PAIN Clinical Updates

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UPCOMING ISSUES

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Update on Fibromyalgia Syndrome

Fibromyalgia Syndrome (FMS) is a pathological entity that has reached definite clinical and scientific recognition only recently. Symptoms compatible with the diagnosis of FMS were previously classified under a variety of labels. "Psychogenic rheumatism," "fibrositis," and "myelasthenia" are just a few examples that show how difficult it has been to define and interpret this syndrome.[1] In 1990, the criteria established by the American College of Rheumatology (ACR) (Table I) represented a turning point for the recognition of FMS. Since then, the number of studies in the field, both clinical and experimental, has increased exponentially, contributing to a better understanding of the syndrome.[2] While subject to discussion and probably to future revision, these criteria have had the merit of creating uniformity in terminology, and remain the standard of reference for clinicians and researchers in the field. To date FMS is perhaps one of the most challenging chronic pain conditions actively under investigation in the world pain community. The most recent findings provide hope for better symptom control.

Epidemiology and Social Impact

FMS is a chronic pain condition whose main features are widespread, often disabling musculoskeletal pain and tenderness, accompanied by a number of nonspecific secondary symptoms [3]. Its prevalence has been reported in various countries, ranging from 2% in the United States and France to 4% in Spain, but frequency rates are progressively increasing, in parallel with a growing awareness of the syndrome and more correct application of diagnostic criteria worldwide.[4] FMS occurs at all ages and in all ethnic groups and cultures. Whereas gender distribution is nearly equal in childhood, the syndrome is up to seven times more common in women than men by the age of 50–60 years.[5] The impact of fibromyalgia on an individual's quality of life and physical function is substantial, comparable with that of rheumatoid arthritis. More than 30% of FMS patients are forced to accept shorter working hours or less physically demanding work to maintain employment. In the United States, about 15% of those with FMS currently receive disability pay because of their symptoms. In a number of other countries, the recognition

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of the social impact of the syndrome is unfortunately still incomplete, and the risk of marginalization is an additional burden to those affected.[1]

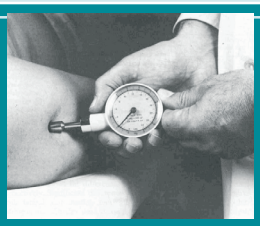
Clinical Presentation and Diagnosis

A detailed clinical history in FMS patients reveals either a gradual or abrupt onset of symptoms, often subsequent to physical or psychological stress.[6] It has been reported in the past that about 22% of patients develop symptoms after a whiplash injury in a minor car accident, though several authors now agree that the initiating role of this kind of physical trauma has perhaps been overestimated.[7] A self-reported history of childhood physical or sexual abuse has also frequently been noted among chronic pain populations, including fibromyalgia patients, and has been associated with poorer adjustment to pain.[8]

Classification Criteria of Fibromyalgia Syndrome *ACR–1990*

1) **From clinical history:** widespread musculoskeletal pain of at least 3 months duration

2) **From examination:** tenderness in at least 11 out of 18 Tender Points (TePs) [pain induced by palpation of TePs with a pressure of 4 kg-f]



Location of TePs (9 symmetrical sites)

Occiput:	suboccipital muscle insertion
Low cervical:	anterior aspect of intertransverse space at C5-C7
Trapezius:	midpoint of upper muscle border
Supraspinatus:	near the origins, above the spine of scapula
Second rib:	upper surface just lateral to second costochondral junction
Lateral epicondyle:	extensor muscle, 2 cm distal to epicondyle
Gluteal:	upper outer quadrant of buttock in anterior fold of muscle
Greater trochanter:	posterior to trochanteric prominence
Knee:	medial fat pad proximal to joint line and condyle

