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# Fibromyalgia

## A bird's eye review of the recent literature

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*Edited by Laura Bazzichi and Arianna Consensi*

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### Pathogenesis

**Authors:** Burgmer M, Pogatzki-Zahn E, Gaubitz M, Stüber C, Wessoleck E, Heuft G, Pfeleiderer B.

**Title:** Fibromyalgia unique temporal brain activation during experimental pain: a controlled fMRI study  
*J Neural Transm* 2009; 117: 123-31.

**Summary:** The goal of the present study was to characterise FMS unique changes in brain activation during experimental tonic pain by comparing brain activity under experimental pain stimulation to patients with chronic pain of somatic origin. The authors hypothesized that brain areas important for cognitive/ affective appraisal of impending pain will show different activation patterns in patients with FMS compared to healthy subjects and patients with RA. To clarify whether these findings are unique to patients with FMS, BOLD-signal patterns during and before tonic experimental pain were compared to healthy controls and patients with rheumatoid arthritis (RA) as a chronic pain disorder of somatic origin. An fMRI-block design before, during and after an incision was performed in patients with FMS (n=17), RA (n=16) and in healthy controls (n=17). Additionally, the correlation of brain activity during the anticipation of pain with the amount of the impending pain was determined. The Authors observed a FMS-unique temporal brain activation of the frontal cortex in patients with FMS. Moreover, areas of the motor cortex and the cingulate cortex presented a FMS-specific relation between brain activity during pain anticipation and the magnitude of the subsequent pain experience. These results support the hypothesis that central mechanisms of pain processing in the frontal cortex and cingulate cortex may play an important role in patients with FMS.

**Editor's note:** The incision of skin induces burning pain and cutaneous hypersensitivity, this pain model seemed to be a good model for elucidating the mechanisms of pain in patients with FMS.

**Authors:** Harris RE, Sundgren PC, Craig AD, Kirshenbaum E, Sen A, Napadow V, Clauw DJ.

**Title:** Elevated insular glutamate in fibromyalgia is associated with experimental pain  
*Arthritis Rheum* 2009; 60: 3146-52.

**Summary:** Since glutamate (Glu) is a major cortical excitatory neurotransmitter that functions in pain neurotransmission, increased levels of insular Glu would be present in FM patients and that the concentration of this molecule would be correlated with pain report. Multiple functional magnetic resonance imaging studies implicate the insula as a region of heightened neuronal activity in this condition. Nineteen

FM patients and 14 age- and sex-matched pain-free controls underwent pressure pain testing and a proton magnetic resonance spectroscopy session in which the right anterior insula and right posterior insula were examined at rest. Compared with healthy controls, FM patients had significantly higher levels of Glu and combined glutamine and Glu (*i.e.* Glx) within the right posterior insula; no group differences were detected for any metabolite within the right anterior insula ( $p>0.11$  for all comparisons). Within the right posterior insula, higher levels of Glu and Glx were associated with lower pressure pain thresholds across both groups for medium pain. Indeed, this aspect of the pathophysiology of FM may be more similar to conditions such as epilepsy or neurodegenerative diseases than to the rheumatic syndromes with which it has historically been associated. For example, in epilepsy, cortical and subcortical neurons appear to be hyperexcitable as a result of elevated concentrations of Glu. FM may simply represent a condition in which glutamatergic "hyperactivity" occurs within brain regions devoted to processing and modulating pain. Enhanced glutamatergic neurotransmission resulting from higher concentrations of Glu within the posterior insula may play a role in the pathophysiology of FM and other central pain augmentation syndromes.

**Editor's note:** This hypothesis is consistent with the fact that one of the pregabalin is a drug Food and Drug Administration-approved medication for FM, whose action is thought to involve inhibition of presynaptic Glu release. Interestingly, this drug is also used in the treatment of epilepsy

**Authors:** Wood PB, Glabus MF, Simpson R, Patterson JC 2nd.

**Title:** Changes in gray matter density in fibromyalgia: correlation with dopamine metabolism  
*J Pain* 2009; 10: 609-18. Epub 2009 Apr 23.

