ABSTRACT

Fibromyalgia (FM), which primarily affects women, is one of several medically unexplained illnesses. In many instances, FM is accompanied by one or more of these illnesses, which often confounds the approach to diagnosis and treatment. Although the pain and tenderness of FM are very real, many patients seen in the primary care setting are not taken seriously and do not receive appropriate treatment. However, the equation has changed with the recent approval of 3 drugs for FM. This article describes FM, reviews the evidence supporting FM as a chronic central pain state (as opposed to a rheumatologic disorder), and explains how FM relates to other medically unexplained illnesses. The article also presents an algorithm for the treatment of FM in clinical practice.

the medical community as well because it encompasses what has been learned about FM in recent years, as described below.

**Fibromyalgia**

Recent statistics from the American College of Rheumatology (ACR) indicate that FM affects 3 million to 6 million Americans, most of them women. Criteria for the classification of FM, which were established by the ACR in 1990 and are essentially the same today, are the presence of 4-quadrant pain and tenderness in at least 11 of 18 tender point sites (Figure) for at least 3 months. Although the 18 sites shown in the Figure are below the neck, many patients with FM also have pain and tenderness in the jaw that may be confused with temporomandibular joint disorder.

Because the musculoskeletal pain of FM suggests a rheumatologic disorder, many patients are referred to a rheumatologist for further evaluation and treatment. However, there has never been any confirmation that the pain of FM is peripheral. Instead, there is increasing evidence that the brain is the source and that FM is the prototypic central pain state.

Patients have normal detection thresholds to sensory stimuli, but decreased detection thresholds to pressure, heat, noise, and electrical stimulation when these stimuli are noxious. The resultant increase in sensory sensitivity may be psychological (eg, “expectancy” or hypervigilance before a physical examination because pain is already present) or neurobiologic (eg, central sensitization or reduced descending pain inhibition).

**Overlapping Syndromes**

As noted in numerous studies, there are several illnesses that have no medical explanation and no definitive diagnostic criteria. Yet, these unexplained illnesses overlap, accounting for considerable comorbidity. In many cases, the “diagnosis” of these illnesses varies with the referral process. For example, diffuse pain and tenderness is considered FM, and the patient is referred to a rheumatologist, whereas flu-like malaise is seen as chronic fatigue syndrome (CFS), and the patient is referred to an infectious disease specialist. Similarly, sensitivity to odors leading to physical symptoms and avoidance behavior is seen as multiple chemical sensitivity (MCS), and the patient is referred to a specialist in environmental or occupational medicine.

The key point for the medical community is that the more unexplained illnesses a patient has, the higher the risk of a comorbid Axis I major depressive disorder (MDD), and the higher the risk of irritable bowel syndrome (IBS), itself an unexplained illness characterized by abdominal pain and altered bowel function.

**Chronic Fatigue Syndrome**

Chronic fatigue syndrome is defined as new-onset fatigue producing a substantial decrease in activity and lasting 6 months or longer. It is accompanied by at least 4 of the following 8 symptoms (sore throat, swollen glands, myalgia, arthralgia, headache, cognitive difficulties, unrefreshing sleep, and exacerbation of symptoms on exertion) and is diagnosed only after medical and psychiatric causes of fatigue have been ruled out. These causes include hypothyroidism, Lyme disease, lupus, eating disorders, bipolar disease, substance abuse, and schizophrenia. Although CFS is less common than FM, it is also more prevalent in women.

Although FM and CFS clearly overlap—37% of patients with CFS studied by this author had comorbid FM and 20% of patients with FM studied by
another group had comorbid CFS—there are differences between the syndromes. For example, spinal fluid levels of substance P are elevated in FM but not CFS, and FM pain but not CFS fatigue respond to treatment with antidepressants.

During the 1990s, many psychiatrists questioned whether CFS was a physical illness or a somatization disorder. One of our studies examining the issue found that prevalence rates for somatization disorder in CFS varied from 0% to 98%, depending on whether symptoms were coded as being physical or psychiatric in etiology. Using strict Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria, the investigators found that the incidence of somatization disorder in CFS was only 2.3%. More recently, the concept of somatization in CFS has lost ground, and the term “somatization disorder” is increasingly being replaced by the term “medically unexplained syndromes.”

