Despite substantial interest and investigation during the past 10 years, fibromyalgia continues to provoke many controversies. The major issues discussed in this review include the diagnostic utility of fibromyalgia, psychiatric and central nervous system factors, therapy and outcome, and compensation and disability. It is important to recognize the psychosocial factors that distinguish patients with fibromyalgia from persons in the community who meet criteria for the syndrome but who do not seek medical care. Such factors may be among the most important in long-term treatment.

Since 1987, when my first review on fibromyalgia (FM) syndrome was published,1 more than 1000 articles on FM have appeared in peer-reviewed journals. Some reports2 suggest that little progress has been made in understanding or treating this disorder. Indeed, the concept of FM remains controversial, and many authors3,4 continue to challenge its existence and diagnostic utility. To review what we have learned about FM during the past decade, I have formulated a series of questions: How has FM been defined? How and when should FM be diagnosed? What is the association between FM and psychiatric illness? Have pathophysiological abnormalities or causes been identified? Can FM be effectively treated? What are the outcome and prognosis? Can FM cause disability? Is the diagnosis of FM useful? I will attempt to answer these questions from my research and experience and a detailed analysis of key investigations reported during the past 10 years.

HOW HAS FM BEEN DEFINED?

Between 10% and 12% of the general population has chronic widespread pain.5,6 Women are affected more than men, and the prevalence of widespread pain increases with age.6 Many persons with chronic musculoskeletal pain do not have a well-defined musculoskeletal disease. The construct of FM was designed to account for persons with such generalized, persistent idiopathic pain.1,7,8 As with any syndrome, the diagnosis of FM is based on a set of predefined symptoms. The mandatory symptom is widespread pain not explained by an inflammatory or degenerative musculoskeletal disorder. There are no “objective markers” of disease. The presence of many tender points in soft tissue locations validates the diagnosis.

Various diagnostic criteria for FM were proposed10,11 and field tested. The 1990 American College of Rheumatology classification criteria8 for FM have been adopted by most investigators in the past 10 years. In that study, 293 consecutive patients with FM were compared with 265 control patients who had regional chronic musculoskeletal pain or a systemic rheumatic disease. Training sessions were used to increase interrater reliability, and independent blinded assessors recorded the history and performed the physical examination. The symptom of widespread pain and the finding of mild or greater tenderness in at least 11 of 18 specified tender points on digital palpation provided a sensitivity of 88% and specificity of 81% in distinguishing FM from other causes of chronic musculoskeletal pain. The American College of Rheumatology study committee found no difference in patients with FM who had a concurrent medical condition. Therefore, in regard to classifica-
The diagnosis of FM is not as straightforward in patients with concurrent medical or psychiatric illness. In such patients, clinicians must be confident that the FM construct explains the patient’s symptoms. Such confidence can only be gained after considerable experience evaluating patients with chronic pain. Some rheumatic disorders with subtle findings on examination, such as the spondyloarthropathies, may be misdiagnosed as FM. Fibromyalgia may coexist with osteoarthritis, and, in elderly patients, it is often mistakenly diagnosed as osteoarthritis. Osteoarthritis, however, generally causes pain on joint movement and generally not widespread constant pain. Fibromyalgia is present in 10% to 40% of patients with systemic lupus erythematosus (SLE) and in 10% to 30% of patients with rheumatoid arthritis. It may be difficult to determine whether patients with rheumatoid arthritis are having an exacerbation of their arthritis or if their symptoms are related to concurrent FM. In such patients, a consultation with an experienced clinician is more cost-effective than ordering several blood tests, radiographs, and imaging studies.

Fibromyalgia may also mimic systemic diseases such as Lyme disease and SLE. Twenty-five percent to 50% of patients referred to Lyme disease clinics never had Lyme disease but, rather, had FM. It is not cost-effective to obtain Lyme serologic tests on such patients and certainly not cost-effective to treat such patients empirically with antibiotics. Approximately 25% of patients referred for possible SLE to a rheumatology clinic had FM and antinuclear antibodies but no other manifestations of SLE. These patients should not be diagnosed as having and treated for SLE. Patients with FM may also present with symptoms that suggest degenerative disc disease or nerve entrapment syndromes.

