

FIBROMYALGIA SYNDROME:
REVIEW OF THE EPIDEMIOLOGY AND MECHANISMS INVOLVED*

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ABSTRACT

Although fibromyalgia syndrome (FMS) affects approximately 3 million to 8 million Americans and has a significant negative impact on daily functioning and quality of life, there is no consensus among clinicians on the cause of FMS, its treatments, or even whether it is a “real” illness. Some clinicians recognize it as a disorder of central and peripheral pain processing, whereas others believe it to be a somatic syndrome with a strong psychological and/or emotional component. To help bridge the divide, this article reviews the clinical features and evaluation of FMS, discusses the crucial role of central sensitization, and examines evidence for several mechanisms thought to contribute to the syndrome. These include peripheral, spinal, and supraspinal mechanisms associated with abnormalities of sensory processing.

(*Adv Stud Med.* 2009;9(4):108-114)

Fibromyalgia syndrome (FMS), one of the most common causes of generalized musculoskeletal pain and tenderness in adults,¹ affects approximately 3 million to 8 million Americans.² Most of those affected (80%) are women, usually between 20 and 60 years of age,² and the majority seek treatment from their primary care physicians.³

Because there is no consensus among clinicians on the precise cause of FMS, its treatments, or even whether it merits consideration as a distinct clinical entity, many patients receive ineffective care. The lack of consensus on FMS as a “real” illness is particularly troublesome because it represents differing approaches to treatment by clinicians who recognize FMS as a disorder of central and peripheral pain processing and by clinicians who believe that it is a somatic syndrome with a strong psychological and/or emotional component.⁴ At present, an accumulating body of scientific evidence supports the former.

As a step toward achieving a clinical consensus, this article presents an overview of FMS, addresses its diagnostic criteria and evaluation, and reviews the findings of neuroimaging and other studies that support the involvement of several mechanisms believed to play a role in its etiology and pathophysiology.

FMS IN PERSPECTIVE

As demonstrated in numerous studies, FMS has a significant negative impact on daily functioning and quality of life (QOL).^{5,9} In one study, patients reported difficulty with climbing stairs (62%), walking 2 blocks (55%), and activities of daily living (35%).⁵ In another, the average 50-year-old woman with FMS reported having less functional ability than the average community-dwelling woman in her 80s.⁶

Other studies found that men and women with FMS had lower QOL scores for personal relationships,

*Based on a presentation developed by Dr Smith for a national symposium series held in October and November 2009.

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career, and mental health,⁷ and that women with FMS had lower QOL scores than women with rheumatoid arthritis (RA), osteoarthritis, chronic obstructive pulmonary disease, and type 1 diabetes.⁸ A Spanish study involving nearly 3000 patients with musculoskeletal pain found that those with FMS had comparable physical impairment but more psychological impairment than those with RA.⁹

Fibromyalgia syndrome is also a major factor in requesting sick leave and disability benefits,^{2,7,10,11} and is associated with increased rates of healthcare utilization and costs.^{5,12,13} As reported in one US study, nearly 20% of patients with FMS applied for disability, with more than 25% of them receiving the benefits.² Another US study found that more than 50% of patients with FMS left the workforce after developing symptoms.⁷ Among those remaining at work, the majority had to reduce their work hours. A study conducted in Spain reported that 31.4% of patients with FMS were on medical leave from work, with slightly more than 50% of them qualifying for temporary disability and slightly less than 50% for permanent disability.¹⁰

A Canadian study compared 3 groups of patients—those with confirmed FMS, those with widespread pain but no FMS, and pain-free controls—and found that those with FMS spent more time in bed (more than double that of patients with pain but no FMS) because of pain during the previous 2 weeks, took more time off from work, and were more likely to be work-disabled and receiving a disability pension.¹¹

DIAGNOSTIC CRITERIA AND CLINICAL EVALUATION

Diagnostic criteria for FMS, as established by the American College of Rheumatology (ACR) in 1990, are outlined in Figure 1, along with an illustration of 18 predesignated tender points.¹⁴ Originally intended for use as a research tool, the ACR criteria may have some limitations when used in clinical practice.¹⁵

Although the requirement that widespread pain must be present for at least 3 months is not a limitation of the ACR criteria, the tender point requirement may be because there are some patients with FMS who may have fewer than 11 of 18 tender points at any given time point.¹⁵ Moreover, the tender point criterion is more selective for females than for males, who may require more than 4 kg/cm² of pressure to elicit a pain response.¹⁵ In addition, the criteria focus on pain and

ignore other components of the constellation of symptoms in FMS, such as fatigue and sleep disturbances.

