Management of Fibromyalgia

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Fibromyalgia is characterized by widespread pain, persistent fatigue, nonrestorative sleep, and generalized morning stiffness. The diagnosis is based on patients' reports of pain and fatigue, clinical findings of multiple tender points, and exclusion of a range of connective tissue and other medical disorders. Treatment of fibromyalgia is multidisciplinary with an emphasis on active patient participation, medications, cognitive behavioral therapy, and physical modalities. No single medication has been found to effectively control all the symptoms, and a rational combination of different medications is often necessary. Currently available medication classes include the selective serotonin uptake inhibitors, the serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, analgesics, hypnotic agents, and anticonvulsants. Treatment modalities should be individualized for patients based on target symptoms and impairment in functioning. As is the case with several chronic disorders, the treatment is often prolonged and improvement may occur slowly. Patience and positive attitude on part of the physician and active involvement of patients and their families in treatment are likely to enhance improvement.

Introduction and Diagnosis

Fibromyalgia is a chronic medical condition characterized by diffuse pain and tenderness at specific anatomic sites, fatigue, nonrestorative sleep, and morning stiffness. The American College of Rheumatology [1] requires only diffuse pain and tenderness as essential for the diagnosis (Table 1), but it also points out well-defined body locations of certain tender points that are associated with fibromyalgia (Fig. 1).

The number of tender points appears to correlate with depression, fatigue, disability, pain, and somatic symptoms [2]. The condition has an estimated overall prevalence of 2%, with significantly more women (3.4%) affected than men (0.5%). Peak prevalence is reported in middle age. Fibromyalgia is reported by 5% to 6% of patients presenting to family medicine clinics; moreover, a sizable 15% to 20% of patients presenting to rheumatologic clinics are diagnosed with fibromyalgia [3]. It is found in patients from most countries, across most ethnic groups, and in all types of climates [4].

Differential Diagnosis

No single laboratory or imaging study is diagnostic of fibromyalgia. However, laboratory investigations may aid in differentiating fibromyalgia from the major rheumatologic disorders, and a host of other nonrheumatologic disorders that it shares symptoms (Table 2).

Fibromyalgia is often associated with other medical disorders including migraine headaches, irritable bowl syndrome, irritable bladder syndrome, restless leg syndrome, complex regional pain syndrome, endocrine dysfunction, and cold intolerance [5]. Psychiatric disorders, such as major depression, dysthymic disorder, and anxiety disorders, are common [6•], and reflect a reaction to the demoralizing effects of chronic disability, and a nonspecific response to the biologic strain imposed on the brain. The subjective suffering and quality of life reduction experienced with fibromyalgia is extreme, and compares mostly with chronic medical conditions, such as urinary incontinence and chronic obstructive pulmonary disease [7].

Etiology

The etiology and pathogenesis of fibromyalgia are not fully known. However, evidence has implicated the following neurophysiologic mechanisms:

Changes in central and peripheral pain perception

It appears that central and peripheral pain mechanisms may be altered in patients with fibromyalgia, resulting in amplification of pain signals [8]. Current theories propose that persistent stimulation of the pain pathways (C-fibers) lead to overactivation of *N*-methyl-D-aspartate receptors in the dorsal horn of the spinal cord [9]. Increased secretion of excitatory neuromodulators, such as substance P, and psychologic factors further escalate the pain perception. The resulting state is referred to as "central sensitization" wherein exquisite pain is produced from innocuous stimuli [10]. Patients with fibromyalgia seem to have reduced blood flow in the caudate and thalamic areas involved in the central processing of noxious signals [11] and elevated concentrations of substance P in the cerebrospinal fluid [12].

Table 1. American College of Rheumatology 1990 criteria for the diagnosis of fibromyalgia

1. History of widespread pain for at least 3 months
   Pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist; in addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present; in this definition, shoulder and buttock pain is considered pain for each involved side; low back pain is considered lower segment pain
2. Pain in 11 of 18 of the following tender point sites on digital palpation:
   Occiput: bilateral, at the suboccipital muscle insertions
   Low cervical: bilateral, at the anterior aspects of the intertransverse spaces at C5 to C7
   Trapezius: bilateral, at the midpoint of the upper border
   Supraspinatus: bilateral, at origins, above the scapula spine near the medial border
   Second rib: bilateral, at the second costochondral junctions, just lateral to the junctions on the upper surfaces
   Lateral epicondyle: bilateral, 2 cm distal to the epicondyles
   Gluteal: bilateral, in upper outer quadrants of the buttocks in anterior fold of the muscle
   Greater trochanter: bilateral, posterior to the trochanteric prominence
   Knee: bilateral, at the medial fat pad proximal to the joint line

Notes
1. Digital palpation should be performed with an approximate force of 4 kg
2. For a tender point considered "positive," the subject must state that the palpation was painful; "tender" is not considered "painful"
3. For classification purposes, patients will be said to have fibromyalgia if the criteria are satisfied
4. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia

(Adapted from Wolfe *et al.* [1].)

