

Series Editor: Bryan A. Liang, MD, PhD, JD

Fibromyalgia Syndrome: Diagnosis and Management

Case Study and Commentary: Fatma Inanici, MD, and Muhammad B. Yunus, MD

DR. LIANG:

Fibromyalgia syndrome (FMS) is a condition characterized by a combination of chronic and diffuse musculoskeletal pain, stiffness, and tenderness, usually accompanied by sleep difficulties and fatigue.¹ The majority of affected patients are women from age 30 to 60 years,² as illustrated by the patient in this case study. Many other designations for FMS exist, including muscular rheumatism, fibrositis, fibromyositis, tension myalgia, musculoskeletal pain syndrome, generalized nonarticular rheumatism, and chronic pain amplification syndrome.^{3,4}

Regardless of the name used, FMS consumes tremendous economic and social resources, in terms of individual loss of mobility, reduced productivity, and disability.⁵ FMS patients average at least a visit a month seeking medical or nontraditional/alternative treatment; 92% of them take at least 1 drug (usually a nonsteroidal anti-inflammatory drug [NSAID]) to treat their FMS, with a mean number of 2.7 fibromyalgia-related drugs per patient.⁶ The average annual medical cost in 1996 for FMS patients was \$2274,⁶ and as many of 25% of patients with FMS receive some form of disability payment or injury compensation.⁷ Such sobering statistics indicate the tremendous burden the disease imposes on these patients and suggest patients' potential inability to obtain and maintain work activities,⁸ a reality that may further exacerbate their condition.

The prevalence of FMS increases with age, with the incidence of the disease peaking among persons age 60 to 80 years.⁹ The incidence of FMS varies with the particular patient sample studied, with an incidence of 7% in the general population,⁶ 2.1% to 5.7% in general medicine clinics and primary care practice,¹⁰ and 10% to 20% in rheumatology clinics.¹⁰ Moreover, geographic prevalence is different around the world; for example, population-based studies in Europe have indicated that overall prevalence of the syndrome is between 1% and 2%,^{11,12} whereas in North America, the prevalence is reported as 2%.¹³ Overall, women are most affected by the

disease; the prevalence of the condition in women is 3.4%, compared with 0.5% in men, with the greatest rate of FMS occurring in women age 50 years and older.¹⁴

FMS is a major cause of disability in the United States and the second most common disorder seen by rheumatologists in North America.¹⁵ In most cases, vague symptoms of pain in women are reported first to primary care providers, thus potentially increasing the time before effective treatment begins. This problem is further exacerbated by the difficulty in diagnosis. Often, FMS is not recognized as a distinct clinical entity, and nonspecific symptoms of muscle pain make clear identification of the syndrome difficult; accompanying psychiatric conditions may further complicate the diagnosis.^{16,17} Additionally, chronic generalized pain, a frequent symptom of FMS, is common in many types of conditions and patients. At least 10.6% of patients in the United States report chronic widespread pain, and 20.1% report chronic regional pain.⁹ Thus, primary care providers have a distinct challenge in accurately diagnosing FMS.

Another consideration making diagnosis of FMS difficult for primary care practitioners is the nonspecific nature of the accompanying pathophysiology. In patients with FMS, pain is usually identified at the fibrous tissues, muscles, ligaments, and tendons. However, there is an absence of histologic signs of inflammation or of any specific cellular abnormalities at the identified locations.¹⁸ Furthermore, the specific pathophysiology of the disease has yet to be elucidated; in fact, it has been suggested that the syndrome is not caused by any single etiologic factor.^{19,20}

Dr. Inanici is from the Department of Physical Medicine and Rehabilitation, Hacettepe University Medical School, Ankara, Turkey. Dr. Yunus is from the Section of Rheumatology, University of Illinois College of Medicine at Peoria, Peoria, IL. Dr. Liang is a Professor of Health Law and Policy, Health Law and Policy Institute, University of Houston Law Center, Houston, TX; and a member of the Hospital Physician Editorial Board.

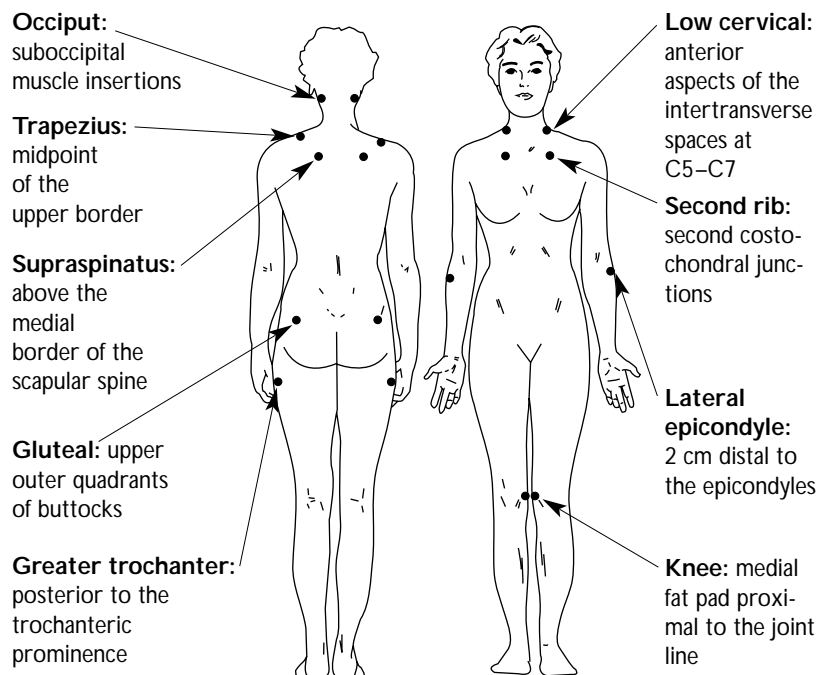


Figure 1. Specified sites of 18 (9 bilateral) tender points in fibromyalgia syndrome. (Adapted with permission from Freundlich B, Leventhal L. Diffuse pain syndromes. In: Klippel JH, editor. Primer on the rheumatic diseases. 11th ed. Atlanta: Arthritis Foundation; 1997. Copyright© 1997 the Arthritis Foundation.)

In addition to the potential multifactorial causes of FMS noted in the case study, the syndrome has also been associated with infection. Causative infectious agents include Epstein-Barr virus, cytomegalovirus, human herpesvirus 6, HIV, and *Borrelia burgdorferi*.²¹⁻²⁴ Indeed, it has been reported that 55% of patients with FMS indicated that their disease symptoms began with a viral syndrome.²⁴

Overall, FMS is a highly disconcerting, difficult disease for both patients and providers to confront. A heightened suspicion of FMS on the part of primary care providers is appropriate for any female patient presenting with diffuse pain. By including FMS in the differential diagnosis, providers may diagnose the condition more quickly and provide the necessary treatment to their patients, while simultaneously limiting the time of experienced pain. At the same time, such provider actions may improve the quality of these patients' lives, as well as reduce the economic costs associated with the disease.