Aside from chronic widespread pain, other symptoms in the constellation may include cognitive impairment, morning stiffness, prior or current symptoms of anxiety and/or depression, and impaired social and occupational functioning.^{14,16} Sexual dysfunction has also been reported to occur frequently.^{17,18} In an individual patient, any one or more of these symptoms may be predominant at presentation.

Evaluation of any patient with generalized pain begins with a careful history and a thorough physical examination, followed by appropriate ancillary testing (eg, electrodiagnostic testing or imaging studies) based on the individual patient's presentation. Similarly, the patient's comorbid condition(s) should also be evaluated. For example, a complete blood count and vitamin levels may be in order for those complaining of concomitant fatigue, whereas a sleep study may be needed for those reporting significant sleep disturbances with daytime somnolence.

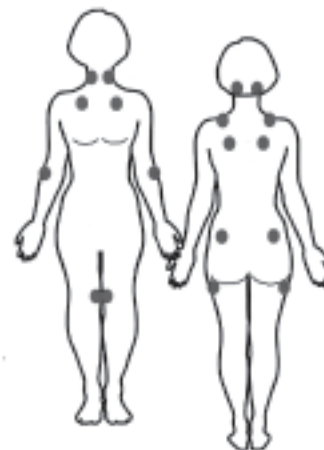
The revised Fibromyalgia Impact Questionnaire developed by Bennett et al¹⁹ can be used to assess the patient's general functioning, overall impact of FMS, and the intensity of pain, tenderness, anxiety, and other symptoms over the previous week (Figure 2).¹⁹

Figure 1. Diagnostic Criteria for FMS

Widespread pain for ≥ 3 months, defined as the presence of all of the following:

- Pain on the right and left sides of the body
- Pain above and below the waist (including shoulder and buttock pain)
- Pain in the axial skeleton (cervical, thoracic or lumbar spine, or anterior chest)

Pain on palpation with a 4-kg/cm² force in 11 of 18 sites.



FMS = fibromyalgia syndrome.

Reprinted with permission from Wolfe et al. *Arthritis Rheum.* 1990;33:160-172.¹⁴

PATHOPHYSIOLOGY OF FMS

The precise mechanisms, etiology, and pathophysiology leading to FMS remain uncertain, but multifactorial processes that may affect peripheral and/or central sensory input and processing are likely contributors. Neuroimaging evidence suggests that central sensitization, which is associated with the release of excitatory neurotransmitters and neuropeptides, may be an underlying cause of FMS.

Central sensitization plays a crucial role in FMS, which is characterized in part by augmented processing of pain in the central nervous system (CNS). The clinical result is hyperalgesia, or pain that is out of proportion to a noxious stimulus, and/or allodynia, or pain in response to an innocuous stimulus.²⁰ Increased brain activation patterns are evident when patients with FMS are exposed to pressure and heat pain stimuli,^{20,21} with patients displaying a normal detection threshold to sensory stimuli, but a decreased threshold to noxious stimuli.²²

Figure 2. The Revised Fibromyalgia Impact Questionnaire

Domain 1 directions: For each of the following 9 questions, check the one box that best indicates how much your fibromyalgia made it difficult to do each of the following activities over the past 7 days:

Brush or comb your hair	No difficulty <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Very difficult
Walk continuously for 20 minutes	No difficulty <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Very difficult
Prepare a homemade meal	No difficulty <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Very difficult
Vacuum, scrub, or sweep floors	No difficulty <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Very difficult
Lift and carry a bag full of groceries	No difficulty <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Very difficult
Climb 1 flight of stairs	No difficulty <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Very difficult
Change bed sheets	No difficulty <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Very difficult
Sit in a chair for 45 minutes	No difficulty <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Very difficult
Go shopping for groceries	No difficulty <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Very difficult