Fibromyalgia often coexists with other common, ill-defined syndromes such as CFS, headache syndromes, IBS, and depression. Based on standard classification criteria, 50% to 70% of patients with FM have a current or past diagnosis of CFS, IBS, migraine, and depression. Each of these disorders has similar symptoms, chronicity, demographics, and therapies. Each of these syndromes also may be associated with a vast array of symptoms, such as facial pain, paresthesias, urinary urgency, sicca symptoms, Raynaud phenomenon, and dysmenorrhea, adding to the diagnostic confusion. These syndromes overlap so extensively that it may be concluded that each represents different presentations of the same general condition. Therefore, little value exists in worrying whether a patient has FM, CFS, or IBS—or all 3 disorders.

**WHAT IS THE ASSOCIATION BETWEEN FM AND PSYCHIATRIC ILLNESS?**

There is strong evidence that major depression is associated with FM. The symptoms of fatigue, sleep disturbances, and cognitive disturbances that are characteristic of FM are also present in depressive ill-
ness. Comorbid disorders, such as migraine and muscular headaches, CFS, IBS, premenstrual syndrome, and atypical facial pain, are prominent in both FM and depression.\(^1\)\(^2\)\(^3\) Patients with FM, as well as patients with these related disorders, often improve with antidepressant medications.\(^4\)\(^5\) A lifetime history of depression has been reported\(^1\)\(^1\)\(^2\) in 50% to 70% of patients with FM. Current major depression, however, was found in only 18% to 36% of patients with FM. Ahles and Yunus\(^6\)\(^7\) did not find a greater prevalence of major depression in patients with FM than in those with rheumatoid arthritis and in healthy controls. Therefore, even in tertiary referral clinics, most patients with FM do not have a current psychiatric illness.

The overlap of symptoms, patterns of comorbidity, family history studies, response to various antidepressant medications, and similar results of neurohormonal studies all demonstrate an association of FM and depression. The nature of that association is controversial. Patients with FM may become depressed because of pain and disability. Conversely, major depression may cause FM, a classic psychosomatic theory. But most patients with FM are not depressed, and the variable temporal relationship of depression and pain militates against the theories.\(^8\)\(^9\) The association more likely relates to a sharing of common biological or psychological factors.\(^10\)

Psychological stress has been found\(^11\) to influence the expression of pain and other core symptoms in FM, mood disorders, chronic headaches, CFS, and IBS. People who believed that emotional trauma was a precipitating event for their FM were more likely to become a patient in a specialty clinic and had greater health care use than those not identifying emotional trauma.\(^12\) Patients with FM and those with IBS who were observed in tertiary referral clinics had a substantially higher incidence of present and past psychiatric illness than those in the community with similar symptoms.\(^13\)\(^14\) In women with IBS, there was a higher incidence of sexual and physical abuse in childhood than in people in the community with IBS symptoms.\(^15\)\(^16\)

Investigators from the University of Alabama Medical Center, Birmingham, have published a series of important observations\(^17\)\(^18\)\(^19\)\(^20\) comparing patients with FM observed by a rheumatologist with people in the community who meet criteria for having FM but who have not been given the diagnosis or treated for it (“FM nonpatients”) (Table 1). The patients and nonpatients were then compared with healthy controls. The core symptoms of FM and objective measures of pain perception, including cerebrospinal levels of substance P and blood flow imaging of the thalamus and caudate nucleus, were similar in FM clinic patients and nonpatients. Significantly greater numbers of current and past psychiatric illnesses were found in the patients with FM (P = .002), but not in the nonpatients, compared with healthy controls. The current and past psychiatric illnesses were directly related to health-seeking behavior.\(^21\)

### Table 1. Comparisons of Patients With Fibromyalgia (FM), Community Residents With FM (Nonpatients), and Normal Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients With FM</th>
<th>Nonpatients With FM</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain duration, mo</td>
<td>88</td>
<td>110</td>
<td>...</td>
</tr>
<tr>
<td>No. of tender points</td>
<td>16</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue, 0 to 10 scale</td>
<td>6.1</td>
<td>4.5</td>
<td>2.7</td>
</tr>
<tr>
<td>Pain intensity, 0 to 10 scale</td>
<td>6.8</td>
<td>4.3</td>
<td>...</td>
</tr>
<tr>
<td>Pain threshold</td>
<td>1.9</td>
<td>2.7</td>
<td>5.2</td>
</tr>
<tr>
<td>Caudate blood flow</td>
<td>0.78</td>
<td>0.78</td>
<td>0.85</td>
</tr>
<tr>
<td>CSF substance P level, fmol/L</td>
<td>19</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>No. of lifetime psychiatric illnesses†</td>
<td>2.8</td>
<td>1.2</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Data are given as means. CSF indicates cerebrospinal fluid; ellipses, not applicable. Modified from Aaron,\(^4\)\(^6\)\(^7\) Mountz,\(^4\)\(^8\) Aaron,\(^4\)\(^9\) Alexander,\(^10\) and Bradley\(^10\) and their colleagues.