DRS. INANICI AND YUNUS:

FMS is a common chronic musculoskeletal pain disorder. Approximately 90% of patients with FMS are women.^{13,25,26} American College of Rheumatology (ACR) criteria for the diagnosis of FMS are widespread pain (pain in the left and right side of the body, above and below the waist, and in the axial skeleton) for at least 3 months and tenderness of at least 11 of 18 tender points on palpation (**Figure 1**).¹³ Allodynia (pain on a

usually nonpainful stimulus such as touch or massage) also occurs in many affected patients. Besides pain, other characteristic symptoms of FMS include fatigue, sleep difficulties, morning fatigue, paresthesias, and subjective swelling of the extremities. Associated features are migraine and tension-type headaches, irritable bowel syndrome (IBS), restless legs syndrome, female urethral syndrome (irritable bladder syndrome), primary dysmenorrhea, sicca syndrome, anxiety, and depression (**Table 1**).^{13,25-27} Some patients also report cognitive dysfunction such as word groping and difficulties with short-term memory and concentration.^{28,29} Associated features are particularly helpful if a patient has 8 to 10 tender points but are not essential for diagnosis of FMS by ACR criteria.

Most patients with FMS have symptoms for 5 to 7 years before a diagnosis is made.^{13,30} Delay in diagnosis of FMS often proves costly and frustrating to the patient and may lead to inappropriate therapy.³¹ Patients commonly have high rates of hospitalization prior to diagnosis of FMS, both for musculoskeletal and nonmusculoskeletal hospitalizations, but these rates decrease following diagnosis.³² Thus, early diagnosis of FMS may prevent costly diagnostic tests and unnecessary treatment and may improve patients' quality of life.

CASE STUDY

Initial Presentation

A 60-year-old woman who is a retired teacher visits her primary care physician for evaluation of severe

fatigue and pain in her neck, hands, shoulders, pelvic girdle area, and legs that have persisted for more than 1 year.

History

The patient explains that she has had mild pain and stiffness in her extremities for almost 5 years but that, over the past year, the pain has become severe, widespread, and persistent. She says, “Now I have pins and needles from head to toe. It hurts badly all over, all the time.” The pain is aggravated by work, stress, cold weather, and humidity and somewhat alleviated by local heat and rest. She says that she cannot hug her grandchildren because pressure or even light touch causes much pain. In addition, the patient reports always feeling tired and says that simple daily activities, such as shopping or cooking, exhaust her. She reports difficulty falling asleep, saying “No matter how long I sleep, I wake up very tired in the morning. There are some days that I don’t want to get out of bed.” She adds that her hands and feet feel swollen and numb and that she has 3 hours of stiffness in her joints on waking.

- **What are the possible causes of this patient’s symptoms?**

A variety of disorders can cause diffuse musculoskeletal pain and fatigue; therefore, a systematic approach to the differential diagnosis is essential. Of the entities listed in **Table 2**, the ones more likely to cause musculoskeletal pain and fatigue in a woman age 60 years are fibromyalgia, polymyalgia rheumatica, vasculitis, and inflammatory arthritides. In addition, hypothyroidism, which causes stiffness and cramping pain, should be considered, particularly because of the patient’s severe fatigue. However, FMS is a likely diagnosis at this point because several characteristic features of FMS are present, including widespread pain, severe fatigue, allodynia (patient cannot hug her grandchildren), and poor sleep.

To narrow the differential diagnosis, the physician should take a complete history, including information about any constitutional symptoms (eg, fever, weight loss), and perform a careful physical examination. Examination of the hands will help to determine the presence of inflammatory arthritides. Because FMS is a likely diagnosis, the patient should be evaluated for tender points. This examination involves teaching the patient to distinguish between pressure and pain by gradually increasing pressure in the lateral epicondylar area and asking the patient to report as soon as pressure changes to pain. The physician should then examine the 18 tender point

Table 1. Fibromyalgia Syndrome Symptoms

Musculoskeletal symptoms

Pain at multiple sites
Stiffness
Sensation of “hurting all over”
Swollen feeling in soft tissues

Nonmusculoskeletal symptoms

Fatigue
Morning fatigue
Sleep difficulties
Paresthesias

Associated symptoms

Tension-type headaches
Migraine
Dysmenorrhea
Irritable bowel syndrome
Restless legs syndrome
Anxiety
Depression
Sicca syndrome
Female urethral syndrome

sites by applying pressure using the tip of the index finger with a force of 4 kg (approximately the amount of pressure required to blanch the nail of the examiner’s finger when pressed against the patient’s forehead).

Further History

On further questioning, the patient reports no fever, increased perspiration, or change in appetite or weight. She has not noted skin thickening or rash, Raynaud’s phenomenon, dry eyes or mouth, vision problems, hair loss, or respiratory difficulties. She does report dry skin and intolerance to cold weather. The patient describes a 2-year history of constipation and abdominal pain relieved by bowel motion but reports no nausea, vomiting, dysphagia, or heartburn. In the past year she has had problems with finding the right words while speaking, concentration, short-term memory, and performing simple mental tasks. She denies significant anxiety or depression but feels “frustrated” by her disabling symptoms and reports some stress caused by her pain and by a demanding husband.

There is no history of allergies. Past medical history includes periodic migraine headache that first occurred at age 26 years and “quit” at 40 years. She now experiences tension-type headaches, which she

Table 2. Common Causes of Chronic Diffuse Musculoskeletal Pain and Fatigue

Musculoskeletal/connective tissue disorders

Fibromyalgia syndrome
Rheumatoid disorders
Systemic lupus erythematosus
Sjögren's syndrome
Polymyalgia rheumatica
Systemic sclerosis
Vasculitis

Chronic fatigue syndrome

Metabolic disorders

Hypothyroidism
Metabolic myopathies/neuropathies
Hyperparathyroidism
Osteomalacia

Neoplastic conditions

Psychiatric disorders

Somatization disorder
Hypochondriasis

describes as diffuse in the scalp and neck but without features of migraine. She was taking naproxen 220 mg as needed for headaches and notes that she had stomach pain if she took more than 1 tablet. The frequency of the headaches has increased in the past year. A gastric ulcer was diagnosed 9 years ago. Six months ago, she had persistent chest pain on the left side. At that time, physical examination and laboratory investigation revealed no intrathoracic pathology. She still occasionally has chest pain, irrespective of rest or exercise. She has no cough, palpitations, or shortness of breath. Recent gynecologic and breast examinations, mammography, and bone mineral density measurement were all within normal limits.

Family history is remarkable for her mother, who had osteoporosis and frequently complained of constipation. For the past 4 years, the patient has been taking acetaminophen 500 mg as needed (usually, 2 or 3 tablets daily), calcium carbonate 500 mg daily, and vitamin D 400 IU daily. She does not smoke and has 1 alcoholic drink per month.

Physical Examination

The patient appears healthy on examination. She is not obese and is mentally alert, with normal speech. Vital

signs include temperature of 36.5°C (97.7°F), regular pulse of 67 bpm, and blood pressure of 120/80 mm Hg. Her skin is dry, and her body and scalp hair is rather sparse. Head, ear, eyes, neck, and thyroid examination are unremarkable; mouth is moist. Temporal arteries are not tender, but mild periorbital puffiness is noted. There is no lymphadenopathy, skin rashes, or skin thickening. Examination of the lungs and heart is unremarkable. Distal artery pulses are palpable, and there is no discoloration of the skin or edema in the extremities. Abdominal examination reveals tenderness in both iliac fossa; no masses are felt, and no bruit is heard. Muscle tone and strength are normal, and there is no muscle atrophy. Light touch, pinprick, joint position, and vibration sensations are normal in the extremities, as are reflexes and results of cranial nerve testing. Cerebellar signs are absent. Musculoskeletal examination reveals normal range of motion of the joints, except for mild pain and some restriction of neck extension, flexion, and rotations. Joints are not swollen or warm, but the fingers and hand joints are diffusely tender. There is no joint deformity. Seventeen of 18 tender point sites are tender, with the patient reporting mild to severe pain on palpation. Palpation of the chest wall shows rather diffuse tenderness. The lumbar region is also tender.