Domain 2 directions: For each of the following 2 questions, check the one box that best describes the overall impact of your fibromyalgia over the past 7 days:

Fibromyalgia prevented me from accomplishing goals for the week.	Never <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Always
I was completely overwhelmed by my fibromyalgia symptoms.	Never <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Always

Domain 3 directions: For each of the following 10 questions, check the one box that best indicates the intensity of your fibromyalgia symptoms over the past 7 days:

Please rate your level of pain	No pain <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Unbearable pain
Please rate your level of energy	Lots of energy <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> No energy
Please rate your level of stiffness	No stiffness <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Severe stiffness
Please rate the quality of your sleep	Awoke rested <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Awoke very tired
Please rate your level of depression	No depression <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Very depressed
Please rate your level of memory problems	Good memory <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Very poor memory
Please rate your level of anxiety	Not anxious <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Very anxious
Please rate your level of tenderness to touch	No tenderness <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Very tender
Please rate your level of balance problems	No imbalance <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Severe imbalance
Please rate your level of sensitivity to loud noises, bright lights, odors, and cold	No sensitivity <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Extreme sensitivity

Scoring: Step 1. Sum the scores for each of the 3 domains (function, overall, and symptoms). Step 2. Divide domain 1 score by 3, divide domain 2 score by 1 (that is, it is unchanged), and divide domain 3 score by 2. Step 3. Add the 3 resulting domain scores to obtain the total Revised Fibromyalgia Impact Questionnaire score. Reprinted with permission from Bennett et al. *Arthritis Res Ther.* 2009;11:R120.¹⁹

Evidence for several mechanisms thought to be involved in the pathophysiology and pain processing abnormalities of FMS are reviewed below.

PERIPHERAL MECHANISMS

Studies to determine whether there are any abnormal findings in the skin of patients with FMS that might contribute to their increased pain sensitivity have shown several differences in FMS skin compared with normal skin.²³⁻²⁸ Patients with FMS have increased expression of *N*-methyl-D-aspartate receptor subunit 2D,²³ higher concentrations of immunoglobulin G deposits in the dermis,²⁴ increased reactivity for collagen III,²⁴ lower total collagen in the endoneurium,²⁵ and a higher number of mast cells²⁴ and cytokines.²⁶

A blinded study demonstrated minor ballooning in the Schwann cell sheaths of unmyelinated peripheral nerves in the skin at non-tender points and major ballooning at tender points in patients with FMS, but no ballooning in normal skin of patients without FMS.²⁷ Another study found that δ -opioid receptors were upregulated 65-fold and κ -opioid receptors were upregulated 35-fold in the skin of patients with FMS compared with skin in normal subjects.²⁸ Levels of μ -opioid receptors were the same in both groups.

SPINAL MECHANISMS

There is considerable evidence that several substances in cerebrospinal fluid (CSF) that are involved in pain response and processing are altered in patients with FMS. Four classic studies have shown that CSF levels of substance P, a neuropeptide, are 2- to 4-times higher in patients with FMS than in normal controls.²⁹⁻³² Additionally, CSF levels of glutamate, an excitatory amino acid, were higher in patients with FMS than in controls, along with CSF levels of 2 neurotrophins, nerve growth factor and brain-derived neurotrophic factor, which were also significantly higher in patients with FMS compared with controls.³³

Russell et al found decreased CSF levels of biogenic monoamine metabolites of norepinephrine and serotonin in patients with FMS versus controls.³⁴ This is consistent with impaired functioning of the descending inhibitory pathways (which utilize norepinephrine and serotonin) in patients with FMS.