Table I

The ACR criteria currently applied for classifying the syndrome are displayed in Table I. By definition, the diagnosis includes *spontaneous chronic widespread pain* that must involve all four limbs and the trunk. The pain is usually described as a persistent, diffuse, deep, aching, throbbing, sometimes stabbing sensation in the muscles; it may be recurrent but is most often continuous, with periodical exacerbations. Pain may be so intense that the patient is unable to perform regular, everyday tasks. *Tenderness* in predetermined body sites called tender points (TePs) can be detected either manually by an experienced examiner or by using a standard pressure algometer (image in Table I). In contrast to the trigger points (TrPs) of myofascial pain syndromes, tender points are simply sites of exquisite pain hypersensitivity in soft tissues that are not included in taut, palpable bands of muscle fibers, do not evoke a local twitch response under snapping palpation, and, mostly, do not refer pain at a distance when stimulated.[9]

In addition to pain, other clinical symptoms are frequently present in various combinations in FMS, including affective dysfunction, nonrestorative sleep or chronic insomnia, nocturnal myoclonus and bruxism, prolonged morning stiffness, daytime tiredness resembling physical fatigue, cognitive deficits, and short-term memory loss. Also frequent are numbness, tingling, dysesthesias in the hands and feet, throbbing occipital pain typical of muscle contraction headache, lightheadedness, dizziness, syncope, abdominal/pelvic pain, diarrhea, constipation, greater urinary frequency and urgency, and sterile dysuria.[1] Indeed, a number of well-defined clinical conditions occur more frequently in FMS patients than in the general population. Depression is described in 40% of FMS patients compared to only 10% of controls and 20% of patients hospitalized for other medical conditions. Anxiety affects 45% of FMS patients compared to 21% of patients with other chronic pains, and it affects 51% of patients with FMS plus other disorders. Irritable bowel syndrome (IBS) is described in up to 70% of FMS patients compared to 20% of controls. Moreover, dysmenorrhea, interstitial cystitis, other rheumatic conditions (rheumatoid arthritis, lupus erythematosus, Sjögren's syndrome), chronic fatigue syndrome, myofascial pain syndrome, low back pain, and temporomandibular joint disorder are significantly more frequent in FMS sufferers than in the general population.[10,11]

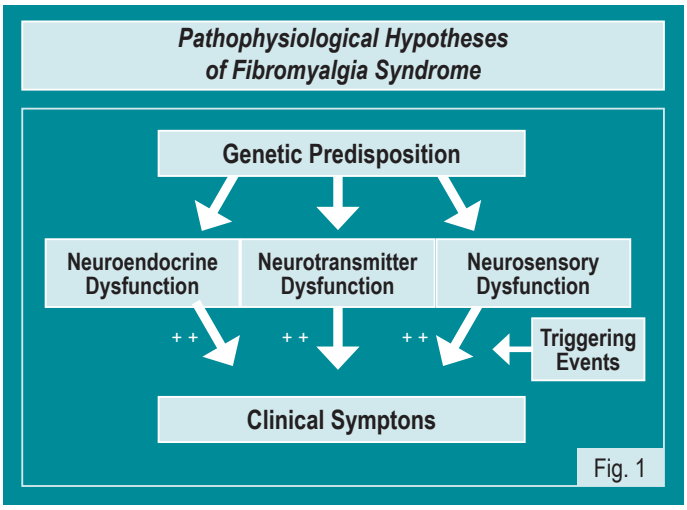
A number of well-defined clinical conditions occur more frequently in FMS than in the general population

The clinical picture of fibromyalgia also involves symptoms related to abnormal reactivity to painful stimuli at all levels of somatic structures. Patients often report that light touch, even contact with clothes, can be intolerably painful, and that everyday tasks, such as combing one's hair, can be extremely uncomfortable.[1]

In spite of this important cohort of clinical symptoms, routine hematological tests, or other tests, such as electromyography or X-rays, may be perfectly normal in the absence of specific comorbidities.[3] As a result, diagnosis of the syndrome in medical practice remains based on clinical criteria.

Pathophysiology

Early research on the pathogenesis of fibromyalgia concentrated on the possible role of peripheral tissues. However, studies have been unable to show any consistent muscle abnormality specifically associated with the syndrome.[1,12] Although the etiology of FMS has not been completely clarified, there is general consensus that altered processing of pain is probably the main contributor to the pathogenesis, arising from a number of neuroendocrine/dysautonomic, neurotransmitter, and neurosensory disturbances.[3] These abnormalities would only be present in genetically predisposed individuals—the mode of inheritance probably being polygenic—although a variety of environmental stressors could act as triggering factors[13] (Fig. 1).



