Fibromyalgia is a common chronic syndrome defined by core symptoms of widespread pain, fatigue, and sleep disturbance. Other common symptoms include cognitive difficulty, headache, paresthesia, and morning stiffness. Fibromyalgia is increasingly understood as 1 of several disorders that are referred to as central sensitivity syndromes; these disorders share underlying causes and clinical features. Tender points are often detected in patients with fibromyalgia and were formerly required for diagnosis. Newly proposed criteria, however, rely on patients’ reports of widespread pain and other somatic symptoms to establish the diagnosis of fibromyalgia. The management of fibromyalgia requires a multidimensional approach including patient education, cognitive behavioral therapy, exercise, and pharmacologic therapy. The present review provides an update on these various aspects of treating a patient with fibromyalgia.

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Fibromyalgia is a chronic, potentially disabling condition defined by core symptoms of widespread pain, stiffness, fatigue, sleep disturbance, and cognitive dysfunction.1,2 As a condition that affects 2% of the US population and is 7 times more prevalent in women than in men,3 fibromyalgia is one of the most common disorders seen by primary care physicians. Patients with fibromyalgia often have a bewildering array of symptoms and a paucity of objective findings, which can frustrate the diagnostic efforts of their health care providers. Test results for diseases of muscle and nerve are normal; serologic studies for autoimmune and infectious diseases are nonrevealing. Given the prevalence of and difficulty in diagnosing fibromyalgia, it is important that primary care physicians be aware of newly proposed diagnostic criteria and advances in the recognition and management of fibromyalgia.

The previous lack of a clear organic basis for fibromyalgia and the increased prevalence of affective disorders in fibromyalgia led some observers to consider it a nondisease or a psychosomatic illness. Recent research, however, has illuminated our understanding of the neurobiological basis of chronic pain syndromes. The current model of understanding fibromyalgia is that it is 1 phenotype of several overlapping syndromes that demonstrate disordered pain regulation referred to as central sensitization.4-6 In the present review, I describe the pathologic process of fibromyalgia and provide current understandings of the diagnosis, comorbid conditions, and management of this challenging disorder.
Pathophysiologic Process

Fibromyalgia replaced the previous term “fibrositis” in the 1980s after exhaustive efforts to prove the existence of inflammatory or other abnormalities of muscle and connective tissue had failed. By then, attention had turned to the central nervous system and the concept of central, or non-nociceptive, pain. More recently, it has been appreciated that fibromyalgia shares similar abnormalities of causation with, and clinical features of, several other disorders. This new understanding led to the concept of a group of conditions that make up central sensitivity syndrome (CSS) (Figure 1). Rather than being a discrete illness, fibromyalgia is now considered 1 phenotype of a much larger spectrum of disorders that overlap substantially in individual patients.

Predisposing Factors for CSS

The underlying cause of CSS disorders is still being explored, but unifying theories have been proposed. A schematic suggesting the possible relationship between the biopsychosocial mechanisms is shown in Figure 2. Genetic, sleep, nervous system, infection, and psychological factors are all potential contributors to the presence of fibromyalgia.

Genetic and Familial Predisposition

There appears to be a strong familial component to fibromyalgia and other CSS disorders. First-degree relatives of patients with fibromyalgia are 8.5 times more likely to have the disorder than the general population. In addition, certain genetic markers for serotonin, dopamine, and catecholamine methyltransferase polymorphisms may be associated with heightened pain sensation.

Sleep Abnormalities

In sleep laboratories, patients with fibromyalgia typically display “alpha-delta intrusion,” as demonstrated by electroencephalography. The resultant loss of restorative delta wave sleep leads to increased fatigue and pain. This cause and effect relationship, however, goes both ways. Normal individuals who are deprived of sleep develop fibromyalgia symptoms, so sleep disturbance can be an inciting pathway to fibromyalgia, as well as a self-sustaining symptom of the condition.