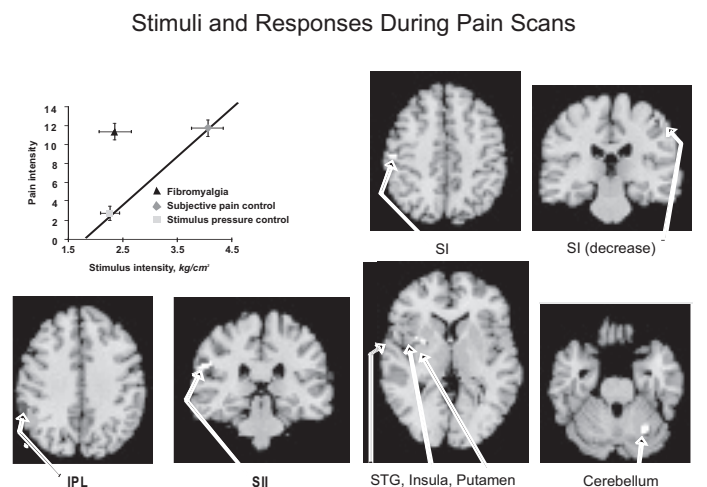
SUPRASPINAL MECHANISMS

The influence of supraspinal mechanisms on pain

and sensory processing in FMS is illustrated in Figure 3.²⁰ Gracely et al utilized functional magnetic resonance imaging (fMRI) to evaluate the pattern of cerebral activation during the application of painful pressure in patients with FMS compared with controls.²⁰ The authors found increased neural activation (ie, increases in the blood oxygen level-dependent signal) in patients with FMS compared to pain-free controls when stimuli of equal pressure magnitude were administered. Regions of increased activity included the primary and secondary somatosensory cortices, the insula, and the anterior cingulate cortex (ACC)—all regions commonly observed in fMRI studies in healthy normal subjects during painful stimuli. When the control group received double the stimulus intensity (4 kg/cm²) as patients with FMS (2 kg/cm²), both groups experienced the same pain intensity and the same areas of the brain “lit up” with similar intensities. These findings are consistent with a “left-shift” in stimulus-response function noted with experimental pain testing, and suggest that patients with FMS experience an increased “gain” in brain sensory processing systems.²⁰

Another study found that patients with FMS and controls had similar pain thresholds to cutaneous C-fiber heat stimulation, but that those with FMS

Figure 3. Augmented Pain Processing in FMS



FMS = fibromyalgia syndrome; IPL = inferior parietal lobule; SI = primary somatosensory cortex; SII = secondary somatosensory cortex; STG = superior temporal gyri.

Reprinted with permission from Gracely et al. *Arthritis Rheum.* 2002;46:1333-1343.²⁰

required significantly lower heat pulse temperatures to generate the same magnitudes of temporal summation of “second pain” (TSSP) than controls.³⁵ These findings strongly support alterations of central pain sensitivity—and not peripheral sensitization or rating bias—as being responsible for the TSSP differences between patients with FMS and normal controls.

Still another study demonstrated that changes in glutamate levels in the insula are associated with changes in multiple pain domains in patients with FMS.³⁶ Specifically, higher glutamate levels enhance glutamatergic neurotransmission and appear to lead to increased pain perception, while reduced glutamate levels are associated with diminished pain perception.

PAIN PATHWAYS AND PAIN MODULATION

Many nociceptive ascending pathways—from the periphery into the spinal cord, up to supraspinal sites in the brain, and eventually to the cerebral cortex—are involved in pain processing. They include spinocervical pathways, spinothalamic pathways, spinobulbar pathways, spinopontine pathways, and postsynaptic dorsal column pathways, among others.

Pain from these pathways is processed in multiple areas in the CNS, which are referred to collectively as the pain matrix.^{37,38} The primary and secondary somatosensory cortices, the thalamus, and the posterior insula appear to be largely related to pain localization and intensity, whereas the ACC, the anterior insula, and the amygdala appear to be largely related to the affective domain or emotional valence of the pain. This affects the behavioral responses to pain and primarily reflects how unpleasant or distressing the pain is to the patient.

In the physiological pain matrix of the brain, these areas and several others, including the cerebellum, exhibit increased regional cerebral blood flow, and/or blood oxygenation, and/or metabolite utilization on fMRI in patients experiencing pain.

