

Fibromyalgia Syndrome's New Paradigm: Neural Sensitization and Its Implications for Treatment

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ABSTRACT. Objectives: To provide fibromyalgia syndrome [FMS] specialists with an overview of information suitable for the education of primary care physicians about current understanding of the mechanism of and treatments for FMS.

Findings: Controlled studies using functional magnetic resonance imaging and other objective markers document FMS as a disorder of increased sensitivity of the central nervous system's pain signaling pathways. This "neural sensitization" model shifts the focus for treatment toward drugs that affect neural pathways. New options include: 5-hydroxytryptamine serotonin receptor antagonists such as ondansetron [Zofran], N-methyl-D-aspartate receptor antagonists such as Ketamine, growth hormone stimulants such as pyridostigmine [Mestinon], anti-seizure drugs such as gabapentin [Neurontin] or pregabalin [Lyrica], gamma hydroxy butyrate-related agonists such as sodium sodium oxybate [Xyrem], and the new serotonin-norepinephrine reuptake inhibitors-class antidepressants such as duloxetine [Cymbalta] and milnacipran. Also recommended is appropriately graded exercise, i.e., conditioning, work on sleep quality, and cognitive behavioral therapy to support coping skills.

Conclusion: Improved understanding of the neural mechanisms involved in FMS and new options for treatment make it imperative that FMS specialists reach out to educate their primary care physician colleagues. doi:10.1300/J094v15n02_08 [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <<http://www.HaworthPress.com>> © 2007 by The Haworth Press, Inc. All rights reserved.]

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INTRODUCTION

My family practice and internal medicine colleagues often ask me two [blunt] questions about the fibromyalgia syndrome [FMS]: 1. Is FMS real and how do you know that? 2. Besides Elavil and Flexeril, is there anything we can do?

This essay is adapted from an invited lecture on FMS I gave to the family practice department at Robert Wood Johnson Medical School. It is not intended as an exhaustive literature review, but as a contribution to an emerging conversation between "fibromyalgia specialists" and primary care physicians, on behalf of our patients.

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Is the Fibromyalgia Syndrome Real? What Kind of "Disease" Is It?

When first defined by the American College of Rheumatology [ACR] in 1990 (1), FMS was viewed as a rheumatological illness—a matter of sore muscles. In contrast, the current “neural sensitization” model focuses on abnormal sensitivity within the central nervous system’s pain signaling pathways (2-4). Put simply, the volume knob for the pain system is turned up to “very high,” amplifying and distorting the patient’s perception of pain. Current thinking emphasizes the likelihood that there are several subtypes of FMS with over-lapping but not identical clinical presentations, mechanisms, and treatments.

The ACR’s criteria for FMS require: 1. a history of widespread chronic pain and 2. abnormal tenderness at 11 or more of 18 designated pain-sensitive anatomic sites, called tender points [TePs]. However, as Russell and colleagues emphasized (2-6), many persons who meet the ACR criteria also display two or more from among the following additional symptoms or syndromes listed on Table 1.

An estimated two percent of adult Americans satisfy the ACR criteria, although some studies rate this higher. If we relax the strict TeP requirement of the ACR criteria, the prevalence

of FMS-like pain increases into the range of six to 10 percent (2-4).

Clauw, writing in Conn’s Current Therapy 2005, suggests, “In clinical practice, most [but not all] individuals who have chronic widespread pain and no inflammatory or mechanical damage that can account for the pain, probably have fibromyalgia, whether or not they meet the required 11 out of 18 tender points” (5).

Evidence That the Fibromyalgia Syndrome Is a Neural Disorder

Fibromyalgia syndrome patients report more severe pain than the identical stimulus produces in healthy persons (9-12). But how do we know that FMS patients actually experience the increased pain that they report (13)?