Autonomic Nervous System Dysfunction

Emotional and physical stress activates the hypothalamic-pituitary-adrenal (HPA) axis. Patients with fibromyalgia have hyperactivity of the HPA axis and the

KEY POINTS

- Fibromyalgia is a common disorder seen predominantly in women. The core features of fibromyalgia are widespread pain, sleep disturbance, and chronic fatigue.
- Rather than being a discrete illness, fibromyalgia is considered 1 phenotype of a much larger spectrum of disorders that overlap in individual patients.
- There are objective abnormalities of central nervous system neurotransmitters in fibromyalgia. Central nervous system sensitization appears to underlie the widespread clinical features of fibromyalgia and other disorders of central sensitivity syndrome.
- In patients with fibromyalgia, tender points are common but are no longer required for the diagnosis of fibromyalgia.
- Indiscriminant testing for antinuclear and other autoantibodies should be avoided in the evaluation of a patient with suspected fibromyalgia.
- Pain sensitivity in the general population is represented by a bell-shaped curve. Patients with increased pain but few or less prominent other symptoms may be considered to have a degree of “fibromyalgianess” that may respond to therapy usually reserved for fibromyalgia.
- Fibromyalgia severity varies widely. Patients with marked tenderness, little depression, and good pain-coping skills respond well to treatment and have a favorable prognosis.
- Managing fibromyalgia requires a combination of pharmacologic and nonpharmacologic treatment.
- A philosophy of “start low, go slow” with exercise and drug therapy improves the likelihood of success in managing fibromyalgia.
with genetic and other susceptibility factors may fail to terminate this transient process, leading to chronic central sensitization.

The evidence for physical trauma as an entry pathway to fibromyalgia has been considered but is controversial, with some studies supporting and others failing to support a relationship.16,17

Psychological Factors and Stress
Depression, anxiety, and difficulty coping with stress are common in patients with fibromyalgia. There is an association between childhood abuse and fibromyalgia—McBeth et al18 suggested that inappropriate learned behavior from living with alcoholic or dysfunctional parents may drive the catastrophizing behavior and learned helplessness that are prevalent in many patients with fibromyalgia. The relationship between these psychological factors and fibromyalgia is bidirectional.

Central Sensitization
Abnormalities in the central nervous system are associated with the intense widespread enhancement of pain in fibromyalgia. For example, Russel and Larson6 found a sustained 2- to 3-fold elevation of CSF substance P and other neuropeptides that facilitate pain in patients with fibromyalgia, as well as diminished metabolites of CSF serotonin, norepinephrine, and dopamine, which act to inhibit pain perception. Pain is the sine qua non of fibromyalgia, and patients with this disorder experience widespread allodynia (perception of pain caused by a stimulus that should not normally cause pain) and hyperalgesia (exaggerated sense of pain in response to a noxious stimulus).

Clinical Manifestations
Widespread musculoskeletal pain is the dominant feature of fibromyalgia.1,2 Proximal regions such as the neck, shoulders, hips, and thighs are most commonly involved, but pain may be felt in the hands and feet.1,2,19 Statements such as “I hurt all over” often alert the physician to sympathetic nervous system, with simultaneous relative hypocortisolism.11 The causal relationship between HPA dysfunction and fibromyalgia is unclear, but early childhood stress could precipitate the HPA abnormality.11

Infection, Inflammation, and Physical Trauma
Inflammatory states may trigger persistent central sensitization in susceptible individuals.12-15 These states include viral and other infections, chronic autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus, and physical trauma. Pro-inflammatory neurotransmitters, including substance P and glutamate, stimulate peripheral nociceptive fibers, which synapse on spinal neurons and lead to temporary central sensitization in normal individuals. For example, patients with severe osteoarthritis have evidence of elevated cerebrospinal fluid (CSF) substance P levels and lowered widespread pain thresholds.15 These responses normalize after joint replacement.15 Individuals

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**Figure 1.**
Common conditions in central sensitivity syndrome.4,5
Diagnosis

The diagnosis of fibromyalgia as a discrete entity has typically been made using the American College of Rheumatology (ACR) 1990 classification criteria, which is widespread pain for more than 3 months and the presence of at least 11 of 18 tender points. Widespread pain is defined as pain on both sides of the body, pain above and below the waist, and the presence of axial pain. The examiner identifies tender points by using the thumb to exert 4.0 kg pressure (sufficient to blanch the thumbnail) at each of the discrete tender points to elicit pain.

