaire difference = 0.5 [0.0–1.0]) but not on wakefulness (difference = 0.3 [-0.2 to 0.8]). **No effects on pain, mood, or quality of life were observed**. AEs were mostly mild to moderate and were more frequent with nabilone. The most common AEs for nabilone were dizziness, nausea, and dry mouth. CONCLUSIONS: Nabilone is effective in improving sleep in patients with FM and is well tolerated. **Low-dose nabilone given once daily at bedtime may be considered as an alternative to amitriptyline.** Longer trials are needed to determine the duration of effect and to characterize long-term safety.

Anesth Analg. 2010 Feb; 110(2):604–10. Epub 2009 Dec 10

Williams DA, Kuper D, Segar M, Mohan N, Sheth M, Clauw DJ

Internet-enhanced management of fibromyalgia: A randomized controlled trial

Both pharmacological and non-pharmacological interventions have demonstrated efficacy in the management of fibromyalgia (FM). Non-pharmacological interventions however are far less likely to be used in clinical settings, in part due to limited access. This manuscript presents the findings of a randomized controlled trail of an Internet-based exercise and behavioral self-management program for FM designed for use in the context of a routine clinical care. 118 individuals with FM were randomly assigned to either (a) standard care or (b) standard care plus access to a Web-Enhanced Behavioral Self-Management program (WEB-SM) grounded in cognitive and behavioral pain management principles. Individuals

were assessed at baseline and again at 6 months for primary endpoints: reduction of pain and an improvement in physical functioning. Secondary outcomes included fatigue, sleep, anxiety and depressive symptoms, and a patient global impression of improvement**. Individuals assigned to the WEB-SM condition reported significantly greater improvement in pain, physical functioning, and overall global improvement. Exercise and relaxation techniques were the most commonly used skills throughout the 6-month period.** A no-contact, Internet-based, self-management intervention demonstrated efficacy on key outcomes for FM. While not everyone is expected to benefit from this approach, this study demonstrated that non-pharmacological interventions can be efficiently integrated into routine clinical practice with positive outcomes.

Pain. 2010 Sep 18. [Epub ahead of print]

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

The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity

OBJECTIVE: To develop simple, practical criteria for clinical diagnosis of fibromyalgia that are suitable for use in primary and specialty care and that do not require a tender point examination, and to provide a severity scale for characteristic fibromyalgia symptoms. METHODS: We performed a multicenter study of 829 previously diagnosed fibromyalgia patients and controls using physician physical and interview examinations, including a widespread pain index (WPI), a measure of the number of painful body regions. Random forest and recursive partitioning analyses were used to guide the development of a case definition of fibromyalgia, to develop criteria, and to construct a symptom severity (SS) scale. RESULTS: Approximately 25% of fibromyalgia patients did not satisfy the American College of Rheumatology (ACR) 1990 classification criteria at the time of the study. The most important diagnostic variables were WPI and categorical scales for cognitive symptoms, unrefreshed sleep, fatigue, and number of somatic symptoms. The categorical scales were summed to create an SS scale. **We combined the SS scale and the WPI to recommend a new case definition of fibromyalgia: (WPI > or =7 AND SS > or =5) OR (WPI 3-6 AND SS > or =9).** CONCLUSION: **This simple clinical case definition of fibromyalgia correctly classifies 88.1% of cases classified by the ACR classification criteria, and does not require a physical or tender point examination.** The SS scale enables assessment of fibromyalgia symptom severity in persons with current or previous fibromyalgia, and in those to whom the criteria have not been applied. It will be especially useful in the longitudinal evaluation of patients with marked symptom variability.

Arthritis Care Res (Hoboken). 2010 May; 62(5):600–10
Comment in: *Arthritis Care Res* (Hoboken). 2010 May; 62(5):583–4

Woolf CJ

Central sensitization: Implications for the diagnosis and treatment of pain

Nociceptor inputs can trigger a prolonged but reversible increase in the excitability and synaptic efficacy of neurons in central nociceptive pathways, the phenomenon of central sensitization. Central sensitization manifests as pain hypersensitivity, particularly dynamic tactile allodynia, secondary punctate or pressure hyperalgesia, aftersensations, and enhanced temporal summation. It can be readily and rapidly elicited in human volunteers by diverse experimental noxious conditioning stimuli to skin, muscles or viscera and, in addition to producing pain hypersensitivity, results in secondary changes in brain activity that can be detected by electrophysiological or imaging techniques. Studies in clinical cohorts reveal changes in pain sensitivity that have been interpreted as revealing an important contribution of central sensitization to the pain phenotype in patients with fibromyalgia, osteoarthritis, musculoskeletal disorders with generalized pain hypersensitivity, headache, temporomandibular joint disorders, dental pain, neuropathic pain, visceral pain hypersensitivity disorders and post-surgical pain. The comorbidity of those pain hypersensitivity syndromes that present in the absence of inflammation or a neural lesion, their similar pattern of clinical presentation and response to centrally acting analgesics, may reflect a commonality of central sensitization to their pathophysiology. An important question that still needs to be determined is whether there are individuals with a higher inherited propensity for developing central sensitization than others, and if so, whether this conveys an increased risk in both developing conditions with pain hypersensitivity, and their chronification. **Diagnostic criteria to establish the presence of central sensitization in patients will greatly assist the phenotyping of patients for choosing treatments that produce analgesia by normalizing hyperexcitable central neural activity.** We have certainly come a long way since the first discovery of activity-dependent synaptic plasticity in the spinal cord and the revelation that it occurs and produces pain hypersensitivity in patients. Nevertheless, discovering the genetic and environmental contributors to and objective biomarkers of central sensitization will be highly beneficial, as will additional treatment options to prevent or reduce this prevalent and promiscuous form of pain plasticity.

Pain. 2010 Oct 18. [Epub ahead of print]