Several lines of research now provide objective evidence of physical abnormalities in the FMS patient’s pain signaling pathways. For example, Gracely et al. (14,15) employed functional magnetic resonance imaging of the brain in a double-blind study measuring cerebral regional blood flow in response to applied physical pressure. Fibromyalgia syndrome patients had increased regional blood flow in multiple areas of the brain at relatively low intensities of pressure. Changes in blood flow coincided with the patient’s report of pain. The same modest pressures, when applied to controls, did not cause pain. Cerebral blood flow changes occurred, but these were much less than among persons with FMS. The authors conclude that “their findings support the hypothesis that fibromyalgia is characterized by cortical or sub-cortical augmentation of pain processing” (14).

Gibson et al., using cerebral evoked potentials as end points, similarly confirmed the increased pain sensitivity reported by FMS patients compared to controls (16). Others have described regional cerebral blood flow and cerebrospinal fluid [CSF] neurochemical abnormalities in FMS, including increased CSF levels of Substance P and decreased CSF levels of serotonin (17-22).

Staud and colleagues (10-12) obtained physical evidence that persons with FMS have abnormal central processing of painful [nociceptive] stimuli. If a painful stimulus is repeated frequently, e.g., less than every three seconds,

TABLE 1. Fibromyalgia Syndrome’s Common Co-Morbid Symptoms

- delayed flare-up of pain hours after modest exertion (6-8)
- irritable bowel syndrome
- non-restorative sleep
- vulvodynia
- irritable bladder syndrome
- interstitial cystitis
- general muscle stiffness
- chronic fatigue syndrome
- periodic leg movement disorder
- neurally mediated hypotension
- chronic headaches
- tempromandibular joint syndrome
- multiple chemical sensitivity
- impaired mental concentration
- anxiety disorders
- depression

the intensity of perceived pain increases. This is called temporal summation [also called wind-up]. Both normal persons and persons with FMS exhibit temporal summation. However, using the same stimulus, the initial intensity of pain was greater in FMS patients than for controls, as was the increasing intensity of pain [temporal summation] with repeated exposure to the stimulus. After the last stimulus in a series, after-sensations of pain were greater in FMS patients and lasted longer afterward than was the case for controls.

Animal models show that local injury can induce a diffusely increased sensitivity to pain and that N-methyl-D-aspartate [NMDA] receptor activation plays a central role (21). Ketamine, an NMDA antagonist, reduces this response (23). Double-blind studies in humans show that ketamine substantially reduces FMS pain (24,25).

Taken together, these studies confirm that FMS patients actually feel the pain they report, and that abnormal neural sensitization plays a central role.

Fibromyalgia Syndrome and Psychological Dysfunction

Arnold and colleagues (26) conclude, “. . . our data are not consistent with the hypothesis that FMS is caused simply by mood disorder; rather, they are consistent with the hypothesis that FMS and mood disorders share important common—and possibly heritable causal factors.”

Quite separate from anxiety or depression is the issue of coping skills. A large proportion of persons with any kind of chronic illness become vulnerable to a pattern of errors of thinking that can undermine their ability to cope. This is true whether or not a person becomes depressed or anxious. For example, small reverses are seen as catastrophes. People lose hope and feel not “in control.” See the section about cognitive behavioral therapy [CBT] under Treatment.

Differential Diagnosis and Evaluation

The differential diagnosis and work-up is not long or complex if we limit ourselves to the ACR criteria’s focus on sore and tender mus-

cles (1). However, in the real world, many patients also present with multi-system complaints including fatigue, poor stamina, poor sleep, cognitive difficulties, irritable bowel syndrome, “brain fog,” etc. Taking these additional symptoms into account provides a broader, more complex, and multi-system view of FMS as an illness, and also a tougher challenge for the clinician. See Tables 2 and 3 for the differential diagnosis and evaluation.