The ACR diagnostic criteria were developed for research purposes but were gradually adopted for clinical diagnosis. Using these criteria for diagnosis is problematic for more than 1 reason. Few primary care physicians perform tender point examinations (or correctly perform tender point examinations). The same can be said for many rheumatologists. Additionally, the case definition of fibromyalgia has evolved in the past 20 years to include cognitive and other symptoms that are not included in the 1990 ACR criteria. Finally,
The growing awareness that pain sensitivity in the general population is represented by a bell-shaped curve.\textsuperscript{21,22} Many musculoskeletal diseases appear capable of triggering the phenomenon of central sensitization with an associated increase in sleep disturbance, fatigue, widespread pain, and other symptoms common in fibromyalgia.\textsuperscript{11-16} If symptoms are sufficiently severe, a diagnosis of fibromyalgia is usually made and treatment is initiated. Patients with fewer or less-prominent symptoms, however, may respond to therapy usually reserved for “complete fibromyalgia.”\textsuperscript{20-22}

**Differential Diagnosis and Laboratory Testing**

The differential diagnosis of fibromyalgia includes disorders that have features of widespread pain and fatigue. These disorders include hypothyroidism, inflammatory and other myopathies, polymyalgia rheumatica, other rheumatic diseases, viral infections, and severe vitamin D deficiency.\textsuperscript{19}

Patients with hypothyroidism often present with substantial fatigue, myalgia, and malaise. Serum creatine kinase (CK) levels may be elevated in patients with hypothyroidism.\textsuperscript{23} The usual features of polymyositis are proximal muscle weakness and elevation of serum CK levels.\textsuperscript{24} Patients with statin-related myopathy may present with muscle weakness or pain or a combination of both. Serum CK levels are often elevated but may be normal in mild disease.\textsuperscript{25} Patients with suspected statin myopathy but with normal serum CK levels often benefit from a trial of observation off of the drug.\textsuperscript{25} It may take several weeks after cessation of the drug for improvement to be noted.\textsuperscript{25} Polymyalgia rheumatica is usually seen in elderly patients who present with marked proximal muscle stiffness greater than muscle pain.\textsuperscript{26} An
The importance of these findings is the recognition that fibromyalgia is a heterogeneous disorder. Group 3 patients often respond well to treatment and have a favorable prognosis. Group 2 patients tend to have a poor response to treatment, and their long-term prognosis is poor.28

Managing Fibromyalgia

The treatment of patients with fibromyalgia requires a combination of pharmacologic and nonpharmacologic modalities, including exercise and cognitive behavioral therapy.

Nonpharmacologic Management

Patient Education

Simply making a diagnosis of fibromyalgia has a positive effect on its management, leading to a reduction in primary care visits, diagnostic testing, and drug prescriptions.29-31 Patient education is the next step. Emphasizing that the patient does not have a serious or life-threatening disease reduces anxiety. Discussing what is known about the imbalance of central nervous system neurotransmitters and the abnormalities of brain blood flow helps to assure the patient that fibromyalgia is a real illness. One useful metaphor to explain central pain processing abnormalities is an overly sensitive home smoke alarm that goes off every time the oven is turned on. It is a false alarm shrieking “fire” in the absence of fire. An overly sensitive pain processing system will shriek pain in the absence of peripheral pathology, but the perception of pain is very real. Websites hosted by the Arthritis Foundation (http://www.arthritis.org/), the National Fibromyalgia Association (http://fmaware.org/site/), and other reputable organizations can provide patients with useful resources to improve their understanding of fibromyalgia.

Setting expectations regarding illness prognosis and the roles of the patient and physician is important. It helps to advise patients that fibromyalgia is a chronic
Pharmacologic Management

Fibromyalgia is a syndrome of many symptoms and comorbidities, and there is growing evidence of abnormalities of several neural pathways including those mediated by serotonin, norepinephrine, substance P, and glutamate and other neurotransmitters. Patients complain of a variety of seemingly unrelated symptoms. Therefore, it is not surprising that there is no single pharmacologic agent capable of effectively addressing all of the potential symptoms of fibromyalgia.

Antidepressants

Antidepressants appear to exert their effects by modulating serotonin and norepinephrine pathways. Tricyclic antidepressants (TCAs) such as amitriptyline, desipramine, and nortriptyline have been shown in short-term studies to improve pain, sleep, fatigue, and overall sense of well-being. However, they are associated with more adverse effects when used at higher doses.

Tricyclic antidepressants are often prescribed initially for patients with fibromyalgia who do not have depression. It is recommended that TCAs be started at very low doses 2 hours before sleep and titrated upward slowly over several weeks (Table). Despite their initial effectiveness, the long-term durability of TCAs has been questioned. Anticholinergic effects (dry mouth and constipation), sedation, and grogginess limit their tolerability. Although cyclobenzaprine is classified as a muscle relaxant, it is structurally a TCA. It has been shown to improve sleep, pain, and overall sense of well-being but appears to have little or no effect on fatigue in patients with fibromyalgia.