Diagnosis

The physician makes a diagnosis of FMS based on the presence of widespread pain and more than 11 tender points. The presence of associated features of FMS, including fatigue, poor sleep, IBS, cognitive difficulties, subjective swelling of the hands, and headaches, support this diagnosis.

- **How common is FMS?**
- **What causes FMS?**

Epidemiology

An estimated 7 million people in the United States have FMS by ACR criteria,^{9,33} but the number with a clinical diagnosis of FMS is likely higher. FMS patients constitute 2.1% to 5.7% of the outpatient internal medicine or family practice clinic population and 10% to 20% of outpatient rheumatology visits.¹⁰ It is the second most common diagnosis in rheumatology clinics.³⁴ The population prevalence of FMS is 2% to 3%. However, FMS is much more common among women (population prevalence of 3.4%–4.9% in women versus 0.5%–1.6% in men),^{9,35} and although it is seen in all age groups,³⁶ its population prevalence increases with age, reaching more than 7% in women age 60 to 79 years.⁹ The clinical features of juvenile fibromyalgia

are similar to those of adult FMS.³⁶ However, men have less fatigue, morning fatigue, and IBS and fewer tender points than do women.³⁷

Etiology

The etiology and pathophysiologic mechanisms of FMS are not fully understood but are considered to be multifactorial. Dysfunction of the neuroendocrine system that leads to an aberrant central pain mechanism with central sensitization is currently thought to be the most important mechanism.^{38–40} Several forms of neuroendocrine dysfunction have been described, including low serum serotonin level, increased substance P in the cerebrospinal fluid, decreased level of insulin-like growth factor 1, and an abnormal hypothalamic-pituitary-adrenal axis.^{38,39,41–43} Poor sleep, physical deconditioning, emotional distress (including anxiety and depression), trauma, and environmental and workplace factors contribute to FMS symptoms in varying degrees in different patients.^{38,39,44–46} (Table 3). Genetic predisposition seems likely.⁴⁷ Psychological factors, including coping skills, are important determinants of pain in a subgroup of patients.⁴⁸ Anxiety, depression, and mental stress are present in 30% to 40% of patients who have FMS,^{13,48} but in most cases they seem to be secondary to chronic pain.⁴⁸

IBS, headaches, restless legs syndrome, chronic fatigue syndrome (CFS), and temporomandibular pain syndrome are more common in FMS patients than in healthy and chronic pain controls, and these conditions cluster in the same group of patients.^{9,13,25–27,48–52} In addition, these conditions share many clinical features (eg, female preponderance, pain without tissue damage, fatigue, poor sleep) and respond to a similar group of medications.^{50,53–60} Based on these observations and evidence of central sensitization in these overlapping syndromes, it was suggested that central sensitization is a common physiologic glue that binds this group of conditions, making them “central sensitivity syndromes.”^{39,61}

• What possible diagnoses warrant further evaluation in this patient?

Other Causes of Musculoskeletal Pain and Fatigue

This patient has FMS by history and physical examination. Although FMS is not a diagnosis of exclusion,^{13,39} conditions frequently coexist with FMS, and laboratory tests and radiography should be performed if clinically indicated to evaluate for conditions in the differential that might contribute to this patient’s symptoms but cannot be reasonably excluded by history and physical examination.

Table 3. Common Factors That Aggravate Fibromyalgia Symptoms

Sleep difficulties
Physical deconditioning, muscle overload, poor posture
Psychological factors: stress, anxiety, depression, poor coping skills
Environmental factors: hot/cold temperature, humidity, noise
Occupational factors: repetitive trauma, ergonomic factors
Physical overuse/unaccustomed exercise
Coexisting/associated conditions: arthritis, neuritis, restless legs syndrome, hypothyroidism, headaches, irritable bowel syndrome, irritable bladder syndrome

Other rheumatic conditions. Polymyalgia rheumatica, with or without temporal arteritis, most often affects patients age 60 years and older, but lack of constitutional symptoms and temporal artery tenderness argues against them. Also, stiffness in the shoulder and pelvic girdles, rather than pain, is a prominent symptom of polymyalgia rheumatica. A normal erythrocyte sedimentation rate (ESR) would exclude this entity. In the absence of constitutional symptoms, vasculitis or a connective tissue disease is unlikely. The patient has no signs of joint inflammation (eg, objective swelling, warmth, erythema) or evidence of systemic inflammatory diseases (eg, fever, weight loss, skin rashes, skin thickening or vasculitic lesions, oral ulcers, dry eyes and mouth, dysphagia, subcutaneous nodules, signs of cardiac or pulmonary involvement, pleural and pericardial effusions, lymphadenopathy, hepatosplenomegaly, neurologic findings), further excluding systemic rheumatic diseases. The patient does have diffuse tenderness in her fingers and hand joints on palpation, but this finding is common in FMS, a disorder of global hyperalgesia. Scleroderma is quite unlikely in the absence of hand changes or Raynaud’s phenomenon. Myopathy, including polymyositis, is unlikely in the absence of muscle weakness, particularly proximal weakness, and muscle pain is not usual in these disorders.

Spinal osteoarthritis primarily affects the lumbar and cervical regions, and the patient has neck and back pain and limitation of range of motion of the cervical spine. A concomitant presence of FMS and osteoarthritis at age 60 years is not uncommon, so it is reasonable to order radiographs of the patient’s neck and spine.

Chronic fatigue syndrome. CFS is characterized by chronic debilitating fatigue, is worsened by even mild

activities, and lasts more than 6 months. Other features include fever, pharyngitis, myalgias, adenopathy, arthralgias, sleep difficulties, cognitive dysfunction (as in FMS), and disorders of mood. Cognitive problems are much more frequent in CFS than in FMS. Fever and pharyngitis are often subjective. In the majority of patients, the illness starts suddenly with an acute “flu-like” illness.^{62,63} FMS and CFS have similar clinical and demographic features, and they also overlap with other similar syndromes (eg, IBS, headaches).^{50,64}

Metabolic disorders. Dry skin, fatigue, cold intolerance, paresthesia, and periorbital puffiness are valuable clues of hypothyroidism. The patient’s bowel symptoms suggest IBS, although constipation may be caused by hypothyroidism in this patient. Primary hypothyroidism is common and generally occurs after age 40 years. The musculoskeletal symptoms of hypothyroidism are stiffness and muscle cramping rather than generalized muscle and joint pain. Thyroid function tests should confirm whether hypothyroidism is present.

Patients with osteomalacia and hyperparathyroidism may have bone pain, proximal muscle weakness, severe pruritus, polyuria, anorexia, nausea, impaired cognitive function, depression, and hypertension. However, widespread muscular pain or muscular tender points are not characteristic features of these diseases; tenderness is usually limited to bone. Osteomalacia occurs in those with inadequate dietary intake of vitamin D, malabsorption, and renal disease. Measurement of serum calcium, phosphate, bone-specific alkaline phosphatase, and parathyroid hormone levels is necessary to assess for metabolic bone diseases; however, these diseases are quite unlikely in this patient.

Infection/malignancy. In patients with chronic infections and malignancy, constitutional symptoms are accompanied by signs and symptoms specific for the organs involved.

