Fibromyalgia
A bird's eye review of the recent literature

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Pathogenesis

Title: Preliminary evidence of increased pain and elevated cytokines in fibromyalgia patients with defective growth hormone response to exercise.
Authors: Ross RL, Jones KD, Bennett RM, Ward RL, Druker BJ, Wood LJ.
Open Immunol J 2010; 3: 9-18.
Summary: This study is based on the growing evidence that fibromyalgia (FM) symptoms are influenced by dysfunction of the hypothalamic-pituitary-hormonal axes (HPHA) and the immune response system. It has been already demonstrated that FM symptoms such as widespread pain, fatigue, sleep disturbance, depression, stiffness and exercise intolerance are related to abnormal levels of growth hormone (GH) and are reminiscent of "sickness behaviour"; a syndrome initiated by the production of pro-inflammatory cytokines in response to various stressors. The authors' aim was to demonstrate that serum cytokine levels and FM symptom severity could have been higher in FM patients with defective growth hormone response to exhaustive exercise compared to those without. Outpatients with FM (n=165) underwent a Modified Balke Treadmill Protocol and GH response to exhaustive exercise was measured in peripheral blood samples, withdrawn before, immediately after and one hour later, after the treadmill test. The sample consisted of 24 non-Hispanic Caucasian females (age 28–60 years) since, interestingly, only 12 of the 165 participants from the parent study mounted a normal GH response to exhaustive exercise (≥ 5ng/dL increase during exercise), and thus restricted the sample size to 12 participants per group. For the comparison group, 12 female participants who did not mount a GH response to exhaustive exercise (0 ng/dL increase during exercise) were randomly selected from the remaining 153 participants. No significant differences on demographic features were found between the 141 participants from the parent group and the 24 participants selected for the secondary analysis group (p=214 to 1.0). Sera from only seven of the 12 participants with HPHA dysfunction were in sufficient quantity and quality to perform immune response system biomarker analysis. The five participants without sufficient sample to analyse did not significantly differ on demographic characteristics from the seven responders whose sera were analysed (p=0.140 to 1.0). FM symptom severity was assessed using the Fibromyalgia Impact Questionnaire (FIQ), number of tender points and cumulative myalgic scores. GH dysfunction was associated with increased pain scores on the FIQ (p=0.024), a greater number of tender points (p=0.014), higher myalgic scores (p=0.001) and higher pre-exercise levels of inflammatory cytokines IL-1α (p=0.021), IL-6 (p=0.012), and IL-8 (p=0.004). These results suggest that a defective growth hormone response to exercise may be associated with increased levels of blood cytokines and pain severity in FM patients.
Editor's note: Although such a small sample size represents an unquestionable limit, this preliminary findings are of considerable interest. The role of HPAP axis in the pathogenesis of FM should be taken into account, not only from the research point of view but also from the clinical one, since only the 7.27% of patients did not show a defective growth hormone response to exhaustive exercise.

Title: Mitochondrial dysfunction and mitophagy activation in blood mononuclear cells of fibromyalgia patients: implications in the pathogenesis of the disease.
Authors: Cordero MD, De Miguel M, Moreno Fernández AM, Carmona López IM, Garrido Maraver J, Cotán D, Gómez Izquierdo L, Bonal P, Campa F, Bullon P, Navas P, Sánchez Alcázar JA.
Arthritis Res Ther 2010; 12(1): R17. [Epub 2010 Jan 28].
Summary: The goal of the study was to assess the mitochondrial dysfunction in blood mononuclear cells of FM patients and to elucidate whether mitochondrial disturbance was involved in the pathophysiology of oxidative stress present in FM. Twenty patients (two male and 18 female patients) recruited from the database of the Sevillian Fibromyalgia Association (AFIBROSE) and 10 healthy controls (two male and eight female patients) were studied. The most prominent features of these FM patients, who all lead a sedentary life, were pain and stiffness. The study consisted of several consecutive phases. CoQ10 levels of FM patients were found to be about 40% lower than those in the control cells. Studying the mitochondrial membrane potential ($\Delta\Psi m$) with flow cytometry, they observed its significant reduction in about the 36% of BMCs from FM patients. In a previous work, the same authors demonstrated the presence of high levels of ROS production in the BMCs of FM patients. To assess the mitochondrial origin of ROS production, BMCs from FM patients and controls were exposed to MitoSOX™ , a red mitochondrial superoxide indicator. Quantification of ROS production with flow-cytometry analysis demonstrated a significant increase in ROS production in mitochondria of BMCs from FM patients with respect to the controls. They also determined lipid peroxidation as a marker of oxidative stress-induced membrane damage by mitochondrial ROS in BMCs and plasma from FM patients. On average, FM patients showed a higher level of lipid peroxidation in both cells and plasma with respect to control subjects. To verify that CoQ10 deficiency also induces activation of autophagy in BMCs from FM patients, they first quantified levels of acidic vacuoles in BMCs by using Lysotracker fluorescence