Selective serotonin reuptake inhibitors (SSRIs) are useful for the management of depression and fatigue but
have been less impressive in improving pain and sleep in patients with fibromyalgia.\textsuperscript{5,40} The selective norepinephrine serotonin reuptake inhibitors (SNRIs) duloxetine and milnacipran have been approved by the US Food and Drug Administration for the management of fibromyalgia and appear to be more effective in relieving fibromyalgia symptoms than are the SSRIs.\textsuperscript{33,36,40} Duloxetine reduces pain and improves a patient’s overall sense of well-being. It has relatively little effect on sleep and is usually taken in the morning. The most common adverse effects are nausea and headache, which tend to improve with continued use. Patients with fibromyalgia and comorbid depression may benefit from SNRIs as initial therapy. As with all fibromyalgia treatments, a “start low, go slow” dosing strategy improves patient compliance.

Tramadol combined with acetaminophen improves fibromyalgia pain.\textsuperscript{33,36} This drug has mild SNRI effects in addition to mild opioid effects.\textsuperscript{5} Care should be taken to avoid excessive combinations of SSRI and SNRI drugs to avoid serotonin syndrome.\textsuperscript{42} Features of serotonin syndrome include mental status changes, autonomic hyperactivity, and neuromuscular hyperactivity.

**Antiepileptic Drugs**

Pregabalin, which is approved by the US Food and Drug Administration for the management of fibromyalgia, and gabapentin appear to inhibit the release of pain pathway neurotransmitters, including substance P and glutamate.\textsuperscript{43} They have been demonstrated to improve pain, sleep, fatigue, and overall quality of life in patients with fibromyalgia.\textsuperscript{3,36,43} They are not approved for the management of depression. They are often used as adjunctive therapy, being added to drugs affecting other pain pathways. Adverse effects that limit their use include dizziness, somnolence, and weight gain.\textsuperscript{43} These symptoms tend to improve with continued use.

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**Table.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose(^a)</th>
<th>Target Dose</th>
<th>Common Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>5-10 mg 2 h before bedtime</td>
<td>25-50 mg</td>
<td>Drowsiness, dry mouth, dizziness</td>
</tr>
<tr>
<td>Desipramine</td>
<td>5-10 mg 2 h before bedtime</td>
<td>25-50 mg</td>
<td>Drowsiness, dry mouth, dizziness</td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>5-10 mg 2 h before bedtime</td>
<td>10-30 mg</td>
<td>Drowsiness, dry mouth, dizziness</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>20-30 mg every morning</td>
<td>30-60 mg</td>
<td>Nausea, headache, dizziness, insomnia</td>
</tr>
<tr>
<td>Milnacipran</td>
<td>12.5 mg every morning</td>
<td>50-100 mg twice daily</td>
<td>Nausea, headache, dizziness, insomnia</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>25 mg at bedtime</td>
<td>100-450 mg</td>
<td>Dizziness, somnolence, weight gain, blurred vision</td>
</tr>
<tr>
<td>Tramadol-acetaminophen</td>
<td>50 mg every morning or at bedtime</td>
<td>50-200 mg</td>
<td>Nausea, headache, dizziness, insomnia</td>
</tr>
</tbody>
</table>

\(a\) A “start low, go slow” approach to drug therapy is recommended to improve likelihood of success in managing fibromyalgia.
Other Drugs

Opioids have not been shown to be effective in the management of fibromyalgia and should be avoided if possible.\(^{3,36}\) Opioid-induced hyperalgesia and long-term adverse effects limit the usefulness of this drug class.\(^{3,36}\)

Nonsteroidal anti-inflammatory drugs exert their primary effect on prostaglandin-associated inflammatory pathways and are not very effective in reducing the central pain of fibromyalgia.\(^{36}\) They are useful, however, in the management of coexisting “pain generators” such as osteoarthritis or degenerative disk disease.

Conclusion

Fibromyalgia is 1 of several overlapping disorders of central sensitivity syndrome. The growing knowledge of the underlying biopsychosocial causes of these disorders is leading to a more rational approach to treatment. Recognizing the heterogeneous nature of fibromyalgia, with marked individual variation in prognosis and response to therapy, aids substantially in its management. An understanding of the different pain-relieving mechanisms of drugs aids in the selection of combinations of therapy that may be more effective in the treatment of patients with fibromyalgia.

References


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