With funding from the National Institutes of Health (NIH), investigators at the CFS Cooperative Research Center (headed by this author) used an empiric approach to compare pure CFS to those with CFS plus FM. They found that patients with pure CFS did worse on cognition than patients with CFS and FM, but that patients with both conditions had worse scores for pain, physical function, and CFS severity (Natelson BH, Unpublished observations) than those with CFS alone.

These findings led the same investigators to probe the central serotonergic neurons of patients with pure CFS, those with CFS and FM, and healthy controls, using an intravenous tryptophan infusion and measuring the release of prolactin. If CFS and FM are alike, the investigators reasoned, the prolactin response should be the same in both groups of patients. However, there are data indicating that FM has a downregulated serotonin system (as it is in MDD) whereas CFS has an upregulated system. The results confirmed that the serotonergic system was downregulated in patients with CFS/FM and controls, but upregulated in those with CFS only (Natelson BH, Unpublished observations).

MULTIPLE COMORBIDITIES

The increased rate of comorbid diagnoses in patients with medically unexplained illnesses was demonstrated in a study of 163 consecutive female patients with CFS. Among these women, 62 had pure CFS, 31 had CFS/MCS, 44 had CFS/FM, and 26 had CFS/MCS/FM. Although the majority of women with pure CFS had no comorbid psychiatric diagnoses, the incidence of anxiety or Axis I MDD lasting more than 2 weeks was higher in those with CFS/MCS or CFS/FM and higher still in those with CFS/FM/MCS. Similarly, the incidence of IBS rose in parallel with the number of comorbidities in a subset of women for whom data were available: 15% in 26 women with CFS alone; 18% in 11 women with CFS/MCS; 38% in 32 women with CFS/FM; and 56% in 18 women with CFS/FM/MCS (Natelson BH, Unpublished observations).

These findings suggest that pure CFS may be different from CFS with other comorbid unexplained illnesses. In other words, patients with more than one of these syndromes are more likely to have other syndromes as well. The increased burden of illness could explain the higher rates of psychiatric diagnoses in these patients.

DEPRESSION

As demonstrated in a study of 533 relatives of patients with FM and 272 relatives of patients with rheumatoid arthritis (RA), both FM and mood disorders, but not RA, aggregate strongly in families (Table 1). The findings suggest that genetic factors are involved in the etiology of FM and pain sensitivity, and that mood disorders and FM may share some of

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relatives (N = 533) of Proband with FM, n (%)</th>
<th>Relatives (N = 272) of Proband with RA, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depressive disorder</td>
<td>157 (29.5)</td>
<td>50 (18.3)</td>
</tr>
<tr>
<td>Bipolar I disorder</td>
<td>7 (1.3)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Bipolar II disorder</td>
<td>7 (1.3)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Any major mood disorder</td>
<td>171 (32.1)</td>
<td>52 (19.1)</td>
</tr>
</tbody>
</table>

FM = fibromyalgia; RA = rheumatoid arthritis.

Data from Arnold et al. 10
these inherited factors. However, it is unclear whether FM shares some of the same neurobiologic underpinnings of MDD or whether FM is a variant of MDD on what some have called an affective spectrum.

Although no family study examining CFS and depression has been done, CFS and depression share many symptoms, such as fatigue, sleep disturbance, cognitive difficulties, and complaints of chest and abdominal pain. However, there are phenomenological differences between CFS and depression. Specifically, CFS, but not depression, is associated with arthralgia, myalgia with tenderness, postexertional fatigue, and the sudden onset characteristic of a viral infection. The latter is also seen in FM, but is more common in CFS.

There is also evidence that CFS is not a variant of MDD. First, CFS does not respond well to antidepressants. Second, CFS is associated with downregulated hypothalamic-pituitary-adrenal axis function (vs upregulated function in MDD). Third, there are differences in psychological functioning, with patients with CFS more likely to characterize their illness as physical rather than psychological and less likely to have personality disorders than those with MDD.