**Summary:** A recent study involving small samples have suggested alterations in gray matter volume in brains of FM patients in the areas involved in phenomena related to the disorder, including enhanced pain perception, cognitive dysfunction, and abnormal stress reactivity. Voxel-based morphometry was used to evaluate anatomical magnetic resonance imaging data from 30 female FM subjects in comparison with 20 age- and gender-matched healthy control subjects. In addition, data from a subset of subjects from both groups who had previously participated in our positron emission tomography study using radiolabelled DOPA, was used to determine whether correlation might exist between gray matter density and dopamine metabolism. The authors found a reduction in gray matter density within the bilateral parahippocampal gyri, right posterior cingulate cortex, and left anterior cingulate cortex, in female with fibromyalgia

and no psychiatric comorbidities. The Authors found strong correlation between an index of corticolimbic dopamine metabolism and gray matter density in these areas, which both receives dopamine projections and controls their activity. Given mounting evidence of abnormal dopaminergic neurotransmission associated with the disorder, the strong correlation between dopamine metabolism and gray matter density provides insight as to the pathophysiology that might contribute to these changes.

## Disease assessment

**Authors:** Salaffi F, Sarzi-Puttini P, Girolimetti R, Gasparini S, Atzeni F, Grassi W.

**Title:** Development and validation of the self-administered Fibromyalgia Assessment Status: a disease-specific composite measure for evaluating treatment effect.

*Arthritis Res Ther* 2009; 11: R125. Epub 2009 Aug 18.

The patient with fibromyalgia and difficult to characterise even by The Fibromyalgia Impact Questionnaire (FIQ) is a composite disease-specific measure validated for fibromyalgia (FM). The objective was to develop and analyse the psychometric properties of a new composite disease-specific index (Fibromyalgia Assessment Status, FAS), a simple self-administered index that combines a patient's assessment of fatigue, sleep disturbances and pain evaluated on the basis of the 16 non-articular sites listed on the Self-Assessment Pain Scale (SAPS) in a single measure (range 0 to 10). The FAS index was constructed using a traditional development strategy, and its psychometric properties were tested in 226 FM patients (209 women, 17 men); a group of 226 rheumatoid arthritis (RA) patients was used for comparative purposes. The FAS index fulfilled the established criteria for validity, reliability and responsiveness. The self-administered FAS is a reliable, valid and responsive disease-specific composite measure for assessing treatment effect in patients with FM.

**Editor's note:** As the FAS index involves the use of only one side of one page, it can be quickly reviewed by clinicians to obtain a simple overview of patient status. In addition, the FAS is easy to understand and explores three fundamental domains of the disease (pain, sleep, fatigue)

**Authors:** Bennett RM, Friend R, Jones KD, Ward R, Han BK, Ross RL.

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

*Arthritis Res Ther* 2009; 11: R120.

**Summary:** The FIQ has been translated into 8 languages and is a commonly used instrument in the evaluation of fibromyalgia (FM) patients. The FIQR was developed in response to known deficiencies of the FIQ with the help of a patient focus group. The aim of this paper is to describe and validate a revised version of the FIQ: the FIQR.

The FIQR was administered online and has the same 3 domains

as the FIQ (that is, function, overall impact and symptoms). It differs from the FIQ in having modified function questions and the inclusion of questions on memory, tenderness, balance and environmental sensitivity. All questions are graded on a 0–10 numeric scale. The FIQR was completed online by 202 FM patients, 51 rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) patients, 11 patients with major depressive disorder (MDD) and 213 healthy controls (HC). The FIQR had good discriminant ability between FM and the 3 other groups; The FIQR is an updated version of the FIQ that has good psychometric properties, can be completed in less than 2 minutes and is easy to score. It also discriminates between FM patients and patients with RA, SLE, and MDD and can be used in online surveys.