and flow-cytometry analysis. Acidic vacuoles were significantly increased in patient BMCs with respect to controls. They also demonstrated that autophagy in CoQ10-deficient BMCs could be mitigated by restoring mitochondrial functionality by CoQ10 supplementation. In addition, the expression of genes involved in autophagic processes, such as BECLIN 1 and MAP-LC3 was studied; autophagic genes were overexpressed in BMCs of five of the eight patients tested as compared with controls. FM patients with increased expression of autophagic genes were those with a most pronounced CoQ10 deficiency. After having shown that autophagy was specific for mitochondria, by BMC extracts analysis of citrate synthase activity, they confirm the presence of mitochondrial degradation or mitophagy in BMCs, performing electron microscopy on control and patient BMCs; it indicated extensive autophagy of mitochondria. This study clearly supports the hypothesis that CoQ10 deficiency, oxidative stress, and extensive mitophagy can contribute to cell-bioenergetics imbalance, compromising cell functionality. Abnormal BMC performance can promote oxidative stress and may contribute to altered nociception in FM. Moreover, autophagy can be beneficial for the cells by eliminating dysfunctional mitochondria, but massive autophagy can promote cell injury and may contribute to the pathophysiology of FM.
Editor's note: this study probably represents a turning point in establishing the crucial role of mitochondria ad oxidative stress in the pathogenesis of FM. We are all wondering for years if oxidative stress is the cause or the effect of the abnormalities documented in fibromyalgia: could this work contain the answer?

Title: Fibromyalgia syndrome is associated with hypocortisolism
Authors: Riva R, Mork PJ, Westgaard RH, Rø M, Lundberg U.
Int J Behav Med 2010; 17 (3): 223-33.
Summary: In this study the authors analyse free salivary cortisol levels in FMS patients compared with healthy controls with a particular focus on the cortisol awakening response (CAR). Salivary cortisol samples were investigated eight times: in the afternoon, after stress provocation, in the evening, before going 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. The results showed that patients with FMS had significantly lower cortisol levels during the day, being most pronounced in the morning (CAR) and, as expected, FMS patients reported more pain, stress, sleeping problems, anxiety, and depression. The results lend support to the hypothesis of a dysfunction in the hypothalamus-pituitary-adrenal axis in FMS patients, with generally lower cortisol values, which are most pronounced upon awakening.
Editor's note: FMS has generally been considered to be stress-related and, consequently, functional changes in the central physiological stress systems have been examined in FMS patients, but the results are inconsistent.

Title: Abnormal overexpression of mastocytes in skin biopsies of fibromyalgia patients
Authors: Blanco I, Béritze N, Argüelles M, Cárcaba V, Fernández F, Janciauskiene S, Oikonomopoulou K, de Serres FJ, Fernández-Bustillo E, Hollenberg MD.
Clin Rheumatol 2010; 29: 1403-12.
Summary: In recent years, clinical, epidemiological, and pathological evidence has suggested that inherited alpha1-antitrypsin (AAT) deficiency might play a role in the development of FMS, probably because of the loss of AAT anti-inflammatory efficacy. Thus, the analysis of inflammation-related markers in FMS cases with congenital AAT deficiency can provide a valuable model to study how inflammatory substances may complement genetic factors leading to the development of fibromyalgia. The most relevant finding of the study was a significantly increased number of mast cells (MCs) in the papillary dermis of all FMS patients than in controls. MCs strongly stained with tryptase, AAT and PAR(2) antibodies, exhibited a spindle-like shape and were uniformly distributed around blood vessels and appendages. MCP-1 and VEGF expressed weak/moderate positivity in most samples, with a higher expression in controls than in FMS patients. No differences in elastase and TNF-alpha were found between both groups. Moreover, no histological differences were found between samples from AAT deficiency and normal AAT phenotypes. These results indicate that FMS is a MC-associated condition. MCs are present in skin and mucosal surfaces throughout the human body, and are easily stimulated by a number of physical, psychological, and chemical triggers to degranulate, releasing several proinflammatory products which are able to generate nervous peripheral stimuli causing CNS hypersensitivity, local, and systemic symptoms.
Editor's note: In recent years, several morphological and immunohistochemical changes have been reported in skin biopsies of FMS patients which suggest that the skin is damaged in FMS patients.