TREATMENT

For mild cases, medication for pain together with lifestyle advice may be all that is needed. However, as Russell and colleagues emphasize (2-4,6,27), when pain is severe or accompanied by other symptoms, the treatment plan should cover at least the following main problem areas: pain, sleep quality, how patient and family are coping with the distress of chronic illness,

TABLE 2. Fibromyalgia Syndrome’s Differential Diagnosis

Class of Illness	Examples
Autoimmune/Inflammatory Disorders*	Temporal arteritis, polymyositis, rheumatoid arthritis, systemic lupus, sicca syndrome, polymyalgia rheumatica
Musculoskeletal Disorders	Spinal disc disease, chiari syndrome, spinal stenosis, poor posture, leg length discrepancy, osteoarthritis, regional myofascial disorder
Psychiatric	Situational stress, anxiety, depression, post-traumatic stress disorder
Infectious Diseases	Lyme disease, hepatitis C
Medication	Statin drugs
Endocrine	Hypothyroid, hypoadrenal, hypo-pituitary, vitamin D deficiency, hyperparathyroid, mitochondrial disorders
Neurological	Multiple sclerosis, polyneuropathy
Sleep Disorders	Non-restorative sleep, R/o specific sleep disorders including periodic leg movement disorder, sleep apnea, narcolepsy

* One can have the fibromyalgia syndrome [FMS] in addition to rheumatoid arthritis, systemic lupus or other inflammatory disorders. The FMS is fairly common in these settings, and often overlooked. Clinically, this is important since different treatments are better for the inflammatory versus the FMS components of the illness.

TABLE 3. Testing to Consider

<p>Laboratory testing should usually include complete blood count, comprehensive metabolic profile, thyroid, creatine phosphokinase, anti-nuclear antibody, and sedimentation rate or C-reactive protein.</p> <p>Consider these additional tests as appropriate: Rheumatoid factor, magnetic resonance imaging of cervical spines, lumbar spines and/or brain, Lyme test, hepatitis C antibody, IgF1, 25-hydroxyvitamin D, cortisol, and tilt table test.</p>

exercise [i.e., conditioning], and whether depression and/or anxiety have developed. Additional problem areas that may have to be addressed include: low blood pressure and/or tachycardia, neurocognitive problems such as concentration or memory problems, fatigue and poor stamina, local or regional peripheral sources of musculoskeletal pain, irritable bowel syndrome, or post-prandial syndrome [reactive hypoglycemia].

For each problem area, patient education and support are important in addition to physical, psychological, and pharmacological attention. Obviously, this kind of treatment is time-consuming and challenging. One cannot usually address only one or two main issues within a single visit. However, the patient requires evidence that you are aware of all their problems and that you take them seriously.

Fibromyalgia syndrome patients may benefit from an initial long visit or two to start the process of education and to allow the patient to ask questions and vent frustrations. After that, many short visits might be better than fewer longer ones, especially for patients with difficulty sustaining cognitive and physical stamina and concentration.

Non-Pharmacological Treatments

Difficulty Coping with Chronic Illness Is Not "All in Your Head"

Short-term cognitive behavioral "talk" therapy, focusing on coping skills, can prevent or interrupt the vicious cycle of physical distress' disrupting coping skills and vice-versa. Approach these issues in a supportive way so the

patient does not feel that you think their illness is "all in your head."

Cognitive behavioral therapy is not a "cure." In fact, formal controlled studies show only a modest degree of benefit "on average." Still, clinical experience suggests that while CBT can make an important difference for selected individuals (28-31), CBT is best done by a clinician who understands and empathizes with the physical toll paid by people with FMS. *The Feeling Good Handbook*, by David Burns, MD (32), is an easy-to-use practical workbook for self-teaching CBT.

Anxiety and depression should be asked about periodically and, if they occur, be treated, as appropriate, with "talk" or pharmacotherapy.

Exercise: The Goldilocks Principle

Most FMS experts recommend exercise as a core FMS treatment since decreased physical activity leads to de-conditioning. De-conditioning, in turn, worsens FMS pain, mood, sleep, etc. Nevertheless, pushing one's limits as in "no pain, no gain" can do much harm and is contraindicated (4,6,28,33-37).

How much exercise is "just right," as Goldilocks might ask? Unfortunately, "just right" differs for different patients and, for the same patient, at different times. Walking half a mile may be appropriate for one person during one period of their illness, while 50 yards might work best for another person at another time.

We cannot rely on the standard heart rate and shortness of breath criteria to gauge exercise tolerance because the adverse effects of over-doing are often delayed. Exercise every other day makes it easier to recognize the delayed flare-up response.