**Editor's note:** It is interesting that the questionnaire includes a new assessment of tenderness that recalls the tender point. The FIQ was originally developed for a predominantly female population, so it can have a gender bias. In the FIQR, however, this tendency is reduced.

## Therapy

**Authors:** Häuser W, Bernardy K, Üçeyler N, Sommer C.

**Title:** Treatment of fibromyalgia syndrome with gabapentin and pregabalin – a meta analysis of randomised controlled trials

*Pain* 2009; 145: 69-81.

**Summary:** Pregabalin (PGB) and gabapentin (GPT) are structural analogues of the neurotransmitter gamma-aminobutyric acid (GABA). By reducing calcium influx at nerve terminals PGB and GPT diminish the release of several neurotransmitters, including glutamate, norepinephrine, and substance P. This mechanism is assumed to be the basis for the drugs analgesic, anticonvulsant, and anxiolytic actions.

Meta-analysis was performed according to the QUORUM guidelines (quality of reporting meta-analyses) and the recommendations of the Cochrane Collaboration when appropriate. The clinical relevance of the RCTs analysed was checked according to the recommendations of the Cochrane Collaboration. The authors found strong evidence for the efficacy of GPT and PGB in reducing pain and sleep disturbances, however, with small effect sizes and weak evidence of a favourable effect on fatigue and mood disorders.

The dosages 300, 450, and 600 mg/d PGB did not differ in pain reduction as to the small effect size. The incidence of some adverse events (dropout rates due to drug related adverse events; side effects like dizziness and somnolence) increased with the dose of PGB. The authors concluded that the usage of GPT and PGB can be considered for the treatment of pain and sleep disturbances in FMS patients, the treatment should start with low dosage and the dosage should be increased slowly with small dosages

Because only one study was available on GPT with a rather small number of patients, this meta-analysis does not allow a conclusive comparison of GPT and PGB.

**Authors:** Häuser W, Bernardy K, Arnold B, Offenbacher M, Schiltewolf M.

**Title:** Efficacy of multicomponent treatment in fibromyalgia syndrome: a meta-analysis of randomised controlled clinical trials

*Arthritis Rheum (Arthritis Care Res)* 2009; 61: 216-24.

**Summary:** The aim of the study is to evaluate the efficacy of multicomponent treatment (educational or other psychological therapy and exercise therapy) of fibromyalgia syndrome (FMS) by a systematical review

The authors screened Medline, PsychINFO, Scopus, and the Cochrane Library (through December 2007), as well as reference sections of original studies, reviews, and evidence-based guidelines. Randomised controlled trials (RCTs) on the multicomponent treatment (at least 1 educational or other psychological therapy with at least 1 exercise therapy) of FMS were analysed.

They included 9 (of 14) RCTs with 1,119 subjects (median treatment time 24 hours) in the meta-analysis. Effects were summarised using standardised mean differences (SMDs) or weighted mean differences (WMDs). There was strong evidence that multicomponent treatment reduces pain fatigue, depressive symptoms and limitations to health-related quality of life (HRQOL) and improves self-efficacy pain and physical fitness at post-treatment. There was no evidence of its efficacy on pain, fatigue, sleep disturbances, depressive symptoms, HRQOL, or self-efficacy pain in the long term. There was strong evidence that positive effects on physical fitness can be maintained in the long term (median follow-up 7 months). There is strong evidence that multicomponent treatment has beneficial short-term effects on the key symptoms of FMS. Strategies to maintain the benefits of multicomponent treatment in the long term need to be developed. Multicomponent therapy should be offered to FMS patients with relevant limitations in daily functioning who do not respond to monocomponent pharmacologic or nonpharmacologic treatment.

**Editor's note:** The complex symptomatology of fibromyalgia requires a multidisciplinary approach including education and exercise in addition to drug therapy to achieve the most efficient management of fibromyalgia.