Differences in cognitive style, as measured by the 4 subscales of the Beck Depression Inventory, are present as well. In a study comparing 17 patients with MDD/CFS and 27 patients with MDD but no CFS, scores on the self-reproach subscale were much higher in those with MDD only, whereas scores in the somatic component subscale were much higher in those with MDD/CFS. Clearly, both groups were depressed, but the quality of their depression was different.

Although CFS is probably not a variant of MDD, the question is still open with regard to CFS and FM. However, although CFS and FM overlap, they are not necessarily variants of one another, but could simply have some common genetic underpinnings.

**Approach to Treatment of Fibromyalgia**

Treatment of FM begins with taking the patient and the patient's symptoms seriously. As shown in the incremental algorithm (Table 2), treatment involves pharmacologic options to relieve pain and tenderness and rehabilitative modalities to improve functioning. The algorithm was developed by this author for use in clinical practice, but the pharmacologic component was used in his recently completed NIH study of vagus nerve stimulation in FM. (Vagus nerve stimulation is currently approved for epilepsy and depression.)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are included in the algorithm because most patients with FM have already tried them, and approximately 15% report that they are helpful. NSAIDs should be continued in these patients.

A tricyclic antidepressant or a serotonin-norepinephrine reuptake inhibitor (SNRI) should be tried next, with the choice based on drug cost and the presence or absence of MDD. Amitriptyline, with its sedative effects, is a reasonable choice for patients with FM who complain of major sleep disturbances.

Antiepileptic drugs are the next option. Therapy should begin with one agent, with a second agent added if the patient still has significant pain. If substantial pain is still present after treatment with 2 antiepileptic drugs, tramadol or even long half-life opiates should be tried, although the latter class of drugs has a limited role in FM.

**Conclusions**

Fibromyalgia is one of several medically unexplained illnesses in which pain and/or other symptoms

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**Table 2. Algorithm for Treating FM**

<table>
<thead>
<tr>
<th>Pharmacologic</th>
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<tbody>
<tr>
<td>• NSAIDs</td>
<td></td>
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<tr>
<td>• Tricyclic or SNRI antidepressant</td>
<td></td>
</tr>
<tr>
<td>(decide on the basis of cost and presence or absence of MDD)</td>
<td></td>
</tr>
<tr>
<td>• At least 1 antiepileptic drug (preferably 2)</td>
<td></td>
</tr>
<tr>
<td>• Tramadol</td>
<td></td>
</tr>
<tr>
<td>• Long half-life opiates</td>
<td></td>
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<tr>
<td>Failure to obtain substantial pain relief defines treatment-resistant FM</td>
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</table>

<table>
<thead>
<tr>
<th>Rehabilitative</th>
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<tr>
<td>• Gentle physical conditioning</td>
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<tr>
<td>• Coaching: a form of psychotherapy oriented to symptom management rather than mood</td>
<td></td>
</tr>
<tr>
<td>• Cognitive-behavioral therapy (an advanced form of coaching) as needed</td>
<td></td>
</tr>
<tr>
<td>• Compliance with rehabilitative and drug regimens</td>
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</tr>
</tbody>
</table>

FM = fibromyalgia; MDD = major depressive disorder; NSAID = nonsteroidal anti-inflammatory drug; SNRI = serotonin-norepinephrine reuptake inhibitor.
are very real, but X rays and laboratory test results are essentially normal. Too often, patients are “written off” and told that “nothing’s wrong.”

Confounding the problem is the fact that these unexplained illnesses overlap so that many patients have multiple comorbidities: FM and CFS; FM, CFS, and MCS; and so on.

The recent approval of 3 drugs for the treatment of FM, along with slowly increasing awareness of FM as a “real” syndrome, has changed the equation for healthcare professionals in primary care practice.

**DISCUSSION**

**TREATMENT ISSUES**

**Dr. Hahn:** The American Pain Society evidence-based guideline for management of FM pain cites studies showing that NSAIDs are not helpful in FM.