Somatization disorder. Patients with somatization disorders usually have subjective symptoms affecting multiple organ and body systems that cannot be explained by a medical condition or known pathophysiologic mechanism. Because FMS is a well-characterized condition with a generally understood pathophysiology,^{38–42} psychogenic pain should not be diagnosed in this patient. Also, symptoms in somatization disorder begin before age 30 years.

• **Is further evaluation of the patient’s chest pain warranted?**

Organic causes of chest pain include ischemic heart disease, pericardial disease, pulmonary diseases, aortic aneurysm, and upper gastrointestinal diseases. The mus-

culoskeletal structures of the thoracic wall are a relatively common source of chest pain that is often mistaken for angina pectoris or pleural pain. FMS is the most common cause of chest pain in patients who have no intrathoracic pathology.^{65–68} The history of pain (ie, location, duration, radiation of pain, and factors that cause, aggravate, or alleviate pain) and symptoms such as shortness of breath, hemoptysis, cough, and palpitation are very useful in distinguishing between intrathoracic and chest wall causes of chest pain. In FMS, the pain is constant but may be aggravated by activities that involve use of chest wall muscles. Chest wall tenderness on palpation often reproduces pain. This patient did not have a typical history of cardiac pain (ie, heavy or squeezing central chest pain lasting 3–10 minutes with radiation to the arm, neck or jaw that is brought on by exertion and relieved by rest). Additionally, she lacked other symptoms and signs of intrathoracic pathology. On the other hand, the diffuse tenderness of the chest wall by palpation, along with other features of FMS, would suggest that her chest pain is caused by fibromyalgia. However, because diseases may coexist, in a patient with a suggestive history and physical examination, intrathoracic disease should be ruled out, even if the patient has FMS.

Laboratory Evaluation

The physician orders routine laboratory tests, including complete blood count; measurement of ESR, C-reactive protein level, serum electrolyte level, and blood glucose level; liver enzyme tests; renal function tests; thyroid function tests; and urinalysis. Anteroposterior, lateral, and oblique radiographs of cervical and lumbar spine are also requested to evaluate the patient’s neck and back pain and limitation of range of motion of the cervical spine. Antinuclear antibody, serum complement, and rheumatoid factor tests are not performed, because the patient does not have symptoms or signs of systemic rheumatic disease.

The results of the laboratory tests are normal, except for an elevated ESR (36 mm/hr) and the following abnormal thyroid function test results: total thyroxine (T_4) level, 3 $\mu\text{g}/\text{dL}$ (normal, 4–11 $\mu\text{g}/\text{dL}$); free T_4 index, 66 (normal, 96–396); thyroid-stimulating hormone (TSH) level, 38 $\mu\text{IU}/\text{mL}$ (normal, 0.4–4.8 $\mu\text{IU}/\text{mL}$). Results of urinalysis are unremarkable. Cervical and lumbar spine radiographs show mild to moderate intervertebral disk-space narrowing, sclerosis of vertebral end plates, and osteophytosis.

• **What is the significance of these findings?**

The elevated TSH level confirms the diagnosis of primary hypothyroidism, and the radiographic findings

confirm the diagnosis of mild to moderate osteoarthritis of the cervical and lumbar spine. At 36 mm/hr, the patient's ESR is elevated but only mildly so, given her age. ESR increases with age and is higher in women. A general rule for calculating the age- and sex-adjusted upper limit of normal ESR for women is age plus 10 divided by 2.⁶⁹ Thus, polymyalgia rheumatica is ruled out in this patient.

As mentioned, co-occurrence of other conditions with FMS is not unusual. FMS may be classified as concomitant when another condition is present and contributes to pain or fatigue of FMS. The clinical characteristics, diagnosis, and management of concomitant FMS are not different from primary fibromyalgia, but concomitant conditions should be treated appropriately since they may add to the patient's symptoms.

• **What is the approach to management of FMS?**

Overview of FMS Management

The goals of FMS management are to alleviate pain and other symptoms, to eliminate or modify possible aggravating factors, to improve sleep quality, to achieve physical fitness, to enhance patient's coping skills, and to improve quality of life.⁷⁰ Management of FMS is usually challenging, because many different factors interact to cause symptoms, and their relative importance varies from patient to patient. Therefore, the approach to treatment should be individualized according to a patient's symptoms and severity of FMS. Both nonpharmacologic and pharmacologic interventions are used to treat FMS patients (Table 4); however, nonpharmacologic approaches should be emphasized before any drug is prescribed. A combination of pharmacologic and nonpharmacologic interventions was found to be more efficacious in improving self-reported symptoms of FMS than pharmacologic treatment alone.⁷¹ Interdisciplinary group treatments are also reported to be beneficial.^{72,73}

Nonpharmacologic therapy. Following diagnosis of FMS, patient education is essential and should be continued in all subsequent visits. The physician should inform the patient about currently known physiologic mechanisms of FMS, including aggravating factors. The patient should be reassured that although FMS can be chronic, it is not a malignant condition and does not cause tissue damage. However, the physician should avoid characterizing FMS as a "benign condition," because patients who have severe and disabling pain often resent this description. A positive and empathetic attitude on the part of the physician is key.

Coexisting or associated conditions may aggravate FMS symptoms by producing an extra burden of stress,

Table 4. Management of Fibromyalgia Syndrome

Nonpharmacologic therapy

- Firm diagnosis, education, reassurance, emotional support
- Cardiovascular fitness training
- Cognitive behavioral therapy
- Electromyography biofeedback
- Relaxation training
- Acupuncture/electroacupuncture
- Physical therapy/manipulation
- Interdisciplinary group treatment

Pharmacologic therapy*

- Simple analgesic agents
 - Acetaminophen
 - Low-dose NSAIDs, if not contraindicated
- Antidepressant agents
 - Tricyclic antidepressant agents (amitriptyline, cyclobenzaprine, doxepin, desipramine, imipramine, nortriptyline)
 - Selective serotonin reuptake inhibitors (fluoxetine, sertraline, paroxetine, citalopram)
 - Others (trazodone, venlafaxine, nefazodone)
- Central analgesics
 - Tramadol
 - Codeine

NSAIDs = nonsteroidal anti-inflammatory drugs.

*Not all the listed drugs have been found to be efficacious by double-blind controlled studies.

pain, or fatigue; by disturbing sleep; and by limiting aerobic activity (Table 3). Because the presence and significance of coexisting conditions differ from patient to patient, the physician should inquire about each of them, discuss them with the patient, and try to eliminate or treat them satisfactorily.

Restoring sleep hygiene, gradually increasing physical fitness, and eliminating any psychological distress are key points of successful management. Poor sleep can be helped by sleeping in a quiet and uncluttered room, keeping regular sleep hours, avoiding alcohol and caffeine in the evening, exercising regularly (but at least 3 to 4 hours before bed time), and avoiding psychological distress. Psychological stresses can be decreased by relaxation techniques, pacing of daily activities, and cognitive approaches. Physical fitness exercises improve physical conditioning; provide resistance to microtrauma; enhance strength, endurance, and flexibility; increase sense of control; and

have relaxation and pain modulation effects.^{74,75} Stretching exercises provide short-term help, but aerobic exercises are the most beneficial. The key is to start exercise at a low level, to increase exercise time gradually, and to exercise regularly. Patient compliance in physical exercise is generally poor. We insist that our patients keep a weekly diary or graph that includes highest sustained pulse rate achieved during exercise and average time spent exercising in a week and ask them to bring the diary or the graph during their next visit. Graphs are better than diaries since they can be read more quickly.

Cognitive behavioral therapy (usually undertaken by a psychologist) includes relaxation training, reduction of negative pain behavior, coping skills training, and fostering of a positive, "I can do" attitude.^{76,77} This modality should be used in patients with poor coping skills.