The neuroendocrine disturbance mainly involves dysfunction of the hypothalamic-pituitary-adrenal axis.[14,15] Compared to controls, FMS patients have low 24-hour serum cortisol levels and an abnormal circadian pattern of cortisol concentration. They also show blunted serum cortisol responses to corticotropin-releasing hormone (CRH); i.e., when CRH is released by the hypothalamus, there is a disproportionately high release of corticotrophin by the pituitary gland and a disproportionately small release of cortisol by the adrenal glands. This result suggests that patients with FMS have an abnormal response to stress, and thus an inadequate reaction to a number of stressful events, including trauma or infection.[16] When the same patients are injected with synthetic CRH, however, the increase in cortisol levels is similar to that shown by healthy controls, which indicates that adrenal tissue sensitivity to exogenous and endogenous CRH may be different in FMS.[15] Moreover, hypothalamic-pituitary-thyroid axis function seems to be altered in fibromyalgia because the release of thyrotropin-releasing hormone stimulates the production of less thyrotropin, triiodothyronine, and thyroxin than normal.[15] The neuroendocrine disturbance also involves altered secretion of growth hormone. Growth hormone levels are reduced during sleep, probably because of the documented disruption of stage 4 of sleep in the vast majority of FMS patients (the phase when the hormone is secreted). Supplementation with growth hormone has provided relatively positive results, at least in a subpopulation of FMS patients; however, the high cost of the hormone, combined with the unpleasantness of the mode of administration, are considerable drawbacks.[1,17]

Fibromyalgia is characterized by a generalized hypersensitivity to painful stimuli, not only in spontaneously painful sites and in tender points, but also in control areas

In addition to neuroendocrine disturbances, FMS is also characterized by dysautonomia, involving persistent hyperactivation of the sympathetic nervous system, with a paradoxical hyporeactivity of the same system to stress.[14,15]

The neurotransmitter disturbance observed in FMS generally consists of altered concentrations of a number of substances involved in pain transmission, with decreased levels of antinociceptive and increased levels of pronociceptive mediators. Serotonin concentration is reduced in the serum and cerebrospinal fluid (CSF) of FMS patients as compared to patients with low back pain and pain-free controls, as is the concentration of the serotonin precursor tryptophan.[1] Substance P levels in the CSF are higher in FMS patients than in controls and fluctuate in relation to the painful symptoms.[1,18] Nerve growth factor concentration is increased in the CSF of fibromyalgia patients, while dopamine transmission is decreased.[3,19,20]

At present, there is evidence for a role of gene polymorphisms in the serotoninergic, dopaminergic, and catecholaminergic systems in the etiology of FMS, but further research is needed in this direction.[13]

With regard to neurosensory dysfunction, a number of studies have shown that various processes in the brain and spinal cord are abnormal in FMS patients. Clinical research studies have shown that FMS is characterized

by a generalized hypersensitivity to painful stimuli, not only in spontaneously painful sites and in tender points but also in control areas. Patients exhibit lower-than-normal pain thresholds to thermal, mechanical, electrical, and chemical stimuli at the level of the skin, subcutis, and/or muscle.[3,9,21] A lower pain threshold has also been documented by using a pain measure known as the nociceptive flexion reflex (NFR), which is measured electromyographically as the withdrawal of a proximal leg muscle in response to an electrical stimulus applied directly to the sural nerve. The NFR threshold refers to the level of stimulus that generates a measurable withdrawal response; this threshold is significantly reduced in FMS patients versus controls.[22]

Overall, most research supports the hypothesis that FMS originates in the central nervous system