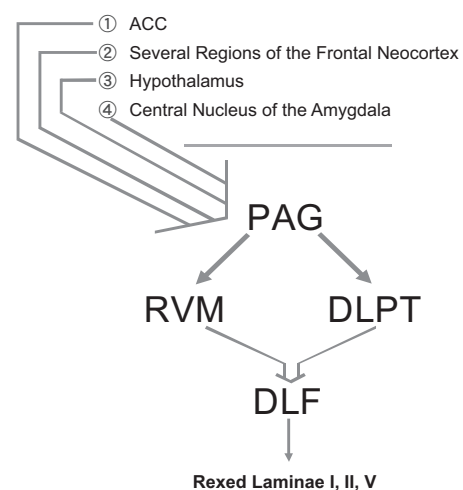
Pain is ameliorated primarily via descending inhibitory circuits, with the major ones being the serotonergic and noradrenergic pathways (Figure 4). Higher supraspinal sites such as the ACC and the hypothalamus feed into the periaqueductal gray (PAG), which then feeds into either the rostral ventral medulla and the dorsolateral funiculus (serotonergic pathway) or the dorsolateral pontine tegmentum and the dorsolateral funiculus (noradrenergic pathway).

Both ACC and PAG are rich in opioid receptors, and those areas may feed into both of the descending pain modulating pathways.

Utilizing fMRI, Pujol et al found that patients with FMS had greater activation in the ACC, insula, and basal ganglia in response to 4 kg/cm² of pressure, whereas controls tended to have greater activation in the somatosensory cortices.³⁹ The results not only confirm the augmented brain response to pain in patients with FMS, but also suggest that functional alterations may be particularly relevant in emotion-related, or paralimbic, regions.

In addition, Jensen et al found that women with FMS required less pressure than age-matched controls to evoke equal pain magnitudes when utilizing fMRI to evaluate cerebral response to provoked pain.⁴⁰ However, the investigators also demonstrated, for the first time, that patients failed to respond appropriately to pain provocation in the primary link to the descending pain inhibitory system, the rostral ACC, resulting in impaired endogenous pain inhibition. The findings of this study validate previous reports of dysfunctional endogenous pain inhibition in FMS.

Figure 4. Descending Pain Modulating Circuits



ACC = anterior cingulate cortex; DLF = dorsolateral funiculus; DLPT = dorsolateral pontine tegmentum; RVM = rostral ventral medulla; PAG = periaqueductal gray.

Courtesy of Howard Smith, MD.

CONCLUSIONS

Despite its significant negative impact on daily functioning and QOL, FMS does not command a consensus among clinicians with respect to its precise cause, its treatment, or even whether it should be considered a “real” disease. An accumulating body of scientific evidence, however, strongly suggests that FMS is a disorder of central and peripheral pain processing rather than a somatic syndrome with a pronounced psychological and/or emotional component.

The precise mechanisms, etiology, and pathophysiology of FMS remain uncertain, but likely involve multiple processes that are largely central in nature. Numerous studies of patients with FMS have demonstrated augmented processing of pain in the CNS; abnormal findings in the skin that might contribute to increased pain sensitivity; and altered CSF levels of substance P, glutamate, nerve growth factor, brain-derived neurotrophic factor, and biogenic monoamine metabolites of norepinephrine and serotonin. In addition to the problem of augmented afferent pain processing, dysfunctional endogenous pain inhibition primarily involving descending inhibitory circuits (eg, the serotonergic and noradrenergic pathways) is thought to be a major contributor to FMS pathophysiology.

CASE STUDY

PRESENTATION AND HISTORY

KS, a 47-year-old librarian with a 6-month history of low back pain, has been referred to the pain clinic by her primary care physician for further evaluation. She is recently divorced and has a body mass index of 33 kg/mm². During her visit, KS says her chronic back pain averages approximately 6 out of 10, but worsens with most activities. She mentions that she tried to alleviate her pain with a nonsteroidal anti-inflammatory drug (NSAID) patch, but it was ineffective.

She also reports severe fatigue that worsens as the day goes on, making it difficult for her to complete a full day of work. As such, she has just cut back to working half a day. Further questioning reveals that she has generalized morning stiffness, with significant aches in the proximal muscles of the arms and legs, and moderately severe insomnia.