Title: Associations between polymorphisms in dopamine neurotransmitter pathway genes and pain response in healthy humans.
Authors: Treister R, Pud D, Ebstein RP, Laiba E, Gershon E, Haddad M, Eisenberg E.
Pain 2009; 147: 187-93.
Summary: It is well established that an identical noxious stimulus can produce different pain responses and it is suggested that genetic factors may contribute to pain perception. The aim of this study was to explore the relationship between functional polymorphisms in dopaminergic candidate genes and sensitivity to pain in healthy subjects using cold and hot pain stimuli. DNA samples were obtained from both participants and their parents. The relationships between pain response and the functional Variable Number of Tandem Repeat (VNTR) polymorphisms of three dopamine-

related genes were investigated using a Transmission Disequilibrium Test (TDT). Significant associations between cold pain tolerance and dopamine transporter gene DAT-1 and monoamine oxidase-A gene MAO-A polymorphisms were found. These results, together with the known function of the investigated candidate gene polymorphisms, suggest that low dopaminergic activity can be associated with high pain sensitivity and vice versa.
Editor's note: The exact role of dopamine in pain processing is not fully understood even if evidence shows that dopamine neurotransmission pathway genes are associated with specific clinical pain syndromes, such as fibromyalgia.

Title: Quantitative electroencephalographic abnormalities in fibromyalgia patients.
Authors: Hargrove JB, Bennett RM, Simons DG, Smith SJ, Nagpal S, Deering DE.
Clin EEG Neurosci 2010; 41: 132-9.
Summary: There is increasing acceptance that pain in fibromyalgia (FM) is a result of dysfunctional sensory processing in the spinal cord and brain, and a number of recent imaging studies have demonstrated abnormal central mechanisms. The objective of this report is to statistically compare quantitative electroencephalogram (qEEG) measures in 85 FM patients with age and gender matched controls in a normative database. FM subject EEG data was compared to EEGs of age and gender matched healthy subjects in the Lifespan Normative Database and analysed using NeuroGuide 2.0 software. Analyses were based on spectral absolute power, relative power and coherence. Based on Z-statistic findings, the EEGs from FM subjects differed from matched controls in the normative database in three features: (1) reduced EEG spectral absolute power in the frontal International 10-20 EEG measurement sites, (2) elevated spectral relative power of high frequency components in frontal/central EEG measurement sites; and (3) widespread hypocoherence, particularly in low- to mid-frequency EEG spectralsegments, in the frontal EEG measurement sites. A consistent and significant negative correlation was found between pain severity and the magnitude of the EEG abnormalities. It is concluded that qEEG analysis reveals significant differences between FM patients compared to age and gender matched healthy controls in a normative database, and has the potential to be a clinically useful tool for assessing brain function in FM patients.
Editor's note: if these results will be confirmed, the quantitative electroencephalogram could be a useful tool for diagnosis and severity assessment.