†Patients with FM differed significantly from nonpatients and controls. For all other variables, there was no difference between patients and nonpatients, and both differed significantly from controls.

After more than a century of research\(^12\)\(^13\) that failed to detect consistent abnormalities in the muscle and other soft tissues in FM, investigations have turned toward the neurosciences.\(^22\) Patients with FM have a generalized hypervigilance to both pain and auditory stimuli.\(^23\) There is evidence for qualitatively altered nociception.\(^24\) The heightened pain response at tender points is now generally accepted to be a manifestation of altered central nervous system processing of nociceptive stimuli.\(^25\)\(^26\) Following electrocutaneous stimuli, patients with FM had diffuse regions of secondary hyperalgesia in the upper extremities. Levels of substance P and abnormal antinociceptive peptides are elevated in the cerebrospinal fluid of patients with FM.\(^27\)\(^28\) Brain imaging demonstrated substantially lower regional cerebral blood flow to the thalamus and caudate nucleus in women with FM compared with normal controls.\(^29\) The caudate nucleus and thalamus signal noxious stimuli, and decreased blood flow to these areas has been demonstrated in other chronic pain disorders. Studies of humans and of animals have noted that females have a lower pain threshold and tolerance and a higher sensitivity to various noxious stimuli.\(^30\)

Slow-wave–sleep abnormalities in FM were initially reported in the early 1970s, and more recent studies\(^31\) suggest that they are prominent. The most frequent finding has been alpha intrusion in non–rapid-eye-movement sleep.\(^32\)\(^33\) These findings are not specific, however, and decreased sleep efficiency is present in children with FM and their mothers.\(^34\)\(^35\) Some studies also have found sleep apnea to be common in men with FM.\(^36\)\(^37\) Periodic leg movements have been reported in some studies.\(^38\)\(^39\)

Research has also found alterations of various neurohor- mones in FM. There is exaggerated corticotropin response to corticotropin-releasing hormone and variable disturbances of sympathetic nervous system activity in FM. Low

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levels of somatomedin C, which reflects growth-hormone release, also have been noted in patients with FM. Evidence of sympathetic-para-sympathetic imbalance, specifically related to neurally mediated hypotension, has been found in FM and CFS.

Evidence does not exist for a single causal agent in FM. Self-reports have identified physical trauma, emotional trauma, and infection as possible precipitating events in patients with this disorder. Despite the similarities of FM and CFS, clinical and serologic studies have not identified an etiologic role for the Epstein-Barr virus, parvovirus, or other viruses in either disorder. Certain infections such as Lyme disease may trigger FM. For example, 10% to 25% of patients with established Lyme disease have the development of FM that persisted for months or years after adequate treatment of Lyme disease. These patients do not respond to protracted or repeated courses of antibiotics but often receive such treatment at a substantial cost.

Cervical spine pain, benign joint hypermobility, and steroid withdrawal have also been identified by some authors as contributing to the pathogenesis of FM. Fibromyalgia developed in 21% of persons who had a cervical spine injury but only 2% of those with a leg fracture. No patient had chronic pain before the trauma. Sex, genetic factors, and comorbid musculoskeletal disorders may each act as nociceptive amplifiers and contribute to the clinical syndrome.

**CAN FM BE EFFECTIVELY TREATED?**

Possible useful variables to measure change in FM clinical trials have included self-reported pain, sleep, and global well-being as well as functional and psychological status. Tenderpoint counts and the alpha-slow-wave–sleep anomaly have not correlated well with symptoms or treatment response. Because of the cost of long-term clinical trials, more attention should focus on meta-analysis and N-of-1 trials.

Randomized clinical trials published during the past decade have demonstrated some efficacy for central nervous system medications, cardiovascular fitness training, regional sympathetic block, electromyographic biofeedback, hypnotherapy, electroacupuncture, and cognitive behavioral therapy (Table 2). Medication therapy has produced meaningful improvement in 30% to 50% of patients. Tricyclic antidepressant medications, particularly amitriptyline hydrochloride, have been most often evaluated. The decrease in pain with the use of these medications has been significant but modest and tends to wane over time. Most trials have been of short duration, and the only study of at least 6 months’ duration demonstrated a gradual loss of medication efficacy. Fluoxetine hydrochloride and amitriptyline were more effective than placebo in reducing FM symptoms, and the combination of both worked better than either alone. In other reports, however, there was no beneficial effect of fluoxetine or of a different serotonin reuptake inhibitor, citalopram, or of tenoxicam and bromazepam. Treatment with alprazolam combined with ibuprofen demonstrated modest improvement. Nonsteroidal anti-inflammatory drugs and corticosteroids, magnesium and malic acid, bright light, S-adenosyl-L-methionine, and topical lidocaine hydrochloride in sphenopalatine blocks were not effective.

