

# New Developments in the Management of Fibromyalgia Syndrome

## [Disclosures](#)

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Fibromyalgia syndrome (FMS) is a common, chronically painful, frequently disabling disorder of unknown origin. The syndrome is characterized by clinical criteria that were designed to classify affected individuals who were being enrolled into research studies. The criteria include 2 simple components, one from the medical history (widespread pain for at least 3 months) and the other from the physical examination (pain elicited by digital palpation with a pressure equivalent to 4 kg at 11 or more of 18 anatomically defined tender points). Proper application of these criteria can distinguish FMS patients from healthy controls and from rheumatic disease patients with a sensitivity and specificity of 88.4% and 81.1%, respectively.<sup>[1]</sup>

## **What We Know Now**

Epidemiologic data indicate that FMS affects at least 2% of the general population in the United States (approximately 5 million persons),<sup>[2]</sup> and a similar prevalence seems to exist worldwide.<sup>[3]</sup> Furthermore, it appears that 6% to 10% of all individuals in a medical physician's waiting room have FMS,<sup>[4]</sup> so most physicians with active clinical practices can expect to relate to at least 1 patient with FMS daily. For the typical patient with FMS, the annual direct medical cost associated with this condition is more than \$2200,<sup>[5,6]</sup> which means that the condition costs the US economy at least \$10 billion each year.

## **Symptoms and Associated Conditions**

In addition to the classification criteria, FMS patients report a variety of other clinical symptoms. These symptoms can include anxiety, depression, occipital headaches, dysfunctional sleep, morning stiffness, digital paresthesia, chest wall pains, irritable bowel, and irritable bladder.<sup>[7-9]</sup> For reasons that are not clear, FMS patients also tend to be accident prone.<sup>[10,11]</sup> Clinical overlap with FMS is documented among a number of other medical conditions, such as nocturnal myoclonus, hypothyroidism, myofascial pain syndrome, chronic fatigue syndrome, irritable bowel syndrome, irritable bladder syndrome (interstitial cystitis), acquired immunodeficiency syndrome, and many of the inflammatory rheumatic diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome.<sup>[12-18]</sup> In the past, there was a common perception that FMS was just a manifestation of depression or some related psychological illness; however, the prevalence of depression in FMS is only about 40%, comparable to that of rheumatoid arthritis, which is a somatic inflammatory condition.<sup>[19]</sup>

The pain associated with FMS appears to involve many physiologic components of nociception,<sup>[20-22]</sup> so the earlier perception that patients were psychosomatic malingerers has been supplanted by the recognition of relevant abnormal laboratory findings. As a result, the disorder has been reconceptualized as a human model for widespread allodynia.<sup>[22]</sup>

### **Biochemical Abnormalities**

The most dramatic laboratory abnormality, found in most FMS patients (> 80%), is a consistently elevated, stable level of cerebrospinal fluid (CSF) substance P (SP).<sup>[23-26]</sup> All of the 4 research groups that have studied the levels of this neuropeptide in FMS CSF have found similarly elevated levels despite populations of patients from different ethnic backgrounds. Furthermore, elevated levels of CSF SP for patients who were not undergoing treatment did not fall spontaneously during a 1-year period.<sup>[27]</sup> In addition, there are correlations of the CSF SP with the excitatory amino acids in the CSF of FMS patients.<sup>[28]</sup> The biogenic amines that naturally regulate the release of substance P are deficient in the CSF of people with FMS.<sup>[29]</sup> There also is growing evidence for abnormalities in the hypothalamic-pituitary adrenal, gonadal, and growth hormone axes.<sup>[30-34]</sup> It is possible that some or all of these abnormalities result directly from the recognized abnormalities in biogenic amines and neuropeptides.<sup>[35]</sup> Finally, as with rheumatoid arthritis,<sup>[36]</sup> the morning serum hyaluronic acid (HA) level has been found to be elevated in FMS, and the change in HA from midmorning to noon correlates with the patient's perceived severity of morning stiffness.<sup>[37]</sup>