Title: Localized 1H-NMR spectroscopy in patients with fibromyalgia: a controlled study of changes in cerebral glutamate/glutamine, inositol, choline, and N-acetylaspartate.
Authors: Fayed N, Garcia-Campayo J, Magallón R, Andrés-Bergareche H, Luciano JV, Andres E, Beltrán J.
Arthritis Res Ther 2010; 12: R134.
Summary: More recently, a growing body of literature suggests that glutamate (Glu), an excitatory neurotransmitter within the central nervous system, may play a role in FM pathology. MRS provides a noninvasive method for characterising chemical and cellular features *in vivo*. The purpose of this study was to investigate whether single-voxel (SV) proton magnetic resonance spectroscopy (MRS), diffusion-weighted imaging (DWI), and diffusion tensor imaging (DTI) detected differences between fibromyalgia (FM) patients and healthy controls. We also searched for correlations between neuroimaging abnormalities and neuropsychological variables. METHODS: Ten patients with FM and 10 gender- and age-matched control subjects were studied. A neuropsychological examination, DWI, DTI, and proton MRS were performed on the brain areas known to be associated with pain processing. Compared with healthy controls, FM patients had significantly higher levels of glutamate + glutamine (Glx) and higher glutamate + glutamine/creatine (Glx/Cr) ratios in the posterior gyrus. Myoinositol (Ins) levels of the right and left hippocampi were significantly lower in FM patients. In FM patients, decreased myoinositol/creatine (Ins/Cr) ratios were found in the left sensorimotor area (p=0.05) and the left hippocampus (p=0.002) and lower levels of choline (p=0.019) and N-acetyl aspartate + N-acetyl aspartyl glutamate (NAA + NAG) (p=0.034) in the left hippocampus. Significant correlations between depression, pain, and global function and the posterior gyrus Glx levels and Glx/Cr ratios were observed. Glx within the posterior gyrus could be a pathologic factor in FM. Hippocampal dysfunction may be partially responsible for the depressive symptoms of FM.
Editor's note: Additional studies with larger samples are required to confirm these preliminary data. This study suggest that hippocampal dysfunction may be in part responsible for some aspects of FM.

Assessment

Title: Virtual reality tasks disclose spatial memory alterations in fibromyalgia.
Authors: Cánovas R, León I, Roldán MD, Astur R, Cimadevilla JM.
Rheumatology (Oxford) 2009; 48(10): 1273-8.
Summary: The objective of the study was to assess performance on virtual reality spatial memory tasks as well as classical neuropsychological tests in patients with fibromyalgia (FM). Fifteen FM patients and fifteen healthy age- and education-matched controls performed the virtual versions of the Morris water maze and the hole board (a virtual version called Boxes room). All participants also completed a comprehensive neuropsychological evaluation that included measures of general intelligence, attention/working memory and visuospatial memory. Both virtual reality tasks were demonstrated to be sensitive to spatial memory alterations. FM patients performed significantly worse than controls in the spatial navigation tasks, showing significantly more errors than their matched controls, while no significant differences were found between patients and controls regarding standard neuropsychological testing. In addition, those FM patients with longer chronicity had lower auditory memory

span, visuospatial memory and general intelligence within their group. These results are the first to demonstrate that there is a spatial learning deficit in people with FM, which suggest that the hippocampal system can be disturbed in this syndrome.
Editor's note: Virtual reality, as this work demonstrated, could probably provide useful tests for neuropsychological research. Despite standard methods, this new technology seems to be able to produce a large amount of information about patients' skills in everyday life, allowing a standardized measurement of them.

Title: Content and criterion validity of the preliminary core dataset for clinical trials in fibromyalgia syndrome.
Authors: Choy EH, Arnold LM, Clauw DJ, Crofford LJ, Glass JM, Simon LS, Martin SA, Strand CV, Williams DA, Mease PJ.
J Rheumatol 2009; 36: 2330-4.

Title: Fibromyalgia syndrome module at OMERACT 9: domain construct.
Authors: Mease P, Arnold LM, Choy EH, Clauw DJ, Crofford LJ, Glass JM, Martin SA, Morea J,Simon L, Strand CV, Williams DA; OMERACT Fibromyalgia Working Group
J Rheumatol 2009; 36: 2318-29.

Summary: Fibromyalgia (FM) is a common condition afflicting 2% of the population and Many clinical trials have been conducted in FM. The Outcome Measures in Rheumatology (OMERACT) initiative has helped to resolve the problem of outcomes measurement variability in rheumatic diseases such as rheumatoid and psoriatic arthritis, by establishing core data sets that should be collected and reported in randomized controlled trials (RCT). Increasing research interest and emerging new therapies for treatment of fibromyalgia have led to a need to develop a consensus on a core set of outcome measures that should be assessed in all clinical trials to facilitate interpretation of the data. Through patient focus groups and Delphi processes, working groups at previous OMERACT 7 and 8 meetings identified potential domains to be included in the core data set: (1) pain, (2) patient global, (3) fatigue, (4) health-related quality of life, (5) multidimensional function, (6) sleep, (7) depression, (8) physical function, (9) tenderness, (10) dyscognition (cognitive dysfunction), and (11) anxiety. A systematic review has shown that instruments measuring these domains are available and are at least moderately sensitive to change. This pooled analysis study aims to develop the core data set by analyzing data from 10 randomized controlled trials (RCT) in FM. Data from this study and previous consensus exercises support inclusion of pain, fatigue, physical function, and multidimensional function as domains in a core data set for clinical trials in FM Results of the study were presented at the OMERACT 9 FM module and were the basis for development of consensus on a core domain construct for fibromyalgia
Editor's note: It is very important to establish an international standard for RCT in FM to facilitate future metaanalyses and indirect comparisons.