Several recent reports suggest that exercise in a pool may be especially useful (36, 37).

Fibromyalgia Syndrome and Sleep Are Intimately Inter-Related

Should every difficult FMS patient have an overnight sleep study (4,38-39)? One could reasonably argue yes, since sleep apnea and periodic leg movement disorder [PLMD] have an increased prevalence. However, most expert advisors leave that to the clinician's judgment.

The clinician should instruct the patient to ask a bed partner to stay awake for at least 30 minutes to observe for muscle twitching, apnea, severe snoring, or struggling for breath.

Because FMS is chronic, there is an unavoidable tension between the goals of improving sleep and of avoiding dependence on sleeping medicines. Sharing these issues with the patient is important, with judgments decisions, in so far as feasible, being arrived at jointly, with the door remaining open to revision in the future.

First priority goes to sleep hygiene maneuvers such as regularity of bed-time, hot baths a few hours before sleep, and staging down in steps throughout the evening. Non-habit forming sedating medicines include: amitriptyline, cyclobenzaprine, trazadone, gabapentin, tizanidine, baclofen, and anti-histamines. Some physicians believe that benefits outweigh risks for longer-term use of zolpidem [Ambien], zaleplon [Sonata], or benzodiazepines such as clonazepam [Klonopin]. One tactic, which may reduce tolerance, is to use sleeping medicines only intermittently, i.e., three times a week.

Pharmacotherapy for Fibromyalgia Syndrome Pain

Table 4 lists the main classes of drugs which have been tested or used for FMS pain (4,40,41).

Before addressing the details, several principles should be kept in mind for this special population. Clinical experience suggests that FMS patients, as a group, may be atypically more “sensitive” to medicine side effects, particularly those patients who also display chronic fatigue, neurocognitive difficulties, irritable bowel syndrome, etc. A substantial proportion of patients are unable to tolerate any given medicine, especially at higher doses. No single drug is likely to work in more than 50 percent of patients. Different mechanisms of pain may be more important in different subgroups, since individuals vary greatly in terms of which medicine will help. Unfortunately, except through their past history and experience with these medicines, we have only a very limited ability to predict which medicine will do best for which individual.

Clinically, it may be helpful to: 1. start new medicines at one half or less of the usual

TABLE 4. Medicine for Fibromyalgia Syndrome Pain

CLASS/Medicine	Evidence Level
TRICYCLICS	A
amitriptyline/Elavil	A
cyclobenzaprine/Flexeril	
SEROTONIN SUBTYPE 3 [5HT3] ANTAGONIST	A
tropisetron [not available in U.S.]	B
odansetron/Zofran	
NMDA ANTAGONIST	A
ketamine [intravenous]	C
dextromethorphan	
GROWTH HORMONE RELATED	B
Growth hormone injections	B
Pyridostigmine/Mestinon	
NOREPINEPHRINE/SEROTONIN REUPTAKE INHIBITORS	B
duloxetine/Cymbalta	C
milnacipran**	
Venflaxine/Effexor	
ANTISEIZURE/GABA agonist	B
pregabalin/Lyrica	C
gabapentin/Neurontin	C
sodium oxybate/Xyrem [also known as GHB]	B
OPIOID-RELATED	B
tramadol/Ultram	C
Narcotic Pain Medicines	
ANESTHETIC	B
lidocaine, intravenous	
SEROTONIN RE-UPTAKE INHIBITORS	B
NSAIDS and COX-2 INHIBITORS	C
DOPAMINE AGONIST	B
pramipexole/Mirapex	C
bupropion/Wellbutrin	
acetaminophen/Tylenol	C
MULTIPLE SCLEROSIS-RELATED	C
tizanidine/Zanaflex	C
Baclofen	

Evidence level: A = 3+ double-blind controlled studies, B = one or two positive double-blind studies, C = mixed results or anecdotal support
5HT3 = 5 hydroxytryptamine serotonin, ** = not available in the United States, GABA = gamma-aminobutyric, GHB = gamma hydroxy butyrate acid, NMDA = N-methyl-D-aspartate, NSAID = non-steroidal anti-inflammatory drugs

For useful clinical guidance, I especially recommend references # 2-6, 27, and 28.

low-end starting dose, 2. escalate slowly over days or weeks, 3. forewarn the patient about potential side effects and that these tend to diminish over several weeks on the medicine, and 4. do not get upset with the patient if he or she does not tolerate one or more medicine.