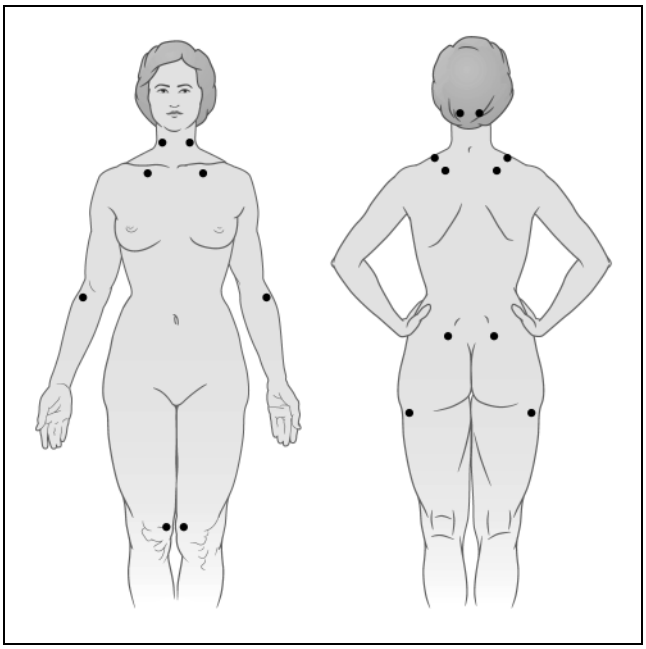

Figure 1. Location of tender points for digital palpation.

Monoaminergic neurotransmitter defects

There is some evidence that serotonin and norepinephrine activity is disturbed in fibromyalgia [13]. This may explain the occurrence of mood, anxiety, fatigue, and sleep disorders. Neurotransmitters play a role in modulation of pain and mood states, and have been implicated in the altered pain perception [14].

Sleep abnormalities

Difficulty in falling asleep, frequent awakenings, and unrefreshed feeling on awakening characterize the sleep pattern of patients with fibromyalgia. Changes in sleep electroencephalogram are notable for intrusion of alpha waves (seen mainly in alert wakefulness) into deep sleep (where delta waves predominate) [15]. Experimental induction of this electroencephalogram pattern in healthy patients was shown to cause muscle tenderness [16]. A slight preponderance of sleep apnea and myoclonic limb jerks is also seen with fibromyalgia [17].

Neuroendocrine changes

Hypofunction of the hypothalamic-pituitary-adrenal axis and the sympatho-adrenal system has been reported in fibromyalgia [18]. Depressed secretion of corticotrophin-releasing factor and cortisol may contribute to the symptoms of depression and fatigue [19]. Growth hormone and insulin-like growth factor also are reduced in a subset of patients. There is at least one study documenting the efficacy of growth hormone treatment for fibromyalgia [20]. Hormonal changes associated with hypothyroidism and menopause can worsen the symptoms of fibromyalgia [21].

Principles of Management

There is no permanent cure for fibromyalgia; therefore, adequate symptom control should be the goal of treatment. False expectations of miraculous remissions should be played down, and emphasis shifted toward more attainable objectives like improving physical and mental health, enhancing work and functional capacities, and symptom-specific treatments. Fostering an attitude of optimism and enhancing problem solving repertoire increases the patient's sense of self-efficacy, which is a crucial step in facilitating the induction of meaningful changes [22••].

Clinicians can choose from a variety of pharmacologic and nonpharmacologic modalities. Unfortunately, controlled studies of most current treatments have failed to demonstrate sustained, clinically significant

Table 2. Differential diagnosis of fibromyalgia

Connective tissue disorders	Nonconnective tissue disorders
Rheumatoid arthritis	Hypothyroidism
Systemic lupus erythematosus	Hepatitis B or C infection
Drug-induced lupus	Lyme disease
Polymyalgia rheumatica	Drug-induced myopathy
Sjögren's syndrome	Cushing syndrome
Polyarticular osteoarthritis	Addison disease
Crystal-induced arthritis	Hyperparathyroidism

Table 3. Multidisciplinary team program

Rheumatologist/ family physicians	Psychiatrist/ psychologist	Physical therapy
Patient and family education	Pharmacotherapy of depression	Muscle conditioning
Medical health maintenance	Cognitive-behavioral therapy	Assistive devices
Pain management	Stress management	

responses. Bennett [23] rightly observed that this realization can overlook valid clinical successes and foster therapeutic nihilism (often to the detriment of patient care). Treatment approaches should be individualized, and keeping in mind the complexity of the condition and the specific needs of each patient. A multidisciplinary treatment program that combines different treatment modalities is ideal for managing fibromyalgia, because few health care providers have the ability and training to deliver all the necessary services needed by those patients (Table 3).