Title: Relationship between fibromyalgia and obesity in pain, function, mood, and sleep.
Authors: Okifuji A, Donaldson GW, Barck L, Fine PG.
J Pain 2010 Jun 8.
Summary: Fibromyalgia syndrome (FMS) is a prevalent and disabling chronic pain disorder. Past research suggests that obesity is a common comorbidity and may be related to the severity of FMS. The objective of the present study was to evaluate the relationships between FMS and obesity in the multiple FMS-related domains: hyperalgesia, symptoms, physical abilities, and sleep. A total of 215 FMS patients completed a set of self-report inventories to assess FMS-related symptoms and underwent the tender point (TP) examination, physical performance testing, and 7-day home sleep assessment. Forty-seven percent of the sample was obese and an additional 30% was overweight. Obesity was related significantly to greater pain sensitivity to TP palpation particularly in the lower body areas, reduced physical strength and lower-body flexibility, shorter sleep duration, and greater restlessness during sleep. The results confirmed that obesity is a prevalent comorbidity of FMS that may contribute to the severity of the problem. The authors found that obesity is common in FMS and may be interrelated to fibromyalgia pain, disability, and sleep. They also found that obesity in FMS was associated with greater pain sensitivity, poorer sleep quality, and reduced physical strength and flexibility. The results suggest that obesity may aggregate FMS and weight management may need to be incorporated into treatments.
Editor's note: Obese individuals typically exhibit abnormalities in the levels of pro- inflammatory indices, such as Interlukin-6 and C reactive protein. The results are also consistent with the findings that obesity is a risk factor for chronic pain. In summary, obesity is a common comorbidity that may complicate the clinical picture of FMS and may be an important risk factor.

Title: The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity.
Authors: Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, Russell AS, Russell IJ, Winfield JB, Yunus MB.
Arthritis Care Res (Hoboken) 2010; 62: 600-10.
Summary: The study deals with the development of 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. In developing new diagnostic criteria, we identified 2 variables that best defined fibromyalgia and its symptom spectrum: the WPI and the composite symptom severity (SS) scale. The evaluations a of widespread pain index (WPI), including a measure of the number of painful body regions (until n 19), associated to the selected of SS scale performed by a com-

posite variable composed of physician-rated cognitive problems, unrefreshed sleep, fatigue, and somatic symptom count to measure fibromyalgia symptom severity The categorical scales were summed to create an SS scale (until n 12). The most important diagnostic variables were WPI and categorical scales for cognitive symptoms, unrefreshed sleep, fatigue, and number of somatic symptoms. 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). 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.

Editor's note: This innovative assessment will be tested in other rheumatic diseases for the enhancement of its specificity. Finally, these preliminary diagnostic criteria also exclude the tender points count.

Therapy

Title: Effect of pilates training on people with fibromyalgia syndrome: a pilot study.

Authors: Altan L, Korkmaz N, Bingol U, Gunay B.

Arch Phys Med Rehabil 2009; 90: 1983-8.