Fibromyalgia patients also show a lower pain threshold to repeated intramuscular electrical stimulation as compared to non-affected persons, indicating that the temporal nociceptive summation is more pronounced in the syndrome. In addition, when given intramuscular infusion of hypertonic saline, FMS patients exhibit muscle pain of longer duration as well as referred pain spreading to a larger area than in controls.[23] These findings indicate a state of central sensitization in the syndrome. Central sensitization is expressed as enhanced excitability of the spinal cord neurons that transmit the nociceptive information to higher centers. It implies spontaneous nerve activity, expanded receptive fields (whose clinical counterpart is a wider distribution of painful areas), and increased stimulus responses, such as abnormal temporal summation, or "wind-up," within the spinal cord.[3] Both human and animal studies have shown that *N*-methyl-D-aspartate (NMDA) receptors are responsible for wind-up and central sensitization. Indeed, in fibromyalgia patients, NMDA-receptor antagonists—such as ketamine and dextromethorphan—attenuate muscle pain at rest, referred pain, muscle hyperalgesia, and experimentally induced wind-up.[24,25]

Treatment must involve a multidisciplinary approach, including a combination of pharmacological and nonpharmacological interventions

In addition to central sensitization, FMS patients also have functional abnormalities in the pathways that descend from the brain to the spinal cord that are normally responsible for downregulating the responses to painful stimuli.[18] The syndrome would thus be characterized by phenomena of amplification of pain signals and/or reduced antinociception.

Aberrant responses to pain in fibromyalgia are also shown by functional brain neuroimaging. As compared to non-affected individuals, FMS patients show activation of different brain areas or a different level of activation of the same areas.[26,27] However, not all the results of the neuroimaging studies are homogeneous; moreover, several of the observed changes are not unique to FMS but also occur in other chronic pain conditions.[3] More and larger studies are needed. Recent research also suggests an accelerated loss of gray matter from the brain in FMS; this finding has driven some authors to speculate about a possible premature aging of the brain in the syndrome, which remains to be explored further.[28] Overall, most research supports the hypothesis that FMS originates in the central nervous system.[21]

Antidepressants are recommended because they decrease pain and often improve function

Prognosis and Treatment

FMS does not threaten patients' lives but can cause severe disability and thus substantially compromise their quality of life. Complete resolution of symptoms is unfortunately almost never achieved, but significant improvement can be obtained with adequate therapy.[1]

The treatment approach to fibromyalgia still lacks precise standardization–-a situation that reflects the incomplete knowledge about pathophysiological mechanisms. Although general lines of treatment have been indicated by many authors over the years, it is emblematic that guidelines from an official organization were issued only last year. The European League Against Rheumatism (EULAR) published a series of recommendations in 2007, based on an accurate analysis of the literature, i.e., published studies on several treatment procedures, and opinions of experts from 11 European countries.[29] EULAR plans to update them every 5 years, in parallel with the development of new treatment strategies.

Specific recommendations in these guidelines take into account general considerations for management of FMS. They stress the importance of a comprehensive evaluation of pain, function, and the psychosocial context of the FMS patient, and they indicate that treatment must involve a multidisciplinary approach, including a combination of pharmacological and nonpharmacological interventions. After discussion with the patient, treatment

modalities should be specifically tailored according to pain intensity, function, and associated features, such as depression, fatigue, and sleep disturbance.

In the indications on pharmacological management of pain control, the use of tramadol is recommended, especially in the re-acutization phases ("flares"). Although other pain treatment options may include simple analgesics, such as paracetamol (acetaminophen) and other weak opioids, corticosteroids and strong opioids are not recommended, nor are nonsteroidal anti-inflammatory drugs (NSAIDs), for which clinical trials have been generally disappointing.[30] Antidepressants are recommended because they decrease pain and often improve function. Tricyclics, especially amitriptyline, are particularly useful, but also recommended are the selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, dual-reuptake inhibitors (serotonin and norepinephrine reuptake inhibitors [SNRIs]), such as venlafaxine or duloxetine or 5-HT_3 receptor antagonists, such as tropisetron. Antiepileptic drugs are also recommended. In this context, the present focus is on pregabalin, which recently received FDA approval specifically for the treatment of FMS in the United States. This second-generation antiepileptic is an $\alpha_2\delta_1$ ligand that binds to, and modulates, voltage-gated calcium channels, reducing calcium influx at nerve terminals and therefore reducing the release of several neurotransmitters, including glutamate, norepinephrine, and substance P. The reduced neurotransmitter release is presumed to account for the analgesic, anticonvulsant, and anxiolytic-like actions of the drug. In a series of randomized, double-blind, placebo-controlled trials of 8–14 weeks' duration, doses of 300–450 mg/day of pregabalin effectively reduced the pain and accompanying symptoms of a significant proportion of FMS patients and improved various quality-of-life domains. Six-month trials demonstrated the durability of the drug's effects on pain and on a variety of secondary measures, such as fatigue and sleep disturbance. Overall, pregabalin was well tolerated, with no new adverse events emerging that have not been reported with its use in other indications. While not all fibromyalgia patients respond to pregabalin, the drug represents an important step forward in FMS treatment.[31]