PHYSICAL EXAMINATION AND DIAGNOSTIC EVALUATION

A thorough physical examination was essentially normal except for the presence of 11 out of 18 classic tender points. Complete blood count, liver and kidney panels, thyroid-stimulating hormone levels, and erythrocyte sedimentation rate were normal.

TREATMENT

The NSAID patches KS used in the past were ineffective because the mechanisms involved in FMS are largely central in nature. She was therefore given a prescription for pregabalin, with the dose slowly titrated to 600 mg/day (200 mg during the day and 400 mg at night), to relieve her pain and insomnia. She also received educational materials, including information on sleep hygiene measures, and started a slow, gradually progressing program of regular aerobic exercise. Although she improved, she was still unable to work a full day, primarily because of fatigue. At this point, she was started on duloxetine 30 mg/day for 1 week, after which the dose was increased to 60 mg/day. She was also referred for cognitive-behavioral therapy.

CURRENT STATUS

She is currently on this regimen and is doing well. She is now working full-time, sleeping better, and her pain is mostly controlled at a tolerable level. She has also joined a computer dating service.

REFERENCES

1. Chakrabarty S, Zoorob R. Fibromyalgia. *Am Fam Physician*. 2007;76:247-254.
2. Wolfe F, Ross K, Anderson J, et al. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum*. 1995;38:19-28.
3. Adler GK, Geenen R. Hypothalamic-pituitary-adrenal and autonomic system functioning in fibromyalgia. *Rheum Dis Clin North Am*. 2005;31:187-202, xi.
4. Johns Hopkins Advanced Studies in Medicine Survey, Fibromyalgia, September–October 2008.
5. Bennett RM, Jones J, Turk DC, et al. An internet survey of 2596 people with fibromyalgia. *BMC Musculoskelet Disord*. 2007;8:27.
6. Jones J, Rutledge DN, Jones KD, et al. Self-assessed physical function levels of women with fibromyalgia: a national survey. *Womens Health Issues*. 2008;18:406-412.
7. Bernard AL, Prince A, Edsall P. Quality of life issues for fibromyalgia patients. *Arthritis Care Res*. 2000;13:42-50.