Pharmacologic therapy. Pharmacologic treatment options for FMS include simple analgesic and antidepressant agents. Because patients often have a negative perception about "antidepressants," particularly patients who are not depressed, we refer to antidepressant agents as "serotonin boosters to help pain and sleep." Amitriptyline, cyclobenzaprine, and a fluoxetine/amitriptyline combination have been shown to alleviate pain, improve poor sleep, and reduce fatigue. These antidepressants have been shown to consistently improve patient-assessed global severity of pain, although they do not always decrease the number of tender points. Amitriptyline is the most widely prescribed tricyclic antidepressant agent used in FMS⁷⁸; it has been shown to be effective in double-blind, placebo-controlled studies.^{79–82} The usual dose is 10 to 50 mg daily. Cyclobenzaprine, a tricyclic antidepressant agent that is marketed as a muscle relaxant, has short-term efficacy in FMS.^{83,84} The combination of fluoxetine with amitriptyline has been shown to be effective⁸⁴; another study showed the combination to be more effective than either drug alone.⁸⁵

Tramadol is a centrally acting analgesic with both μ opioid-receptor binding and norepinephrine and serotonin reuptake inhibition; it has been found to decrease pain in a controlled study.⁸⁶ The usual dose is 100 to 400 mg daily. Although a beneficial effect of acetaminophen in FMS has not been reported by blinded and controlled studies, some patients find this relatively safe drug helpful. Many patients also report benefit from NSAIDs, but data do not support the efficacy of an NSAID alone in FMS. NSAIDs may be prescribed for a concomitant disease such as osteoarthritis with the usual precautions regarding adverse effects. Acetaminophen 500 mg with codeine 30 mg 3 to 4 times daily may be prescribed during a flare or in dif-

ficult patients with severe symptoms who do not respond to other interventions.⁸⁷ Injection of lidocaine into tender points is a valuable adjunctive therapy in patients with a limited number of painful sites that are especially bothersome.⁸⁸ Patients who receive injections should apply ice at injected sites for 20 minutes each hour for 4 to 6 hours and rest the injected areas for 48 hours to avoid postinjection flare of pain.

Amitriptyline, cyclobenzaprine, a fluoxetine/amitriptyline combination, citalopram, and tramadol have been found to be efficacious in treating FMS by double-blind controlled studies.⁷⁰ A stepwise approach to pharmacologic treatment may be used. Mildly symptomatic patients may be treated with simple analgesics and low-dose tricyclic antidepressants; moderately affected patients may be prescribed the maximum tolerated dose of tricyclic antidepressants or a combination of tricyclic antidepressants and selective serotonin reuptake inhibitors. Low-dose central analgesics (ie, tramadol) may be prescribed if the patient does not have a history of alcoholism or other drug addictions. In severe cases, other medications in the same classes as those above and tender point injection with a local anesthetic agent may be useful.

Management of the Patient's FMS

The patient is prescribed levothyroxine 25 μ g daily for her hypothyroidism. Evaluation of the progress of treatment of primary hypothyroidism consists of measurement of serum total T_4 and TSH levels and assessment of clinical status, bearing in mind that in a FMS patient, fatigue is unlikely to improve satisfactorily, even when TSH level is normal. For her cervical osteoarthritis, the patient is advised to avoid activities that are particularly stressful to the neck, to apply moist heat for relaxation of tight neck muscles as needed, and to perform active range-of-motion exercises.

The physician discusses the nature of FMS with the patient and gives her an information booklet on the condition. Factors that aggravate her symptoms—sleep difficulties, cold weather, emotional stress—are discussed. To restore sleep hygiene, she is advised to avoid heavy meals, caffeine, or alcohol before bedtime and to eliminate disturbing factors such as noise and light from her sleep environment. She is asked to sleep/wake on a regular schedule and to sleep at least 7 to 8 hours each night. The patient is advised to walk for exercise or swim in a warm pool for 5 minutes daily and to gradually increase the time to 30 minutes daily (ie, in 2- to 3-minute increments every week). Walking on a treadmill or riding an exercise bicycle are recommended in case of low outdoor temperature. The

goal of physical exercise is to achieve cardiovascular fitness with an appropriately elevated pulse rate during exercise. Additionally, she is taught stretching exercises for her aching muscles. The importance and benefits of exercise (eg, pain relief, relaxation, better sleep) are emphasized. She is also referred for physical therapy, including stretching, local heat application, massage, and ultrasound therapy.

The physician prescribes amitriptyline 10 mg at bedtime, to be increased to 20 mg after a week if tolerated. He explains that the amitriptyline is prescribed to improve the patient's sleep and pain and not as an antidepressant agent. He also tells the patient that it might take 3 to 4 weeks for the amitriptyline to work and informs her about its possible adverse effects. The physician increases the acetaminophen dose to 3 to 4 g daily. The patient is scheduled for an office visit in 4 weeks.

Follow-up

4 Weeks. At 4 weeks after diagnosis, the patient's TSH level is 12 μ IU/L, and there is some improvement in her fatigue. The physician increases the dose of levothyroxine to 50 μ g daily. At 8 weeks, the patient's pain has improved somewhat but the fatigue remains the same; her TSH level is 10 μ IU/L. The physician increases the dose of levothyroxine to 75 μ g daily. Her sleep and headaches have improved, but she still has pain in her neck, hands, shoulders, legs, and—particularly—arms and thighs, as well as stiffness and morning fatigue. She reports that physical therapy has helped to some extent.

12 Weeks. At 12 weeks, the patient is regularly taking amitriptyline 20 mg daily at bedtime and does not complain of any adverse effects except for dry mouth. She is doing stretching exercises as regularly as possible but generally experiences postexercise pain after 20 minutes of brisk walking. She is taking 6 tablets of acetaminophen (500 mg each tablet) daily. The physician prescribes the cyclooxygenase-2 (COX-2) inhibitor rofecoxib at a dose of 12.5 mg daily, because the osteoarthritis of her cervical spine could be contributing to her neck pain and acetaminophen has not been helpful. A COX-2 inhibitor is selected because the patient had previous gastrointestinal intolerance with naproxen, has a history of gastric ulcer, and has mildly increased risk of peptic ulcer disease at age 60 years. The physician schedules TSH measurement in 4 weeks and asks the patient to return for an office visit in 6 weeks. The patient comments that she is feeling rather discouraged.

18 Weeks. The patient still complains of significant pain and fatigue, although both have improved. Physical examination reveals that her skin dryness and peri-

orbital puffiness are much improved. There is some restriction of the neck range of motion with pain, as before. Sixteen of 18 tender points are painful on palpation. Because the patient's TSH level 2 weeks earlier was 9 μ IU/L, the dose of levothyroxine is increased to 100 μ g daily.

To reassure the patient, the physician discusses her symptoms and aggravating factors and the chronic nature of FMS again. The physician encourages her to take an active role in the management of her symptoms and to have an optimistic attitude. He advises the patient to modify the exercise program according to her pain but to continue exercising regularly, with gradual increases in the exercising time, and to continue the physical therapy program. He also asks the patient to apply moist heat on the most painful sites. The physician increases the amitriptyline to 40 mg daily (since dry mouth is still mild) and the levothyroxine to 125 μ g daily after 1 week. The next office visit is scheduled for 2 months later.