Specific EULAR recommendations on nonpharmacological management include heated pool treatment, with or without exercise, and in some cases individually tailored exercise programs (aerobic exercise and strength training). Cognitive behavioral therapy may prove beneficial in certain patients. Based on the specific needs of the patient, relaxation, rehabilitation, physiotherapy, and psychological support also can help.[29,30]

Not included in the official guidelines issued by EULAR, but gaining increasingly more importance in the international literature, is treatment of the so-called "peripheral triggers or peripheral pain generators" in FMS. Clinical observations show that FMS patients who also present sources of nociceptive pain in their somatic periphery, such as myofascial pain syndrome from trigger points or a painful joint, have an exacerbation of their typical fibromyalgia pain. This situation is very frequent, given the high level of comorbidity of FMS with other somatic pain conditions.[1] The phenomenon probably occurs because of a summation effect; the increased input from the periphery enhances the level of central neuronal excitability, thus precipitating the clinical picture of diffuse pain.[32] Proper identification of these peripheral pain generators and effective treatment—often by local therapy, such as trigger point injections—are thus important preliminary steps in the therapeutic approach to FMS, frequently allowing a dose reduction of the typical drugs to be employed for the "central pain."

Pregabalin effectively reduces the pain and accompanying symptoms in a significant proportion of FMS patients

What Does the Future Hold?

The coming years are likely to see a number of changes in the diagnostic approach to FMS and in its management, based on the growing wealth of experimental findings on the pathophysiology of the syndrome. Revised identification criteria will probably be adopted and, hopefully, more targeted therapeutic tools will be found for optimal control of the symptoms. Even at present, however, increased awareness of this condition in the medical and scientific community, as well as in the population at large, are providing positive results. Only a few decades ago, patients with FMS were highly likely to be dismissed by their physicians as "neurotic," especially as they were mostly middle-aged women–-in other words, "imaginary patients." This lack of validation added a further burden to sufferers. Today, the FMS patient is at least attributed full credibility and most often given the necessary understanding and support to cope with the symptoms. This change represents a key element in improved knowledge and effective handling of this complex syndrome.