An aerobic exercise program has been more effective than simple relaxation or stretching. Enhanced cardiovascular fitness was achieved and sustained during these trials. The prognosis and outcome of FM and related conditions are adversely affected by inappropriate coping strategies and by catastrophic beliefs. Cognitive-behavior therapy is a logical approach to change such beliefs and has been proved an effective tool in FM and CFS. Cognitive-behavior and stress-reduction programs were helpful in patients when compared with historical or wait-listed controls. Group education improved the quality of life in patients with FM, although adding a structured cognitive component was of no added benefit and led to higher health care costs.

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**Table 2. Treatments for Fibromyalgia With Proven Efficacy in Controlled Clinical Trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carette et al, Goldenberg et al, Bennett et al</td>
<td>Amitriptyline hydrochloride</td>
<td>Usually 25-50 mg at bedtime</td>
</tr>
<tr>
<td>Jaeschke et al, and Carette et al</td>
<td>Cyclobenzaprine hydrochloride</td>
<td>10-30 mg/d</td>
</tr>
<tr>
<td>Bennett</td>
<td>Dothiepin hydrochloride</td>
<td>75 mg used</td>
</tr>
<tr>
<td>Caruso et al</td>
<td>Fluoxetine hydrochloride</td>
<td>One trial found no improvement, but the other did; combination of fluoxetine and amitriptyline was more effective than either alone</td>
</tr>
<tr>
<td>Wolfe et al and Goldenberg et al</td>
<td>Nonmedicinal</td>
<td>Cardiovascular fitness training</td>
</tr>
<tr>
<td>McCain et al, Martin et al, and Wigers et al</td>
<td>Electromyographic biofeedback</td>
<td>Aerobic fitness was compared with stretching and relaxation</td>
</tr>
<tr>
<td>Ferraccioli et al</td>
<td>Hypnotherapy</td>
<td>. . .</td>
</tr>
<tr>
<td>Haanen et al</td>
<td>Electroacupuncture</td>
<td>. . .</td>
</tr>
<tr>
<td>Deluze et al</td>
<td>Cognitive behavioral therapy</td>
<td>. . .</td>
</tr>
<tr>
<td>White and Nielsen and Goldenberg et al</td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>

*EMG indicates electromyographic; ellipses, not applicable.
WHAT ARE THE OUTCOME AND PROGNOSIS?

In outcome studies, the symptoms of FM remain stable over time. In the longest follow-up study from a single medical center, 29 patients with FM were surveyed 1, 3, and 14 years after diagnosis. Although 16 (55%) of 29 patients still reported moderate to severe pain, fatigue, and sleep disturbances, 19 (66%) of 29 felt better than when first diagnosed 14 years earlier, and 16 (73%) of 22 thought that their symptoms interfered little, if at all, with work.

In a multicenter outcome study, 538 patients were prospectively observed for 7 consecutive years. Patients with FM averaged 10 outpatient medical visits per year and used a mean of 3 FM-related drugs. The mean yearly per patient cost in 1996 dollars was $2274, similar to costs for the treatment of osteoarthritis. The major contributors to cost were hospital admission and drugs. Nonsteroidal anti-inflammatory drugs were most commonly prescribed, even though they have not been of proven efficacy. Comorbidities, disability, and disease severity correlated with total costs. Even in these rheumatology centers with a special interest in FM, there was only slight improvement in health satisfaction and no significant change (P=0.66) in functional disability or symptoms during the 7 years. Sixty percent of these patients rated their health as fair or poor. Among the 6 centers, there were marked differences in symptom severity and outcome. Correlations between the symptoms at first and last assessment were high (r = 0.82).

In contrast, community-based studies of FM report a better overall outcome. In 1 report from Australia, 25% of patients were in remission 2 years after the diagnosis. Another study demonstrated better outcome in patients with chronic pain observed by general practitioners than in those treated by specialists. These reports reflect the same trend that has been noted in patients with CFS, IBS, chronic widespread pain, and headaches. Persons in the community with chronic pain have better outcome than tertiary referral patients. Health care use and functional status are related more to premorbid and current psychosocial factors than to the core symptoms of the syndromes.