27 Weeks. Two months later, the patient's TSH level is 4.3 μ IU/L (normal), but her fatigue and pain are only mildly improved compared to the previous visit. The neck pain, however, is significantly improved. The patient reports that she was better for 2 months, but then her pain and fatigue gradually worsened. She has difficulty falling asleep again and has frequent awakenings. She says that she cannot tolerate exercise anymore. She notes increased stress with interpersonal relationships, both in family and in social environments, because the severe pain and fatigue interfere with daily functioning. She says that she is "beginning" to feel depressed. Physical examination shows that her skin dryness and periorbital edema have nearly disappeared. The tender points on palpation seem worse; on questioning, the patient says that 4 areas are particularly painful. Fluoxetine 20 mg in the morning is added, and the 4 most symptomatic tender points areas are injected with 0.5 mL of 1% lidocaine. The physician asks her to continue heat therapy at home and to return in 10 weeks.

37 Weeks and 44 weeks. The patient's pain and fatigue have improved, but the fatigue remains troublesome. Her TSH level is 4.2 μ IU/L. She reports that the tender point injections have helped significantly and overall she feels better. She is asked to return in 3 months.

At 44 weeks, the patient says that she has "slipped back" and now has much pain and fatigue and is unable to carry out daily activities. She hurts all over but does not, however, feel more depressed. On physical examination, all tender points are markedly tender.

Range of motion of the neck and low back are mildly restricted and somewhat painful. The physician injects the most symptomatic tender point areas again. Given her continued symptoms, she is referred to a psychologist with expertise in cognitive behavioral therapy and coping skills. Despite pain, regular physical exercise is encouraged. Neither the dose of fluoxetine nor the dose of amitriptyline is increased, because fluoxetine may increase amitriptyline levels and cause adverse effects. The patient is asked to return in 10 weeks. The patient's TSH level is normal, so further increasing the levothyroxine is not likely to be helpful.

54 Weeks and beyond. The patient has continued cognitive behavioral therapy and previous medications, and she is exercising regularly. Her symptoms remain moderately severe, but she is able to perform daily activities better than before. Tender point injections are repeated every 3 to 4 months, as necessary. Because the patient has no personal or family history of seizure, she is permitted to take tramadol 50 to 150 mg (1–3 tablets) daily on an as-needed basis. She is not to exceed 3 tablets (150 mg) in 24 hours because she is taking amitriptyline and fluoxetine.

- **What factors should be considered over the long term in patients with FMS?**

FMS over the Long Term

As this case demonstrates, FMS is a chronic condition characterized by remissions and exacerbations of symptoms. Patients with an acute flare-up, often triggered by physical or emotional distress, may be treated with reassurance, physical therapy, relative rest, injection of tender points, and increasing the dosage of medications up to maximum tolerated dose. In patients who do not respond sufficiently to the optimal dose of first-choice drugs (eg, amitriptyline, cyclobenzaprine), it is reasonable to prescribe another drug (eg, doxepin, imipramine, desipramine, tramadol, trazodone, nefazodone, paroxetine, citalopram, sertraline). Benzodiazepines such as alprazolam 0.25 to 0.5 mg,⁸⁹ lorazepam, or buspirone may be useful in some patients, particularly those who have significant anxiety. However, long-term use of benzodiazepines should be avoided whenever possible because of potential dependence and withdrawal seizures associated with them. Hypnotic agents such as zolpidem⁹⁰ may be prescribed in patients whose sleep difficulties have not been adequately improved by sleep hygiene and tricyclic agents, although these agents do not help pain.^{70,90} Hypnotic agents should be taken at bedtime or after supper if there is morning grogginess. Patients whose compliance is low may be referred to a

supervised group exercise program. Significant psychologic distress can be helped by emotional support combined with higher doses of antidepressant agents than are used for pain management; however, psychiatric referral should be made when these attempts do not result in symptom improvement. The patient was doing fairly well as of the last visit, but exacerbations would not be uncommon in the future. Follow-up studies of more than 11 years have shown that FMS symptoms remain essentially unchanged over this time period.⁹¹

Systemic diseases and other musculoskeletal or non-musculoskeletal conditions may develop during the course of FMS. Any new symptom that is not compatible with a diagnosis of FMS or a change in the nature of symptoms should be evaluated carefully, because it may be a clue indicating new, coexistent disease. Failure to recognize and treat concomitant conditions may augment patient's symptoms and result in unsuccessful management of FMS. A diagnosis of associated restless legs syndrome and periodic limb movement disorder should not be missed, because both are likely to disturb sleep and can be treated with specific therapy such as benzodiazepines (clonazepam 0.5–1.5 mg daily), dopaminergic drugs (L-dopa or carbidopa/levodopa combination), anticonvulsant agents (gabapentin or carbamazepine), and opioids (codeine, propoxyphene, and hydrocodone).^{92–96} The addictive property of many of these drugs should be kept in mind. Clonazepam 0.5 mg at bedtime is usually prescribed first, followed by dopaminergic drugs. It has been reported that periodic limb movement disorder symptoms may be worsened by tricyclic agents that block noradrenaline uptake⁹⁷ and by selective serotonin reuptake inhibitors.⁹⁸ In addition, restless legs syndrome may be induced or exacerbated by mianserin, a tetracyclic antidepressant agent,⁹⁹ and by paroxetine¹⁰⁰ and sertraline.¹⁰¹ However, these observations are mostly based on case reports, and further studies are needed to confirm them.

- **What is the impact of FMS in terms of quality of life and cost?**

Quality of Life

As this case also demonstrates, FMS can cause a high level of functional disability and have a significant negative impact on quality of life (QOL). The severity of self-assessed disability in FMS is similar to that of rheumatoid arthritis and osteoarthritis.^{7,102–104} Pain, fatigue, and weakness are most often reported to affect working capacity.¹⁰⁵ Although most patients are able to remain employed and work most or all days, they often require job modifications, changes in ergonomics, and a reduction in work

hours.^{7,106,107} FMS patients have reported poorer QOL compared with patients with rheumatoid arthritis, osteoarthritis, permanent ostomies, chronic obstructive pulmonary disease, insulin-dependent diabetes, and healthy controls.^{103,108} In addition, patients with FMS have been reported to have similar impairments of QOL as patients with systemic inflammatory arthritis.^{109,110} Moreover, impaired QOL in patients with FMS may adversely affect their families.¹¹¹

Costs

The average yearly cost per patient associated with FMS has been estimated at approximately \$1000 in 1991¹¹² and \$2274 in 1996.⁶ Patients average almost 10 visits to outpatient clinics for traditional medical treatment and 2 visits for nontraditional therapy each year. Additionally, FMS is an increasingly important reason for disability claims and payments.^{113,114} In a 6-center study of disability status among 1604 patients with FMS in the United States, 26.5% reported receiving at least 1 form of disability payment.⁶ In Canada, McCain reported that private insurers pay more than \$200 million annually in long-term disability claims for FMS.¹¹⁵ In Norway, the most common reason for long-term disability payments in 1988 was FMS.¹¹⁶

SUMMARY

FMS is a common, painful, disabling condition. The diagnosis of FMS with widespread musculoskeletal pain and 11 or more tender points among 18 sites specified by ACR criteria is not difficult. However, physicians should be familiar with the symptoms, associated disorders, and—importantly—technique of tender point examination. Those not trained in proper technique of this examination tend to undercount the number of tender points. However, some patients may not have an adequate number of tender points even in expert hands but should be treated for FMS if other symptoms are present.