Pharmacologic Management

The main symptoms targeted for drug treatment are pain, sleep disturbance, depression, and fatigue. Addressing symptoms associated with comorbid conditions (*eg,* irritable bowl and migraine) is also important. The commonly prescribed medications fall into the classes of antidepressants, anxiolytics, analgesics, and miscellaneous medications. Multiple drug sensitivities may limit the initiation and maintenance of drug therapy, and, in such cases, starting with a low dose with small gradual increases seems the best strategy. Habituation to the drug effect may occur and can be reduced by resorting to drug holidays [24••]. Polypharmacy is common given the diversity of symptoms. In such cases, medications should be combined with a clear understanding of their indication and proposed mechanism of action, in addition to well-defined target symptoms to minimize drug interactions and additive side effects.

Antidepressants

Lifetime history of depression has been reported in 50% to 70% of patients with fibromyalgia, and current major depression is diagnosed in approximately 18% to 36% of patients [25]. Antidepressants treat the underlying mood disorder, anxiety, sleep disturbance, fatigue, and pain to varying extent. Their enhancement of central and peripheral monoaminergic neurotransmission may explain their effectiveness in fibromyalgia. Controlled clinical trials for the treatment of fibromyalgia have been difficult because of the complexity of the syndrome, lack of consensus regarding outcome measures, and the high placebo response rate of patients leading to small effect sizes [26•,27].

Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are advantageous because of their favorable side effect profile, and should generally be regarded as the first-line treatment. Although anecdotal evidence supports the use of SSRIs in fibromyalgia, published data come from only five placebo-controlled studies (two with citalopram [28,29] and three with fluoxetine [30–32]). Table 4 summarizes the controlled studies with SSRIs. In the studies with citalopram, no significant differences were found between the treatment and placebo groups in the global assessment of improvement. With fluoxetine, one study showed no superiority over placebo, whereas the other two did demonstrate significant improvement in depression, pain, and fatigue.

Paroxetine at a dose of 20 mg per day was shown to reduce symptoms in a single blind 3-month study [33]. Sertraline showed promising results in an open-label study with doses ranging between 25 and 200 mg per day for 6 weeks [34]. In a more recent study, Wetherhold *et al.* [35] examined 82 women with fibromyalgia randomized to receive paroxetine (20 mg per day), nabumetone (2000 mg per day), or a combination of paroxetine (20 mg per day) and nabumetone (2000 mg per day). Patient received each treatment regimen for a period of 8 weeks. The study demonstrated that the combination regimen was superior to nabumetone alone, but not to paroxetine alone, in improving the signs and symptoms of fibromyalgia, which suggests that paroxetine was responsible for the improvement in the combined regimen. Despite the lack of conclusive data, clinical experience suggests that SSRIs should be tried in patients with fibromyalgia, in particular those with symptoms of anxiety, depression, or fatigue.

Serotonin and norepinephrine reuptake inhibitors

This group includes medications that have serotonin and norepinephrine reuptake inhibition properties; venlafaxine, bupropion, and nefazodone are examples. Venlafaxine (mean dose=167 mg per day) was shown in an open-label study to be efficacious, especially with patients who had lifetime comorbid depressions and anxiety [36]. Support

Table 4. Controlled clinical trials of selective serotonin reuptake inhibitors in fibromyalgia

Study	Design	Patients, *n*	Dosage, *mg per day*	Duration, *w*	Comment
[28]	Citalopram vs placebo	40	20 to 40	16	Citalopram was greater than placebo
[29]	Citalopram vs placebo	22	20 to 40	8	Citalopram was equal to placebo
[30]	Fluoxetine vs placebo	60	10 to 80	12	Fluoxetine was greater than placebo
[31]	Fluoxetine vs placebo	42	20	6	Fluoxetine was equal to placebo
[32]	Amitriptyline and placebo vs amitriptyline and fluoxetine vs fluoxetine and placebo vs placebo and placebo	19	25 (amitriptyline); 20 (fluoxetine)	6	Amitriptyline and fluoxetine was greater than amitriptyline and placebo; fluoxetine and placebo was greater than placebo

for bupropion and nefazodone is mainly anecdotal. These agents may be more effective in combating fatigue by virtue of their norepinephrine enhancing properties, and generally have less propensity to cause sexual side effects than SSRIs. Hypertension and nausea may be associated with venlafaxine. Seizures were reported with bupropion, especially at dosages above 450 mg per day. Nefazdone has a black-box warning for hepatic toxicity.