CAN FM CAUSE DISABILITY?

The issue of disability in FM is similar to that in any chronic pain disorder. Can pain cause disability? How can we measure pain and disability in conditions with no objective criteria? Patient-perceived work disability has been similar in FM and rheumatoid arthritis. No valid instruments are able to assess disability in patients with FM. Functional impairment has been documented in these patients. A number of factors were found to be independently associated with impaired function, including pain levels, self-assessed disability, pending litigation, education, sense of helplessness and coping ability, and psychological distress.

The issue of causation, especially in the workplace, has become especially contentious. A longitudinal multicenter survey of 1604 patients with FM found that 27% received at least 1 form of social security or other disability payments. Two thirds of patients were working. The likelihood of receiving disability pensions for FM reflects the current diagnostic interest as well as the status of insurers approving claims for chronic pain in specific countries. A “diagnosis” of FM in the workplace may promote disability by fostering the notion of “soft tissue injury.” Evidence to determine whether there is a causal relationship between trauma and FM is currently inadequate. Until such a relationship is established, the terms “posttraumatic” or “secondary” FM should not be used.

A person’s perception of the relationship of FM symptoms to trauma has an important effect on outcome. Those who identify trauma as a cause have greater levels of pain, more interference with daily activities, and greater disability than those with FM of an idiopathic onset. The perception of physical trauma as a precipitating event is also a greater determinant of disability than that of emotional trauma. Patients who met criteria for CFS and FM had particularly high rates (51%) of unemployment.

An even more contentious issue is whether financial compensation should be awarded to patients with disability due to FM. An individual physician may choose to be an advocate for a patient with FM seeking such compensation, provided the patient meets diagnostic criteria and that symptom severity, activity level, work capacity, psychosocial factors, and current work status support the claim. Disability should not be based on the diagnosis of FM but, rather, on an evaluation of the effect of chronic pain and distress on the person. Job dissatisfaction, work disability, and litigation however, have an adverse effect on outcome in FM. This situation is similar to that of other idiopathic pain disorders, sometimes related to trauma or certain occupations.

IS THE DIAGNOSIS OF FM USEFUL?

Every specialty of medicine has assigned diagnostic labels to chronic illness in which causation and pathogenesis are not understood. Fibromyalgia is simply a label to use when patients have chronic, unexplained diffuse pain. The classification criteria for FM have been validated in numerous clinic and population-
Fibromyalgia is a clinical syndrome. It is not a disease but, rather, a common group of symptoms that can be reliably identified in medical clinics and in the community. Although FM is most recognizable when there are no concurrent medical or psychiatric illnesses, it is important to diagnose it when it is associated with rheumatic diseases or Lyme disease because treatment will be different. It may not be important to differentiate FM from associated disorders such as CFS, IBS, or idiopathic chronic pain. Most patients with FM do not have a current psychiatric illness. There is a higher incidence of psychiatric disorders in patients in tertiary referral centers who have FM than in community controls with FM. Current and past episodes of psychological distress and psychiatric diagnoses are directly related to health care use in patients with FM. There is no single etiologic factor, although physical and emotional trauma and infections may trigger FM. It is best thought of as a disorder of pain perception, presumably involving neurohormonal dysregulation. Physicians and patients need to understand that the medical model of specific cause and effect may not apply to disorders such as FM. There is no single highly effective treatment. Medicines that affect pain perception, sleep, and mood have been useful and should be integrated with activity, exercise, and educational programs. Most patients with FM observed in tertiary referral centers report little change in their symptoms over time. The outcome is directly related to psychosocial factors, including past and current psychological distress and work status or disability issues. As with any chronic illness, patients in the community do better than those observed in specialty clinics. Ten percent to 30% of patients describe being work impaired from FM. Physicians should discourage inactivity and disability because, if these are prolonged, there is an adverse effect on prognosis. Finally, patients have found a diagnostic label to be reassuring, and the diagnosis has decreased costly testing and health care use. The concern that a diagnostic label will enhance the medicalization of common symptoms is a realistic one, but when chronic pain or fatigue or mood disturbances become so
prominent that they interfere with daily activities, it is appropriate to identify these abnormal levels of suffering as a syndrome that requires medical attention.

Fibromyalgia was described in the early 1800s but has only recently emerged as a common musculoskeletal diagnosis. Its recognition as a discrete syndrome is largely due to the acceptance of subjective symptoms present in a large number of people. Researchers and policymakers should focus on the biopsychological influences that determine which persons in the community with FM become patients and seek medical help.

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