Education, reassurance, psychological support, and reminders to exercise regularly are important in all follow-up visits. Tender point injection is a valuable adjunctive therapy in any step of treatment. Physical therapy may help to reduce pain. A combination of pharmacologic and nonpharmacologic interventions provides better results than either approach alone. Various other nonpharmacologic modalities such as electroacupuncture or electromyogram biofeedback may be tried when a patient is not doing well. **HP**

Adapted from Inanici F, Yunus MB. Fibromyalgia syndrome: diagnosis and management. JCOM J Clin Outcomes Manage 2001;8(4):55–67.

REFERENCES

1. Ang D, Wilke WS. Diagnosis, etiology, and therapy of fibromyalgia. *Compr Ther* 1999;25:221–7.
2. Goldenberg DL. Fibromyalgia and related syndromes. In: Klippel JH, Dieppe PA, Arnett FC, et al, editors. *Rheumatology*. 2nd ed. St. Louis: Mosby; 1998:15.1–15.12.
3. Goldenberg DL. Fibromyalgia. In: Klippel JH, Dieppe PA, Brooks P, et al, editors. *Rheumatology*. St. Louis: Mosby; 1994:16.1–16.12.
4. Harmon CE. Fibromyalgia: Treatments worth trying. *IM—Intern Med* 1996;17:64–75.
5. Solomon DH, Liang MH. Fibromyalgia: scourge of humankind or bane of a rheumatologist's existence? *Arthritis Rheum* 1997;40:1553–5.
6. Wolfe F, Anderson J, Harkness D, et al. A prospective, longitudinal, multicenter study of service utilization and costs in fibromyalgia. *Arthritis Rheum* 1997;40:1560–70.
7. Wolfe F, Anderson J, Harkness D, et al. Work and disability status of persons with fibromyalgia. *J Rheumatol* 1997;24:1171–8.
8. Bennett RM. Fibromyalgia and the disability dilemma. A new era in understanding a complex, multidimensional pain syndrome. *Arthritis Rheum* 1996;39:1627–34.
9. Wolfe F, Ross K, Anderson J, et al. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum* 1995;38:19–28.
10. Wolfe F. Fibromyalgia: the clinical syndrome. *Rheum Dis Clin North Am* 1989;15:1–18.
11. Jacobsson L, Lindgarde F, Manthorpe R. The commonest rheumatic complaints over six weeks' duration in a twelve-month period in a defined Swedish population. Prevalences and relationships. *Scan J Rheumatol* 1989;18: 353–60.
12. Prescott E, Kjoller M, Jacobsen S, et al. Fibromyalgia in the adult Danish population: I. A prevalence study. *Scand J Rheumatol* 1993;22:233–7.
13. 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;33:160–72.
14. Clark S, Odell L. Fibromyalgia syndrome: Common, real—and treatable. *Clin Rev* 2000;10:57–62.
15. Wolfe F. Fibromyalgia. *Rheum Dis Clin North Am* 1990; 16:681–98.
16. Alnigenis N, Barland P. Following clues to fibromyalgia syndrome. *J Musculoskel Med* 2001;18:381–8.
17. Aaron LA, Bradley LA, Alarcon GS, et al. Psychiatric diagnoses in patients with fibromyalgia are related to health care-seeking behavior rather than to illness. *Arthritis Rheum* 1996;39:436–45.
18. Burckhardt CS, Jones KD, Clark SR. Soft tissue problems associated with rheumatic disease. *Lippincotts Prim Care Pract* 1998;2:20–9.
19. Holland NW, Gonzalez EB. Soft tissue problems in older adults. *Clin Geriatr Med* 1998;14:601–11.
20. Keel P. Pain management strategies and team approach. *Baillieres Best Pract Res Clin Rheumatol* 1999;13:493–506.

21. Maurizio SJ, Rogers JL. Recognizing and treating fibromyalgia. *Nurse Pract* 1997;22:18–26, 28, 31.
22. Bennett RM. The fibromyalgia syndrome. In: Kelley WN, Sledge CB, Ruddy S, et al, editors. *Textbook of rheumatology*. Philadelphia: WB Saunders; 1997:511–9.
23. Dinerman H, Steere AC. Lyme disease associated with fibromyalgia. *Ann Intern Med* 1992;117:281–5.
24. Buchwald D, Goldenberg DL, Sullivan JL, Komaroff AL. The “chronic, active Epstein-Barr virus infection” syndrome and primary fibromyalgia. *Arthritis Rheum* 1987;30:1132–6.
25. Yunus MB, Masi AT, Aldag JC. A controlled study of primary fibromyalgia syndrome: clinical features and association with other functional syndromes. *J Rheumatol Suppl* 1989;19:62–71.
26. Yunus MB, Masi AT, Calabro JJ, et al. Primary fibromyalgia (fibrositis): clinical study of 50 patients with matched normal controls. *Semin Arthritis Rheum* 1981;11:151–71.
27. Bengtsson A, Henriksson KG, Jorfeldt L, et al. Primary fibromyalgia. A clinical and laboratory study of 55 patients. *Scand J Rheumatol* 1986;15:340–7.
28. Glass JM, Park DC, Crofford LJ. Cognitive function in fibromyalgia [abstract]. *Arthritis Rheum* 2000;43:S209.
29. Katz RS, Heard A, Mills M, Leavitt F. Delineating the structure of fibromyalgia: fibrofog, a clinical subtype. *Arthritis Rheum* 2000;43:S209.
30. Goldenberg DL. Fibromyalgia syndrome. An emerging but controversial condition. *JAMA* 1987;257:2782–7.
31. Bennett RM. Confounding features of the fibromyalgia syndrome: a current perspective of differential diagnosis. *J Rheumatol Suppl* 1989;19:58–61.
32. Cathey MA, Wolfe F, Kleinheksel SM, Hawley DJ. Socioeconomic impact of fibrositis. A study of 81 patients with primary fibrositis. *Am J Med* 1986;81(3A):78–84.
33. Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 1998;41:778–99.
34. Marder WD, Meenan RF, Felson DT, et al. The present and future adequacy of rheumatology manpower: A study of health care needs and physician supply [editorial]. *Arthritis Rheum* 1991;34:1209–17.
35. White KP, Speechley M, Harth M, Ostbye T. The London Fibromyalgia Epidemiology Study: the prevalence of fibromyalgia syndrome in London, Ontario. *J Rheumatol* 1999;26:1570–6.
36. Yunus MB, Masi AT. Juvenile primary fibromyalgia syndrome. A clinical study of thirty-three patients and matched normal controls. *Arthritis Rheum* 1985;28:138–45.
37. Yunus MB, Inanici F, Aldag JC, Mangold RF. Fibromyalgia in men: comparison of clinical features with women. *J Rheumatol* 2000;27:485–90.
38. Yunus MB. Towards a model of pathophysiology of fibromyalgia: aberrant central pain mechanisms with peripheral modulation [editorial]. *J Rheumatol* 1992;19:846–50.
39. Yunus MB, Inanici F. Fibromyalgia syndrome: clinical features, diagnosis, and biopathophysiologic mechanisms. In: Baldry PE, Yunus MB, Inanici F. *Myofascial pain and fibromyalgia syndromes: a clinical guide to diagnosis and management*. New York: Churchill Livingstone; 2001:351–77.
40. Bennett RM. Emerging concepts in the neurobiology of chronic pain: evidence of abnormal sensory processing in fibromyalgia. *Mayo Clin Proc* 1999;74:385–98.
41. Russell IJ. Advances in fibromyalgia: possible role for central chemicals. *Am J Med Sci* 1998;315:377–84.
42. Bennett RM, Cook DM, Clark SR, et al. Hypothalamic-pituitary-insulin-like growth factor-I axis dysfunction in patients with fibromyalgia. *J Rheumatol* 1997;24:1384–9.
43. Crawford LJ, Demitrack MA. Evidence that abnormalities of central neurohormonal systems are key to understanding fibromyalgia and chronic fatigue syndrome. *Rheum Dis Clin North Am* 1996;22:267–84.
44. Aaron LA, Bradley LA, Alarcon GS, et al. Perceived physical and emotional trauma as precipitating events in fibromyalgia. Associations with health care seeking and disability status but not pain severity. *Arthritis Rheum* 1997;40:453–60.
45. Waylonis GW, Perkins RH. Post-traumatic fibromyalgia. A long-term follow-up. *Am J Phys Med Rehabil* 1994;73:403–12.
46. Waylonis GW, Ronan PG, Gordon C. A profile of fibromyalgia in occupational environments. *Am J Phys Med Rehabil* 1994;73:112–5.
47. Yunus MB, Khan MA, Rawlings KK, et al. Genetic linkage analysis of multicase families with fibromyalgia syndrome. *J Rheumatol* 1999;26:408–12.
48. Yunus MB. Psychological aspects of fibromyalgia syndrome: a component of the dysfunctional spectrum syndrome. *Baillieres Clin Rheumatol* 1994;8:811–37.
49. Sivri A, Cindas A, Dincer F, Sivri B. Bowel dysfunction and irritable bowel syndrome in fibromyalgia patients. *Clin Rheumatol* 1996;15:283–6.
50. Buchwald D. Fibromyalgia and chronic fatigue syndrome: similarities and differences. *Rheum Dis Clin North Am* 1996;22:219–43.
51. Yunus MB, Aldag JC. Restless legs syndrome and leg cramps in fibromyalgia syndrome: a controlled study. *BMJ* 1996;312:1339.
52. Wallace DJ. Genitourinary manifestations of fibrositis: an increased association with the female urethral syndrome. *J Rheumatol* 1990;17:238–9.
53. Inanici F, Yunus MB, Aldag JC. Clinical features and psychologic factors in regional soft tissue pain: comparison with fibromyalgia syndrome. *J Musculoskeletal Pain* 1999;7:293–301.
54. Nicolodi M, Sicuteri F. Fibromyalgia and migraine, two faces of the same mechanism. Serotonin as the common clue for pathogenesis and therapy. *Adv Exp Med Biol* 1996;398:373–9.
55. Fass R, Fullerton S, Tung S, Mayer EA. Sleep disturbances in clinic patients with functional bowel disorders. *Am J Gastroenterol* 2000;95:1195–2000.