Tricyclics Anti-Depressant Medicines

Most physicians first use amitriptyline [Elavil] or cyclobenzaprine [Flexeril], a muscle relaxant related to the tricyclics. Both have favorable double blind studies (42,43). Other tricyclics, such as nortriptyline [Pamelor] may be effective, but double-blind studies have not been done.

Tricyclics can be very useful in FMS, as they are for headache and other pain syndromes. However, no more than of half of patients respond favorably. The degree of benefit can be large, but often it is modest.

Side effects include sedation, dry mouth, prolonged QT interval, and weight gain. These can be problems even at the relatively low doses of amitriptyline typically used, i.e., 10, 20, or 30 mg every night.

5-Hydroxytryptamine Serotonin Receptor Antagonists

Although not widely publicized in the United States [US], several double-blind studies from Europe found substantial short term benefit for serotonin 3 receptor antagonists.

Tropisetron, which is available in Europe, has shown benefit in several studies. In one 10-day long double blind study of 418 patients, tropisetron was superior to placebo for improving pain and TePs (44).

Odansetron [Zofran], a 5-hydroxytryptamine serotonin receptor antagonist available in the US, has anecdotal support for FMS.

The main problem with 5-hydroxytryptamine serotonin receptor antagonists is that it may cause serious constipation and/or ischemic colitis. My personal experience is that only a small minority of patients tolerate odansetron on an on-going basis. However, for those that do, it can be worthwhile.

N-Methyl-D-Aspartate Receptor Antagonists

Double-blind studies show that a single infusion of the NMDA antagonist anesthetic, ketamine, can often reduce FMS pain for hours or even days (24,25).

Unfortunately, intravenous ketamine requires very careful monitoring due to potential cardiac and psychiatric side effects. Keta-

mine's street name "Special K" reflects its high potential for abuse.

The Alzheimer's medicine, memantine [Namenda] has NMDA receptor blocking activity, as does relatively high dose dextromethorphan. These have not been tested adequately for FMS.

Growth Hormone

Nearly 90 percent of FMS patients fail to show the expected rise in growth hormone levels immediately after exercise (45). Pyridostigmine [Mestinon] enhances parasympathetic nervous system action by slowing the metabolism of acetylcholine. Perhaps surprisingly, in FMS, pyridostigmine also improves the growth hormone response to exercise (46). Although this improvement occurs within hours, there is no evidence for short-term improvement of symptoms. However, in a six-month long study, Jones and Bennett (47) reported that continuous treatment with pyridostigmine at 60 mg three times daily was more effective than placebo for improving fatigue, sleep quality, and over-all quality of life. I suggest starting at less than the full dose. Anecdotally, pyridostigmine timespan tablets 180 mg twice daily may be better tolerated than the conventional tablet at 60 mg three times daily.

Do not use pyridostigmine if there is heart block or bradycardia. Abdominal cramps, increased salivation, sweating, increased bronchial secretion, diarrhea, and hyperacidity can be problems.

Dr. Bennett has also found that growth hormone injections over six months were more effective than placebo, but the degree of benefit tended to be modest (reference).

Norepinephrine Serotonin Reuptake Inhibitors

One postulated mechanism for amitriptyline's benefit is its ability to enhance both norepinephrine and serotonin neurotransmission. Blocking reuptake receptors or transporters increases the amount of these neurotransmitters that is available to affect function in the central nervous system.

Newer norepinephrine serotonin reuptake inhibitors [NSRI]-class medicines have double

blind data showing benefit in FMS. Duloxetine [Cymbalta], recently approved for use both as an anti-depressant and for diabetic neuropathy, showed improvement for FMS in one double-blind study (48). Milnacipram, another NSRI anti-depressant, not yet approved, may also help FMS (49). Duloxetine was effective whether or not the patients were also depressed. Effexor is also an NSRI when used at high doses. Double-blind studies on FMS have not been done. Effexor showed little promise in two open label pilot studies.