Summary: This randomized, prospective, controlled, and single-blind trial was designed with the purpose to investigate the effects of Pilates on pain, functional status, and quality of life in fibromyalgia. Fifthy women were recruited and randomly assigned into 2 groups. None of the participants had an accompanying rheumatoid disease, unstable hypertension, severe cardiopulmonary problems, or any psychiatric disorder affecting participant compliance. They had to discontinue NSADs (only acetaminophen was allowed, but not the morning of the assessment day). In group 1, a Pilates exercise program of 1 hour was given by a certified trainer to 25 participants 3 times a week for 12 weeks. The protocol consisted on 9 modules: postural education, search for neutral position, sitting exercise, antalgic exercises, stretching exercises, proprioceptivity improvement exercises, and breathing education. Resistance bands and 26cm Pilates balls were used as supportive equipment. In group 2, which was designed as the control group, 25 participants were given a home exercise. This exercise program consisted of relaxation techniques based on the published regimen by Ost (Behav Res Ther 1987;25:397-409) and dynamic (slow, controlled leg and arm swings), active stretching (ie, bringing the leg up high and holding it there without anything to keep it in that extended position), and passive stretching (ie, reaching out to the feet while sitting up). Exercise in both groups was stopped at the end of week 12, and all were reevaluated at the end of week 24 after a period of 12 weeks free from exercise. In both groups, pre- and post-treatment evaluations was performed by one of the authors, who was blind to the group allocation. The primary outcome measures were pain (visual analogue scale) and Fibromyalgia Impact Questionnaire (FIQ). Exploratory outcome measures were number of tender points, algometric score, chair test, and Nottingham Health Profile. Twenty-five Pilates exercise and 24 relaxation/stretching exercise participants completed the study. In group 1, significant improvement was observed in both pain and FIQ at week 12 but only in FIQ at 24 weeks. In group 2, no significant improvement was obtained in pain and FIQ at week 12 and week 24. Comparison of the 2 groups showed significantly superior improvement in pain and FIQ in group 1 at week 12 but no difference between the 2 groups at week 24. The authors suggest Pilates as an effective and safe method for people with FMS.

Editor's note: This is the first clinical study designed to investigate the role of the Pilates method in FMS treatment. Further research with more participants and longer follow-up periods could help assess the therapeutic value of this popular physical exercise method, which is based on isometric contractions and causes less fatigue than aerobic exercises.

Title: Anodal transcranial direct current stimulation of the motor cortex ameliorates chronic pain and reduces short intracortical inhibition.

Authors: Antal A, Terney D, Kühnl S, Paulus W.

J Pain Symptom Manage 2010; 39: 890-903.

Summary: Consecutive sessions of transcranial direct current stimulation (tDCS) over the primary motor cortex (M1) may be a suitable therapy to treat chronic pain, as it can modulate neural activities in the stimulated and interconnected regions. The present study investigated the analgesic effect of five consecutive days of anodal/sham tDCS using subjective (visual analogue scale [VAS]) and objective (cortical excitability measured by transcranial magnetic stimulation [TMS]) measurements. Patients with therapy-resistant chronic pain syndromes (trigeminal neuralgia, poststroke pain syndrome, back pain, fibromyalgia) participated. As this clinical trial was an exploratory study. In a recent study (Fregni F *et al*. *Pain* 2006), patients were randomised to receive sham or active tDCS over the left or right motor cortex (2 mA, 20 minutes for five consecutive days). There was a significant improvement in pain perception after anodal stimulation of the M1 but not after sham stimulation. A follow-up study reported a similar decrease in pain perception in a patient group with fibromyalgia (Fregni F *et al*. *Arthritis Rheum* 2006). Based on the aforementioned results, the authors decided to changed three parameters related to the stimulation: 1) the intensity of stimulation was 1 mA (2 mA in the first mentioned study); 2) related electrode size was 4 x 4 cm to increase the focality of the stimulation (5 x 7 cm in the previous studies); and 3) a crossover design was used in 13 participants who received both types of stimulations. Furthermore, they examined the possible intracortical effects of repeated tDCS over M1 using paired-pulse stimulation. Finally, the possible side effects of the stimulation were evaluated by a questionnaire developed by the same

research group. Twelve patients, who underwent both anodal and sham tDCS, were analysed using a crossover design. An additional nine patients had only anodal or sham stimulation. tDCS was applied over the hand area of the M1 for 20 minutes, at 1mA for five consecutive days, using a randomised, double-blind design. Pain was assessed daily using a VAS rating for one month before, during, and one month post-stimulation. M1 excitability was determined using paired-pulse TMS. Anodal tDCS led to a greater improvement in VAS ratings than sham tDCS, evident even three to four weeks post-treatment. Decreased intracortical inhibition was demonstrated after anodal stimulation, indicating changes in cortico-cortical excitability. No patient experienced severe adverse effects; seven patients suffered from light headache after anodal and six after sham stimulation. Results confirm that five daily sessions of tDCS over the hand area of the M1 can produce long-lasting pain relief in patients with chronic pain. An interesting question to be solved in the near future is the optimal duration and repetition rate of tDCS sessions. In the present study, the effects built up during the first three stimulation sessions, being mild in many patients immediately after the initial stimulation but quite clear after the fourth or fifth days.