### **Treatment**

The most common approach to treatment of FMS is multimodal and includes patient education, psychological support, physical modalities such as exercise, and medications.<sup>[38]</sup> The perception that pain medications, with their potential risks, are not indicated in FMS because it is a benign condition<sup>[39]</sup> has now been countered by the documentation of objective evidence that FMS patients are actually experiencing the pain they describe.<sup>[21,40,41]</sup> Medication therapy of FMS has variously involved over-the-counter preparations,<sup>[42]</sup> analgesics,<sup>[43]</sup> and antidepressants,<sup>[44,45]</sup> but patients seldom achieve complete relief from any kind of monotherapy.<sup>[38]</sup>

### **Questions Persist**

Many questions remain regarding the abnormal biochemical and physiologic processes in FMS, their relationships to the FMS symptoms, and their best management. For example:

- 1. Have the abnormal biochemical and physiologic properties of the central nervous system been acquired by some quirk of maladaptation or were they programmed by a genetic abnormality?**

- 2. To what extent can the biochemistry of pain be manipulated by psychological or psychophysiological intervention?**
- 3. Which steps in the nociceptive process might be strategically altered in FMS to produce clinical benefit?**
- 4. Would patients with FMS benefit clinically if it were possible to normalize the CSF SP concentration?**
- 5. Would anticonvulsants that stabilize central nervous system neurons by raising the threshold for a depolarization also reduce the amount of pain experienced by FMS patients?**
- 6. Are over-the-counter remedies just as effective as those provided by traditional pharmaceutical companies?**

### **What We Are Learning**

The answers to these fairly broad questions could have critical importance to the management of FMS and on the amount of discomfort people with this condition will have to experience over time. Several abstracts presented at the 66th Annual Meeting of the American College of Rheumatology (ACR) this year addressed some of these questions.

#### **Benefit From Normalization of SP?**

A previous attempt to influence the effects of the elevated CSF SP levels in FMS involved administration of a potent blocker of its receptor, neurokinin-1, in the spinal cord.<sup>[46,47]</sup> A second approach took advantage of the natural effect of a biogenic amine agonist to inhibit the release of SP into central nervous system tissue, since several of the biogenic amine neurochemicals are known to be deficient in patients with FMS CSF.<sup>[29]</sup>

Tizanidine is a relatively new, centrally acting,  $\alpha_2$ -adrenergic agonist that has been approved for the treatment of spasticity, such as that occurring in patients with multiple sclerosis or spinal cord injury. This agent is believed to act like norepinephrine by inhibiting polysynaptic pathways involved in the activation of motor neurons. Ono and colleagues<sup>[48]</sup> have documented the effects of tizanidine\* and clonidine\* on the in vitro release of SP from slices of rat spinal cord tissue. In this study, exposure of the cord tissue to 10  $\mu$ mol/L of clonidine or tizanidine significantly reduced veratridine-induced release of SP in vitro. If tizanidine were to exhibit the same effects on human spinal cord tissue in vivo, it might be possible to document a reduction in the elevated levels of CSF SP in patients with FMS.

This hypothesis was the basis for an open-label study conducted by Russell and colleagues<sup>[49]</sup> from the University of Texas Health Science Center in San Antonio. The study focused on a single biological outcome variable (change in CSF SP level with tizanidine treatment) as the primary outcome variable. Because it had been previously demonstrated<sup>[27]</sup> that FMS CSF SP levels do not fall spontaneously (without treatment), it was accepted that any observed fall in CSF SP levels during medication treatment would represent a therapeutic effect.

The study enrolled 25 primary FMS patients who met the ACR classification criteria for that condition and 23 completed 8 weeks of on-therapy follow-up. Patients discontinued use of FMS medications for 2 weeks before their baseline assessment. Radioimmunoassay for SP was performed on CSF samples at baseline and on stable monotherapy at week 8. The tizanidine dose ranged from 4 mg at bedtime to 24 mg/d in divided doses, as tolerated. Secondary outcome variables measured at the same visits included serum HA levels and clinical assessments such as the Sleep Efficiency Scale (SES), the Stanford Health Assessment Questionnaire (HAQ), the Fibromyalgia Impact Questionnaire (FIQ), the Pain Visual Analog Scale (PVAS), the Tender Point Index (TPI), and the Average Pain Threshold by dolorimetry.