Gamma-Aminobutyric Acid-Related

Gabapentin [Neurontin], approved for seizure disorders, is also used for pain syndromes, including FMS. Anecdotal reports are encouraging. However, sedation, mental cloudiness, and other side effects often limit dosing. Higher-than-standard dosing may be needed for optimum effect on pain.

Side effects include sedation, dizziness, ataxia, nystagmus, double vision, and tremor. Because of sensitivity to side effects, I usually start patients off with a 100 mg test dose given at night. I then build up to at least 300 mg every night before adding daytime dosing. If daytime dosing is not tolerated, I may slowly increase the nighttime treatment dose, as tolerated.

Although gabapentin has a structural similarity to the neurotransmitter gamma-aminobutyric acid, its mechanism of action is unknown, and is not necessarily related to GABA.

Pregabalin [Lyrica], now in advanced testing for diabetic neuropathy, was more effective than placebo in one double-blind study of FMS (49). Crofford and colleagues (50) randomized more than 500 FMS patients to one of three dose levels of pregabalin or placebo over eight weeks. The highest dose, 450 mg per day, was more effective than placebo for reducing pain, improving sleep, and daytime fatigue. Side effects included dizziness and sedation. Pregabalin may work through a calcium channel mechanism.

Sodium oxybate [Xyrem] is a GABA-B receptor agonist has been approved by the Food and Drug Administration for a sub-type of narcolepsy. Two double-blind studies show benefit for FMS (51,52). A large clinical trial is in process. "On the street" sodium oxybate, also

known as gamma hydroxy butyrate, has been exploited as a "date rape" drug. Sodium oxybate has respiratory depressant effects as well as potential for abuse and addiction. To prevent abuse and assure physician and patient education for proper use of this medicine, all US prescriptions for Xyrem are processed through a single mail-order pharmacy. Especially encouraging has been data that, unlike others sleeping meds, sodium oxybate increases stage 3-4 non-rapid eye movement sleep.

Selective Serotonin Reuptake Inhibitors

Fluoxetine [Prozac] has had mixed results in double-blind studies of FMS pain. Arnold et al. found benefit in a 12-week long study using flexible dosing from 10 to 80 mg daily (53). Goldenberg et al. found fluoxetine superior to placebo, especially when combined with tricyclics, giving fluoxetine in the morning and the tricyclic at night (54). However, other studies have found benefit for mood but not for pain (55).

Opioid Related

Tramadol/Ultram is beneficial for FMS pain and its addictive potential is relatively low (56,57). Adding acetaminophen to tramadol [e.g., Ultracet] may have synergistic benefit (58). However, be aware of potential liver toxicity of acetaminophen, at least in part due to interference with glutathione dependent detoxification pathways. Although support is mainly indirect, I recommend adding 300-600 mg daily of oral N-acetyl cysteine for patients who take acetaminophen on a regular basis. Oral N-acetyl cysteine, an equivalent of "Mucominist," is available at health food stores. Do not mix acetaminophen with alcohol.

We currently lack evidence-based guidelines for balancing the potential benefits of long-term narcotic pain medicines against the risks of addiction, drug abuse, and dose-escalating tolerance. Some clinicians recommend long-term use. Others prescribe narcotics only for break-through pain.

Dopamine agonists are effective for PLMD, which is often co-morbid with FMS. One double-blind study showed premipexole/Mirapex to improve FMS pain, and this effect seemed to

be independent of the benefit for PLMD. However, relatively high doses were used in this study, which caused a high incidence of nausea.

Non-steroidal anti-inflammatory drugs, cox-2 inhibitors, and acetaminophen are recommended by many physicians, despite a lack of controlled studies (59). There is some data to suggest that acetaminophen may be synergistic with Tramadol.

Corticosteroids provide little benefit (60). If corticosteroids help, consider that an inflammatory process might have been missed, e.g. polymyalgia rheumatica, rheumatoid arthritis, or systemic lupus.

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