**Authors.** Russell J, Perkins AT, Michalek JE, and the Oxybate SXB-26 Fibromyalgia Syndrome Study Group

**Title:** Sodium oxybate relieves pain and improves function in fibromyalgia syndrome. A randomised, double-blind, placebo-controlled, multicenter clinical trial

*Arthritis Rheum* 2009; 60: 299-309.

**Summary:** In early open-label trials of sodium oxybate in patients with narcolepsy, some patients with coexisting FMS showed improvement in their FMS-related symptoms, in addition to improvement in their narcolepsy symptoms. The objectives of this proof-of-concept, 8-week, randomised, double-blind, placebo-controlled, parallel group, dose-ranging study were to determine whether sodium oxybate would

be more effective than placebo in reducing the severity of pain, dysfunction, and insomnia in patients with FMS, and to assess the safety and side-effect profile of sodium oxybate in patients with FMS.

Patients with FMS were randomised, after discontinuing their pre-study medications for FMS, to receive 4.5 gm or 6 gm of sodium oxybate or matching placebo once per night for 8 weeks. Sodium oxybate has a half-life of 30–60 minutes. To maintain efficacy in controlling sleep, the total daily dose of the medication was equally divided between a bedtime dose and a second dose 2.5–4 hours later. The primary outcome variable (POV) was a composite score for changes from baseline in 3 co-primary self-report measures: patient's pain rating (in daily electronic diaries) on a visual analogue scale (PVAS), the Fibromyalgia Impact Questionnaire (FIQ) score, and the Patient Global Impression of Change (PGI-C). Secondary measures included subjective sleep outcomes (on the Jenkins Scale for Sleep) and quality-of-life measures. The intent-to-treat population included 188 patients with FMS, 78% of whom completed the trial. Significant benefit was observed with both dosages of sodium oxybate, according to changes in the POV and subjective sleep quality. Improvements in the PVAS score were significantly correlated with sleep outcomes. Each of the sodium oxybate treatment groups in this study demonstrated improvements in both the physical and the fatigue-related components of the FIQ, as well as improvements in the pain and vitality domains of the SF-36, suggesting that sodium oxybate therapy-induced improvements in pain and fatigue translate into better quality of life. Sodium oxybate was well tolerated overall; dose-related nausea and dizziness tended to resolve with continued therapy and the side-effect profile of sodium oxybate was similar to that previously reported in the treatment of narcolepsy. Further study of sodium oxybate as a novel therapeutic option for FMS is warranted.

**Editor's note:** In many patients with fibromyalgia, sleep disorders may precede the onset or worsening of the disease.  $\gamma$ -aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system

**Authors:** Clauw DJ, Mease P, Palmer RH, Gendreau RM, Wang Y

**Title:** Milnacipran for the treatment of fibromyalgia in adults: a 15-week, multicenter, randomised, double-blind, placebo-controlled, multiple-dose clinical trial

*Clin Ther* 2008; 30 (11).

**Summary:** Milnacipran is a dual norepinephrine-serotonin reuptake inhibitor and these types of drugs have been reported to have analgesic effects in animal models of hyperalgesia and allodynia; decreased cerebrospinal fluid levels of norepinephrine, serotonin, and dopamine metabolites have been found in FM patients compared with healthy controls and it may be particularly associated with symptoms of fatigue, decreased energy and lack of motivation. This is multicentre (86 centres in USA), double blind, placebo-controlled

trial undertaken to evaluate the efficacy and safety profile of milnacipran in a larger population of FM patients. Of 2270 patients screened, 399 were randomised to receive milnacipram 100 mg/die, 396 received 200 mg/die and 401 placebo for 15 weeks. Because this was a pivotal registration trial, the primary endpoints were chosen to investigate the efficacy

for the treatment of FM and for the treatment of pain. Patients treated with milnacipram experienced significant improvements in pain, patient global status physical function and fatigue. The analgesic response to milnacipran began as early as 1 week after the start of treatment and was sustained throughout the study.