The average CSF SP level fell significantly ( $P = .02$ ) with tizanidine therapy but did not normalize to below 20 fmol/mL. Among the secondary measures, the mean serum HA level fell numerically but that reduction was not significant. SES ( $P = .02$ ), PVAS ( $P = .01$ ), HAQ ( $P = .01$ ), and FIQ ( $P = .02$ ) scores improved but the others did not change significantly, and none of the clinical changes correlated with the decrease in CSF SP levels. Interestingly, several key clinical variables correlated with the smaller decrease in HA ( $P = .03$  to  $.04$ ). One subject left the study because of abnormal liver function and another because of hallucinations. Five patients experienced transaminitis, which responded to tizanidine dose reduction or discontinuation.

This was an open-label study so the influence of placebo on the clinical variables could not be assessed. However, the primary outcome variable for the study was an objective laboratory test (CSF SP) that should be less subject to hopeful enthusiasm. The critical observation was that potent alpha<sub>2</sub>-agonist therapy significantly reduced the levels of CSF SP in this FMS cohort. This finding supports the hypothesis that excess CSF SP production in FMS is caused by recognized deficiencies of endogenous, caudally directed, inhibitory biogenic amines.

What is not known is whether the reduction in CSF SP in this study was achieved entirely by inhibiting afferent neuron production of SP or whether it included inhibition of SP production in brain and spinal interneurons as well. It is certainly possible that serotonergic activity would be additive or synergic with that of the tested alpha-adrenergic agent. Other inhibitory receptors may also be active in this regard.

The secondary outcome measures in the reported study were also of interest. Tizanidine treatment of FMS patients was accompanied by significant improvement in the subject's perception of their sleep, subjective pain, and reported physical function. None of the secondary outcome measures from baseline to week 8 of tizanidine therapy correlated with the change in CSF SP levels. This may have been true because the levels of CSF SP did not actually normalize under the conditions of this study. It may be necessary to therapeutically reduce the CSF SP levels to normal because small increases could be sufficient to amplify nociception. On the other hand, a trend toward falling serum HA levels correlated with improvements in clinical scores. These findings suggest that serum HA may be a useful measure of clinical response to therapy in FMS. Thus, in this study, tizanidine was well tolerated and may be clinically useful in the treatment of FMS; however, transaminase levels should be monitored during continuous therapy.

### **Inhibition of Serotonin and Norepinephrine**

Zijlstra and associates<sup>[50]</sup> from the Department of Rheumatology at centers in Enschede and Rotterdam, the Netherlands, cooperated in a study that examined the benefits of the antidepressant venlafaxine\* for patients with FMS. The mechanism of the proposed benefit of venlafaxine in FMS relates to its recognized inhibition of both serotonin and norepinephrine reuptake into neurons that have released them into a central nervous system synapse. The investigators alluded to a previous open-label trial that suggested benefit of this drug in 6 of 15 study participants.<sup>[51]</sup> Wisely, the current investigators proceeded to a randomized, placebo-controlled trial.

Ninety primary FMS patients who met ACR criteria were randomized to receive venlafaxine at 75 mg/d (n = 45) or placebo (n = 45) for 6 weeks. The sample size was reasonable, standard outcome measures were used, and the statistical analysis was appropriate. The only real difference in outcomes between the groups was that significantly more of the subjects in the venlafaxine group dropped out of the study because of adverse effects ( $P = .01$ ).

Although venlafaxine inhibits the reuptake of both serotonin and norepinephrine, the differential ratios of the effects on these 2 biogenic amine receptors are known to vary with the dosage. In low doses, venlafaxine can behave like a selective serotonin reuptake inhibitor (SSRI), but at higher dosages it more effectively inhibits norepinephrine reuptake as well. The 75-mg/d dosage is in the low range and probably was primarily influencing serotonin. A previous study with a low dose of a different medication, the SSRI fluoxetine, was effective for relieving anxiety, depression, and insomnia in FMS but not for the pain.<sup>[52]</sup> A more recent study using substantially larger dosages was more successful with subjective pain.<sup>[53]</sup>