**Dr. Natelson:** I have patients who are already on NSAIDs when they first come to see me, and they usually say the NSAIDs help. In my practice, I use what I call the Natelson 6-week rule. If I start a patient on a drug, I make it clear that we will decide whether or not it has helped after 6 weeks. If it helps, we continue the drug; if it does not help, we stop.

**Dr. Lipman:** We often see patients with localized myofascial pain in addition to FM. Many of them take NSAIDs for the myofascial pain and they report that they feel a little bit better globally. The evidence, however, indicates that NSAIDs are not useful for FM per se.

**Dr. Bainbridge:** Are there any specific drug combinations that you like to use?

**Dr. Natelson:** If you mean using an SNRI and an antiepileptic, yes, depending on the circumstances. If a patient with FM comes to the office and I make the diagnosis of comorbid MDD, I will prescribe duloxetine because it is approved for both conditions. If there is any improvement, either in mood or pain, after 6 weeks, I will continue with it; if it does not help, we stop.

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**Assessing Outcomes**

**Dr. Strassels:** Do you use any formal tools to assess progress or effectiveness?

**Dr. Natelson:** In clinical practice I use 4-quadrant pain and tender point counts. Thus, if a patient has 3-quadrant or 2-quadrant pain, or fewer tender points, that is an improvement. For research studies, I use tools that measure outcomes, such as the SF-36 (Short Form 36) and the pain questionnaires.

**Dr. Lipman:** We use the Fibromyalgia Impact Questionnaire for studies, but it is not practical in the clinical setting. We are now finishing the validation of a new short form of the TOPS, or Treatment Outcomes of Pain Survey, that measures 14 physical and psychological outcome dimensions. Unlike the SF-36, it has the sensitivity to assess pain for individual patients. The TOPS short form generates histograms for each of the 14 domains, and you can sit down and show the patient from visit to visit, assuming that they are at least 1 month apart, what type of progress there is. However, one of the major problems with our patients is that they often deny they are doing better even when we can show them evidence that they are.

**Dr. Natelson:** How long does it take to complete the new short form?

**Dr. Lipman:** About 9 to 10 minutes, and all 30 patients in our pilot study found that to be acceptable. At 25 to 35 minutes, the full TOPS is much too long for clinical practice.

**Dr. Strassels:** It is important to ask a patient, “Are you doing better?” But it is also useful to ask, “In what ways do you think you’re doing better or not doing better?” That may be of interest to managed care physicians and pharmacists.

The SF-36 does not necessarily tell you what is going on if the person’s functioning is lower than the level the question asks about. For example, asking about having problems walking a mile is not useful in people who never walk a block. But there are some interesting developments: we have the SF-36, the SF-12, and the SF-8, and now there is some talk about whether or not the SF-8 will eventually replace the SF-36.

**Coverage Issues**

**Dr. Penna:** Are you seeing any pushback from health plans with regard to covering treatment of medically unexplained illnesses?

**Dr. Hahn:** Under the Oregon Health Plan, FM is not a covered entity. As soon as that diagnosis is there, nothing that requires prior authorization will be covered.

**Dr. Natelson:** That is the problem with branding or stigmatizing. It prevents us from helping people who are suffering.

**Dr. Lipman:** The problem with FM, which is a
syndrome as opposed to a disease, is in the primary care community, where some physicians label patients as having FM without considering the comorbidities. That is when third-party payers start objecting. The key for managed care is to make sure that there are appropriate referral patterns. Managed care would not leave an untreated or undertreated patient with a serious cardiac arrhythmia in a primary care practice, but would refer that patient to a cardiologist. The same should be true with FM.

Pharmacists should know which physicians and physical therapists in their communities are the best for treating FM, and refer accordingly. Pharmacists should also know that not all physical therapists are the same. Aggressive physical therapy is appropriate for acute injuries, but not for chronic pain, which requires very gentle physical conditioning. When pharmacists are developing their referral patterns, they should learn which physical therapists in the community are specifically trained and experienced in managing chronic as opposed to acute painful musculoskeletal disorders.

REFERENCES