8. Burckhardt CS, Clark SR, Bennett RM. Fibromyalgia and quality of life: a comparative analysis. *J Rheumatol*. 1993;20:475-479.
9. Carmona L, Ballina J, Gabriel R, et al. The burden of musculoskeletal disease in the general population of Spain: results from a national survey. *Ann Rheum Dis*. 2001;60:1040-1045.
10. Ubago Linares Mdel C, Ruiz Pérez I, Bermejo Pérez MJ, et al. Clinical and psychosocial characteristics of subjects with fibromyalgia. Impact of the diagnosis on patients' activities. *Rev Esp Salud Publica*. 2005;79:683-695.
11. White KP, Speechley M, Harth M, Ostbye T. The London Fibromyalgia Epidemiology Study: direct healthcare costs of fibromyalgia syndrome in London, Canada. *J Rheumatol*. 1999;26:885-889.
12. Berger A, Dukes E, Martin S, et al. Characteristics and healthcare costs of patients with fibromyalgia syndrome. *Int J Clin Pract*. 2007;61:1498-1508.
13. Hughes G, Martinez C, Myon E, et al. The impact of a diagnosis of fibromyalgia on health care resource use by primary care patients in the UK: an observational study based on clinical practice. *Arthritis Rheum*. 2006;54:177-183.
14. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum*. 1990;33:160-172.
15. Wolfe F. Stop using the American College of Rheumatology criteria in the clinic. *J Rheumatol*. 2003;30:1671-1672.
16. Mease PJ, Clauw DJ, Arnold LM, et al. Fibromyalgia syndrome. *J Rheumatol*. 2005;32:2270-2277.
17. Orellana C, Casado E, Masip M, et al. Sexual dysfunction in fibromyalgia patients. *Clin Exp Rheumatol*. 2008;26:663-666.
18. Kalichman L. Association between fibromyalgia and sexual dysfunction in women. *Clin Rheumatol*. 2009;28:365-369.
19. Bennett RM, Friend R, Jones KD, et al. The Revised Fibromyalgia Impact Questionnaire (FIQR): validation and psychometric properties. *Arthritis Res Ther*. 2009;11:R120.
20. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum*. 2002;46:1333-1343.
21. Cook DB, Lange G, Ciccone DS, et al. Functional imaging of pain in patients with primary fibromyalgia. *J Rheumatol*. 2004;31:364-378.
22. Gracely RH, Grant MA, Giesecke T. Evoked pain measures in fibromyalgia. *Best Pract Res Clin Rheumatol*. 2003;17:593-609.
23. Kim SH, Jang TJ, Moon IS. Increased expression of N-methyl-D-aspartate receptor subunit 2D in the skin of patients with fibromyalgia. *J Rheumatol*. 2006;33:785-788.
24. Eneström S, Bengtsson A, Frödin T. Dermal IgG deposits and increase of mast cells in patients with fibromyalgia-relevant findings or epiphenomena? *Scand J Rheumatol*. 1997;26:308-313.
25. Ribel-Madsen S, Gronemann ST, Bartels EM, et al. Collagen structure in skin from fibromyalgia patients. *Int J Tissue React*. 2005;27:75-82.
26. Salemi S, Rethage J, Wollina U, et al. Detection of interleukin 1 beta (IL-1 beta), IL-6, and tumor necrosis factor-alpha in skin of patients with fibromyalgia. *J Rheumatol*. 2003;30:145-150.
27. Kim SH, Kim DH, Oh DH, Clauw DJ. Characteristic electron microscopic findings in the skin of patients with fibromyalgia: preliminary study. *Clin Rheumatol*. 2008;27:219-223.
28. Salemi S, Aeschlimann A, Wollina U, et al. Up-regulation of delta-opioid receptors and kappa-opioid receptors in the skin of fibromyalgia patients. *Arthritis Rheum*. 2007;56:2464-2466.
29. Vaerøy H, Helle R, Førre O, et al. Elevated CSF levels of substance P and high incidence of Raynaud phenomenon in patients with fibromyalgia: new features for diagnosis. *Pain*. 1988;32:21-26.
30. Russell IJ, Orr MD, Littman B, et al. Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome. *Arthritis Rheum*. 1994;37:1593-1601.
31. Liu Z, Welin M, Bragee B, Nyberg F. A high-recovery extraction procedure for quantitative analysis of substance P and opioid peptides in human cerebrospinal fluid. *Peptides*. 2000;21:853-860.
32. Bradley LA, Alarcón GS. Is Chiari malformation associated with increased levels of substance P and clinical symptoms in persons with fibromyalgia? *Arthritis Rheum*. 1999;42:2731-2732.
33. Sarchielli P, Mancini ML, Floridi A, et al. Increased levels of neurotrophins are not specific for chronic migraine: evidence from primary fibromyalgia syndrome. *J Pain*. 2007;8:737-745.
34. Russell IJ, Vaerøy H, Javors M, Nyberg F. Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis. *Arthritis Rheum*. 1992;35:550-556.
35. Staud R, Bovee CE, Robinson ME, Price DD. Cutaneous C-fiber pain abnormalities of fibromyalgia patients are specifically related to temporal summation. *Pain*. 2008;139:315-323.
36. Harris RE, Sundgren PC, Pang Y, et al. Dynamic levels of glutamate within the insula are associated with improvements in multiple pain domains in fibromyalgia. *Arthritis Rheum*. 2008;58:903-907.
37. Melzak R, Wall PD. Pain mechanisms: a new theory. *Science*. 1965;150:971-979.
38. Casey KL. Toward a neurophysiology of pain. *Headache*. 1969;8:141-153.
39. Pujol J, López-Solà M, Ortiz H, et al. Mapping brain response to pain in fibromyalgia patients using temporal analysis of fMRI. *PLoS One*. 2009;4:e5224.
40. Jensen KB, Kosek E, Petzke F, et al. Evidence of dysfunctional pain inhibition in fibromyalgia reflected in rACC during provoked pain. *Pain*. 2009;144:95-100.