### **Using a Novel Anticonvulsant**

Pregabalin is a second-generation anticonvulsant agent similar to gabapentin but about 6-fold more potent. Because of their structural similarity to gamma aminobutyric acid, these

drugs were believed to function as neural inhibitors; however, their mechanism of action may actually relate to inhibition of the preganglionic calcium-gated channel. In animal models of chronic pain, pregabalin has been found to be effective in raising the pain threshold, reducing allodynia, increasing slow-wave nonrapid eye movement sleep, relieving anxiety, modulating acute pain symptoms, and reducing colon-related pain.<sup>[54-59]</sup> However, it may also induce nocturnal myoclonus.<sup>[60]</sup>

An 8-week, multicenter, randomized, double-blind, placebo-controlled study by Crofford and coworkers<sup>[61]</sup> from the University of Michigan, Ann Arbor, and colleagues from several other institutions evaluated the efficacy and safety of pregabalin\* in patients with FMS. Patients diagnosed as having primary FMS completed a 1-week baseline phase before the 8-week, fixed-dose treatment phase. A total of 529 patients were randomized to receive placebo, 150 mg/d, 300 mg/d, or 450 mg/d of pregabalin. Patients used an 11-point numeric rating scale to measure and record their pain level in a daily pain diary. Secondary outcome measures were assessed with the Short Form McGill Pain Questionnaire (SF-MPQ), the sleep quality diary, the Medical Outcomes Study (MOS) Sleep Scale, the Multidimensional Assessment of Fatigue, the Patients' Global Impression of Change (PGIC), the Clinical Global Impression of Change (CGIC), and the 36-Item Short-Form Health Survey.

Patients treated with the highest dose, 450 mg/d, of pregabalin experienced significant improvement in the end point mean pain score ( $P < .001$ ) compared with those receiving placebo and were more likely to experience a 50% reduction in pain from baseline to end point ( $P = .003$ ). Likewise, the mean SF-MPQ and visual analog scale pain scores were both significantly improved at each follow-up visit and at the end point for this treatment group compared with placebo. For patients receiving either 300 or 450 mg/d, other variables, such as the mean sleep quality, fatigue, and CGIC and PGIC scores at end point were improved significantly. Patients in all treatment groups demonstrated significantly improved MOS-Sleep Index scores. In total, 48 patients (9%) withdrew from the study because of adverse side effects (most commonly dizziness and somnolence) and 44 (8%) because of poor efficacy.

This study represents an important achievement in the field of FMS and specifically for patients with FMS for several reasons:

- **A new medication in the therapeutic armamentarium for FMS offers the clinician an additional option for patients who have experienced intolerance to earlier medications.**
- **This drug expands by one the classes of drugs that have demonstrated benefit in the management of the central neuropathy of FMS.**

- **Although it is not necessarily true that other members of the anticonvulsant family of drugs will be helpful for this condition, researchers who pioneer the development of designer drugs now have another model to consider.**
- **The drug is backed by a major pharmaceutical house with the resources to carry it through the Food and Drug Administration (FDA) to achieve an indication.**
- **An FDA-approved indication will provide a form of legitimacy to the FMS diagnosis that will promote better acceptance of the disorder, in part, because there is an accepted efficacious treatment the physician can use when the diagnosis is made.**
- **The usual process of pharmaceutical marketing will require clever advertisements and continuing medical education programs that will also inform physician prescribers how to properly diagnose the condition.**
- **Pharmaceutical marketing programs, particularly the new trend toward direct patient marketing, will raise awareness of the disorder among patients with undiagnosed conditions, nonphysician health care professionals, politicians, and the general public.**
- **Education programs will require additional discussion of other agents of different classes that have been found to be effective for FMS, and these other agents will become better known.**
- **Profits from the success of one drug on the market indicated for FMS will encourage other companies to risk creative entry and investment in the field.**

### **Over-the-Counter Approaches to FMS**

The previously mentioned studies examined single-agent medications that were subjected to rigid federal controls and have been or will be licensed for distribution by prescription only. The following clinical study was performed with similar care but used an over-the-counter, multi-ingredient, nutraceutical (EM Power+) that had not been subjected to the same standards regarding production or proof of efficacy. This study, conducted by Martin and colleagues<sup>[62]</sup> from the University of Calgary, Calgary, Alberta, Canada, was randomized and placebo-controlled for 6 months and then extended to an open-label follow-up for an additional 3 months. The studied agent contains 36 "natural" ingredients and has been reported<sup>[63]</sup> to show efficacy in the treatment of FMS.