References

1. Russell IJ. In: Mense S, Simons DG, editors. Muscle pain: understanding its nature, diagnosis and treatment. Philadelphia: Lippincott Williams & Wilkins, 2001.
2. Wolfe F, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160–72.
3. Abeles AM, Pillinger MH, Solitar BM, Abeles M. Narrative review: the pathophysiology of fibromyalgia. Ann Intern Med 2007;146:726–34.
4. Perrot S, Dickenson AH, Bennett RM. Fibromyalgia: harmonizing science with clinical practice considerations. Pain Pract 2008;8:177–89.
5. Mease P. Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. J Rheumatol Suppl 2005; 75:6–21.
6. Van Houdenhove B, Egle U, Luyten P. The role of life stress in fibromyalgia. Curr Rheumatol Rep 2005;7:365–70.
7. Tishler M, Levy O, Maslakov I, Bar-Chaim S, Amit-Vazina M. Neck injury and fibromyalgia: are they really associated? J Rheumatol 2006;33:1183–5.
8. Fillingim RB, Edwards RR. Is self-reported childhood abuse history associated with pain perception among healthy young women and men? Clin J Pain 2005;21:387–97.
9. Vecchiet L, Giamberardino MA, de Bigontina P, Dragani L. Comparative sensory evaluation of parietal tissues in painful and nonpainful areas in fibromyalgia and myofascial pain syndrome. In: Gebhart GF, Hammond DL, Jensen TS, editors. Proceedings of the 7th World Congress on Pain. Progress in Pain Research and Management, vol. 2. Seattle: IASP Press; 1994.
10. Buskila D, Cohen H. Comorbidity of fibromyalgia and psychiatric disorders. Curr Pain Headache Rep 2007;11:333–8.
11. Kato K, Sullivan PF, Evengård B, Pedersen NL. Chronic widespread pain and its comorbidities: a population-based study. Arch Intern Med 2006;166:1649–54.
12. Simms RW. Fibromyalgia is not a muscle disorder. Am J Med Sci 1998;315:346–50.
13. Buskila D, Sarzi-Puttini P, Ablin JN. The genetics of fibromyalgia syndrome. Pharmacogenomics 2007;8:67–74.
14. Martinez-Lavin M. Biology and therapy of fibromyalgia. Stress, the stress response system, and fibromyalgia. Arthritis Res Ther 2007;9:216–25.
15. Sarzi-Puttini P, Atzeni F, Diana A, Doria A, Furlan R. Increased neural sympathetic activation in fibromyalgia syndrome. Ann NY Acad Sci 2006;1069:109–17.
16. Crofford LJ. Neuroendocrine abnormalities in fibromyalgia and related disorders. Am J Med Sci 1998;315:359–66.
17. Jones KD, Deodhar P, Lorentzen A, Bennett RM, Deodhar AA. Growth hormone perturbations in fibromyalgia: a review. Semin Arthritis Rheum 2007;36:357–79.
18. Kosek E. In: Cervero F, Jensen TS, editors. Handbook of clinical neurology. Edinburgh: Elsevier, 2006.
19. Giovengo SL, Russell IJ, Larson AA. Increased concentrations of nerve growth factor in cerebrospinal fluid of patients with fibromyalgia. J Rheumatol 1999;26:1564–9.
20. Wood PB. Stress and dopamine: implications for the pathophysiology of chronic widespread pain. Med Hypotheses 2004;62:420–4.
21. Schweinhardt P, Sauro KM, Bushnell MC. Fibromyalgia: a disorder of the brain? Neuroscientist 2008; Epub Feb 12.
22. Desmeules JA, Cedraschi C, Rapiti E, Baumgartner E, Finckh A, Cohen P, Dayer P, Vischer TL. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. Arthritis Rheum 2003;48:1420–9.
23. Sörensen J, Graven-Nielsen T, Henriksson KG, Bengtsson M, Arendt-Nielsen L. Hyperexcitability in fibromyalgia. J Rheumatol 1998;25:152–55.
24. Staud R, Vierck CJ, Robinson ME, Price DD. Effects of the *N*-methyl-D-aspartate receptor antagonist dextromethorphan on temporal summation of pain are similar in fibromyalgia patients and normal control subjects. J Pain 2005;6:323–32.
25. Graven-Nielsen T, Aspegren Kendall S, Henriksson KG, Bengtsson M, Sörensen J, Johnson A, Gerdle B, Arendt-Nielsen L. Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients. Pain 2000;85:483–91.
26. Cook DB, Stegner AJ, McLoughlin MJ. Imaging pain of fibromyalgia. Curr Pain Headache Rep 2007;11:190–200.
27. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 2002;46:1333–43.
28. Kuchinad A, Schweinhardt P, Seminowicz DA, Wood PB, Chizh BA, Bushnell MC. Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain? J Neurosci 2007;27:4004–7.
29. Carville SF, et al. EULAR evidence-based recommendations for the management of fibromyalgia syndrome. Ann Rheum Dis 2008;67:536–41.
30. Sarzi-Puttini P, Buskila D, Carrabba M, Doria A, Atzeni F. Treatment strategy in fibromyalgia syndrome: where are we now? Semin Arthritis Rheum 2007; Epub Oct 30.
31. Crofford LJ, Mease PJ, Simpson SL, Young JP Jr, Martin SA, Haig GM, Sharma U. Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6-month, double-blind, placebo-controlled trial with pregabalin. Pain 2008;136:419–31.
32. Borg-Stein J. Management of peripheral pain generators in fibromyalgia. Rheum Dis Clin North Am 2002;28:305–17.

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