Editor's note: Although FM patients may have access to a large variety of drugs, treatment failure is not so uncommon. It is often difficult for the physician to immediately find the right therapy and the risk of side effects – even worse than the pain itself – is rather high. Also the compliance represents a crucial issue to face, because of the frequent psychiatric or psychological patients aspects. Thus, the need for new therapeutic interventions is growing and neuromodulatory approaches with brain stimulation could be the right answer.

Title: A randomized trial of tai chi for fibromyalgia

Authors: Wang C, Schmid CH, Rones R, Kalish R, Yinh J, Goldenberg DL, Lee Y, McAlindon T.

N Engl J Med 2010; 363: 743-54.

Summary: Tai chi is a mind-body practice that originated in China as a martial art. It combines meditation with slow, gentle, graceful movements, as well as deep breathing and relaxation, to move vital energy (or qi) throughout the body. It is considered a complex, multicomponent intervention that integrates physical, psychosocial, emotional, spiritual, and behavioral elements. This is a single-blind, randomised trial of classic Yang-style tai chi as compared with a control intervention consisting of wellness education and stretching for the treatment of fibromyalgia. This trial shows that tai chi is potentially a useful therapy for patients with fibromyalgia. The effect was evident in the FIQ score and in the measures used to assess pain, sleep quality, depression, and quality of life, and these benefits were sustained at 24 weeks.

Editor's note: Evidence-based guidelines suggest that fibromyalgia is typically managed with multidisciplinary therapies involving medication, cognitive behavioural therapy, education, and exercise. Because of its mind-body attributes, tai chi could be especially well suited to the treatment of fibromyalgia even if the biologic mechanisms by which tai chi might affect the clinical course of fibromyalgia remain unknown.

Title: A European multicenter randomized double-blind placebo-controlled monotherapy clinical trial of milnacipran in treatment of fibromyalgia.

Authors: Branco JC, Zachrisson O, Perrot S, Mainguy Y; Multinational Coordinator Study Group.

J Rheumatol 2010; 37: 851-9 [Epub 2010 Feb 15].

Summary: Milnacipran is approved by the US Food and Drug Administration (FDA) for the management of FM. Several double-blind, placebo-controlled trials conducted in the US have demonstrated the efficacy of milnacipran in the treatment of FM. The aim of this study randomised, double-blind, placebo-controlled, multicentre study investigated the efficacy and safety of milnacipran in the treatment of fibromyalgia (FM) was to confirm the efficacy and safety of milnacipran 200 mg/day for the treatment of FM in a European population. Outpatients diagnosed with FM according to 1990 American College of Rheumatology criteria (n=884) were randomized to placebo (n=449) or milnacipran 200 mg/day (n=435) for 17 weeks (4-week dose escalation, 12-week stable dose, 9-day down-titration), followed by a 2-week posttreatment period. The primary efficacy criterion was a 2-measure composite responder analysis requiring patients to achieve simultaneous improvements in pain and a rating of "very much" or "much" improbe on the Patient Global Impression of Change scale. If responder analysis was positive, Fibromyalgia Impact Questionnaire (FIQ) was included as an additional key primary efficacy measure. At the end of the stable dose period (Week 16), milnacipran 200 mg/day showed significant improvements from baseline relative to placebo in the 2-measure composite responder criteria (p=0.0003) and FIQ total score (p=0.015). Significant improvements were also observed in multiple secondary efficacy endpoints, including Short-Form 36 Health Survey (SF-36) Physical Component Summary (p=0.025), SF-36 Mental Component Summary (p=0.007), Multidimensional Fatigue Inventory (p=0.006), and Multiple Ability Self-Report Questionnaire (p=0.041). Milnacipran was safe and well tolerated; nausea, hyperhidrosis, and headache were the most common adverse events. This study demonstrated that milnacipran 200 mg/day (100 mg bid) was safe and effective for treatment of FM in a European population.

Editor's note: Demonstrating that the efficacy and tolerability of milnacipran in a European population are equivalent to those in a US population is important in addressing the substantial healthcare burden of FM in Europe. Milnacipran is an effective and safe treatment for pain and other predominant symptoms of FM.