Ninety-nine patients with FMS (ACR criteria) were enrolled and randomized to receive 24 tablets per day of the investigated agent (n = 51) or matching placebo (n = 48). Assessments included the total myalgic score (TMS, identical to the TPI), the FIQ, a Self-Efficacy Scale (SEF), the Center for Epidemiology Scale for Depression (CESD), a quality-of-life scale (QOL), and the Illness Intrusiveness Response Scale (IIRS).

The study found comparable improvements in both participant groups. No significant benefit for the FMS symptoms was attributable to the nutraceutical preparation. There was no agent-specific improvement in the TMS, FIQ, SEF, CESD, QOL, or IIRS during the blinded drug phase of the trial. Curiously, there was some improvement in the TPI score during the final 3 months when all subjects were taking the active agent on an open-label basis. The investigators concluded that these results argue against nutritional deficiencies being a causative factor in FMS and against the efficacy of this nutraceutical for FMS.

Patients with FMS are sometimes suspicious of traditional medicine and wish to use only natural products that they can purchase over the counter. Such purchases may have the benefit of giving the patient the perception of self-control over their FMS symptoms. An important problem with the interpretation of the data from such a study is that most nutraceutical preparations contain multiple ingredients. Several interpretative conundrum scenarios can be imagined in response to careful study of such an agent:

- **If statistically significant benefits were observed after careful blinded comparison with a placebo intervention, one would not know which of the 36 ingredients was critical to the outcome (although that issue may not really matter to the improved subjects).**
- **If an adverse effect occurred it would be impossible to determine with confidence which of the 36 components was responsible, and it would be similarly difficult to remove 1 component from the mixture to maintain the presumed benefits from the other 35 components.**
- **If a lack of benefit from such a mixture were observed, one might still wonder whether one of the ingredients was actually moderately beneficial, but opposing effects from some other ingredient prevented it from being experienced or observed.**
- **Whether benefit or lack of benefit was observed with a multicomponent nutraceutical, it would be difficult to know how to use the information to advance to the next generation agent or develop similar preparations, because there would be no direct class comparisons (as is possible with comparisons between each of the SSRI drugs or tricyclic drugs). Each new preparation of nutritional ingredients would have to be tested independently to discern the presence of any therapeutic merit.**

## Summary

Fibromyalgia is a common syndrome of widespread soft tissue pain that is substantially underserved by the medical profession and the pharmaceutical industry. This field of inquiry and the patients with FMS would be better served by an improved understanding of the biologic and physiologic processes responsible for the symptoms of FMS. One over-the-counter nutraceutical agent has been properly tested and found not to meet expectations for treatment of FMS. In one study presented at the ACR annual meeting, venlafaxine\* was tested for FMS and, surprisingly, was found to offer no statistical benefit. However, the finding that elevated levels of CSF SP in FMS respond to a potent alpha-adrenergic agonist drug (tizanidine\*) provides encouragement to try other similar interventions, including combinations of drugs with recognized separate inhibitory activity at specific sites in the pathogenesis of FMS. Finally, another trial found that the investigational agent pregabalin\* improved many of the typical symptoms of FMS. Thus, 2 therapeutic agents with different mechanisms of action may now be added to the FMS therapy armamentarium.

Some important questions have yet to be addressed. What kinds of biochemical and physiologic changes predispose individuals to developing the disorder and how have these rendered patients susceptible to FMS? Can these changes be manipulated by psychological or psychophysiological interventions? Which steps in the nociceptive process might be altered to produce clinical benefits? This year's ACR meeting provided a number of key answers to critically important questions. Undoubtedly, next year will prove equally rich in ideas.

\*The United States Food and Drug Administration has not approved this medication for this use.

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