91. Wolfe F, Anderson J, Harkness D, et al. Health status and disease severity in fibromyalgia: results of a six-center longitudinal study. *Arthritis Rheum* 1997;40:1571–9.
92. Montplaisir J, Godbout R, Poirier G, Bedard MA. Restless legs syndrome and periodic limb movements in sleep: physiopathology and treatment with L-dopa. *Clin Neuropharmacol* 1986;9:456–63.
93. Horiguchi J, Inami Y, Sasaki A, et al. Periodic leg movements in sleep with restless legs syndrome: effect of clonazepam treatment. *Jpn J Psychiatry Neurol* 1992;46:727–32.
94. Restless legs syndrome detection and management in primary care. National Heart, Lung and Blood Institute Working Group on Restless Legs Syndrome [published erratum appears in *Am Fam Physician* 2000;62:736]. *Am Fam Physician* 2000;62:108–14.
95. Silbert MH. Restless legs syndrome. *Mayo Clin Proc* 1997;72:261–4.
96. Krueger BR. Restless legs syndrome and periodic limb movements of sleep. *Mayo Clin Proc* 1990;65:999–1006.
97. Ware JC, Brown FW, Moorad PJ, et al. Nocturnal myoclonus and tricyclic antidepressants [abstract]. *Sleep Res* 1984;13:72.
98. Dorsey CM, Lukas SE, Cunningham SL. Fluoxetine-induced sleep disturbance in depressed patients. *Neuropsychopharmacology* 1996;14:437–42.
99. Paik IH, Lee C, Choi BM, et al. Mianserin-induced restless legs syndrome. *Br J Psychiatry* 1989;155:415–7.
100. Sanz-Fuentenebro FJ, Huidobro A, Tejadas-Rivas A. Restless legs syndrome and paroxetine. *Acta Psychiatr Scand* 1996;94:482–4.
101. Hargrave R, Beckley DJ. Restless legs syndrome exacerbated by sertraline. *Psychosomatics* 1998;39:177–8.
102. Cathey MA, Wolfe F, Kleinheksel SM. Functional ability and work status in patients with fibromyalgia. *Arthritis Care Res* 1988;1:85–8.
103. Burckhardt CS, Clark SR, Bennett RM. Fibromyalgia and quality of life: a comparative analysis. *J Rheumatol* 1993;20:475–9.
104. Hawley DJ, Wolfe F. Pain, disability, and pain/disability relationships in seven rheumatic disorders: a study of 1,522 patients. *J Rheumatol* 1991;18:1552–7.
105. White KP, Speechley M, Harth M, Ostbye T. Comparing self-reported function and work disability in 100 community cases of fibromyalgia syndrome versus controls in London, Ontario: the London Fibromyalgia Epidemiology Study. *Arthritis Rheum* 1999;42:76–83.
106. Yunus MB. Fibromyalgia syndrome: blueprint for a reliable diagnosis. *Consultant* 1996;36:1260–74.
107. Henriksson C, Liedberg G. Factors of importance for work disability in women with fibromyalgia. *J Rheumatol* 2000;27:1271–6.
108. Kaplan RM, Schmidt SM, Cronan TA. Quality of well being in patients with fibromyalgia. *J Rheumatol* 2000;27:785–9.
109. Martinez JE, Ferraz MB, Sato EI, Atra E. Fibromyalgia versus rheumatoid arthritis: a longitudinal comparison of the quality of life. *J Rheumatol* 1995;22:270–4.
110. Da Costa D, Dobkin PL, Fitzcharles MA, et al. Determinants of health status in fibromyalgia: a comparative study with systemic lupus erythematosus. *J Rheumatol* 2000;27:365–72.
111. Neumann L, Buskila D. Quality of life and physical functioning of relatives of fibromyalgia patients. *Semin Arthritis Rheum* 1997;26:834–9.
112. Simms RW, Cahill L, Prashker M, Meenan RF. The direct costs of fibromyalgia treatment: comparison with rheumatoid arthritis and osteoarthritis. *J Musculoskeletal Pain* 1995;3:127–32.
113. Wolfe F, Potter J. Fibromyalgia and work disability: is fibromyalgia a disabling disorder? *Rheum Dis Clin North Am* 1996;22:369–91.
114. Bombardier CH, Buchwald D. Chronic fatigue, chronic fatigue syndrome, and fibromyalgia. Disability and health-care use. *Med Care* 1996;34:924–30.
115. McCain GA, Cameron R, Kennedy JC. The problem of long-term disability payments and litigation in primary fibromyalgia: the Canadian perspective. *J Rheumatol Suppl* 1989;19:174–6.
116. Bruusgaard D, Evensen AR, Bjerkdal T. Fibromyalgia—a new cause for disability pension. *Scan J Soc Med* 1993;21:116–9.

Copyright 2002 by Turner White Communications Inc., Wayne, PA. All rights reserved.