Tricyclic antidepressants

This is the class of antidepressants most extensively studied in fibromyalgia, and they have been efficacious in treating chronic pain syndromes and depressive symptoms. A meta-analysis of nine placebo-controlled trials of tricyclic antidepressants, including tertiary amine tricyclic antidepressants (amitriptyline, dotheipin, maprotiline, and clomipramine) and cyclobenzaprine, found an overall moderate effect size [26•,27]. Table 5 summarizes the major controlled trials with tricyclic antidepressants.

In most of the studies, however, less than standard antidepressant doses were used, with an overall short duration of treatment. Blood levels were not obtained in any of the studies; also, secondary amines, such as nortriptyline, which are better tolerated, were not studied. Tricyclic antidepressants improve sleep by virtue of their sedative action, and also reduce pain by their effect on monoamine neurotransmission along the pain pathways. Standard antidepressant dosages should be used for at least 6 weeks before a trial is considered unsuccessful. Combination with an SSRI may be indicated, but care must be taken to avoid adverse pharmacokinetic interactions [37]. Amitriptyline, in particular, seems to have better results in combination with fluoxetine rather than alone. Tricyclic antidepressants are fairly anticholinergic (dry mouth, constipation, blurry vision, and arrhythmias), block alpha-1 receptors (hypotension and dizziness), and have antihistaminic properties (sedation and weight gain). These pharmacodynamic attributes make them dangerous for overdose and bothersome for those with heart disease, asthma, and glaucoma, even at therapeutic doses.

Analgesics

Nonsteroidal anti-inflammatory drugs are beneficial in reducing peripheral pain. Ibuprofen and naproxen are preferred over acetaminophen [46]. Recalcitrant pain may require opiates in a minority of patients [24••]. Although the risk of addiction of appears small in chronic pain patients without a history of substance abuse, tolerance to analgesic effects of opiates may develop. Patients that elect this route may be less motivated to pursue nonpharmacologic treatments. They also risk aggravation of their depression and cognitive dysfunction. Most patients find fentanyl patches better tolerated, and that their quality of life is better than when using oral morphine [24••]. Tramadol (50 to 400 mg per day) works by a dual mechanism being a weak opioid agonist and an inhibitor of serotonin and norepinephrine reuptake in the dorsal horn [24••]. It has not been shown to have a potent effect on the pain of fibromyalgia, but is regarded to have less potential for physical dependence than opiates. To reduce the incidence of nausea and vomiting it should be started with low dosages and increased slowly. Seizures can occur particularly if combined with antidepressants.

Gabapentin is an anticonvulsant, but is established as a treatment for chronic neuropathic pain [47]. It is mildly sedating and can be used singly or as an adjunct to antidepressants. Other anticonvulsants of potential use include tiagabine, topiramate, and lamotrigine. Preliminary reports support their use for neuropathic pain, but there are no published data available to support their use in fibromyalgia [48].

Anxiolytic and hypnotic agents

Anxiety can be managed in most cases by appropriate doses of antidepressants. Benzodiazepines, such as clonazepam, may be used for muscle spasms and comorbid myoclonic limb jerks. Alprazolam was stud-

Table 5. Controlled clinical trials with tricyclic antidepressants in fibromyalgia

Study	Design	Patients, *n*	Dosage, *mg per day*	Duration, *w*	Comment
[38]	Amitriptyline vs placebo	59	50	9	Amitriptyline was greater than placebo
[39]	Dothiepin vs placebo	52	75	8	Dothiepin was greater than placebo
[40]	Cyclobenzaprine vs placebo	63	10 to 40	12	Cyclobenzaprine was greater than placebo
[41]	Cyclobenzaprine vs placebo	40	10 to 40	6	Cyclobenzaprine was greater than placebo
[42]	Amitriptyline vs cyclobenzaprine vs placebo	98 (amitriptyline); 86 (cyclobenzaprine)	50 (amitriptyline); 30 (cyclobenzaprine)	26	Amitriptyline and cyclobenzaprine was greater than placebo
[43]	Amitriptyline vs placebo	20	25	8	Amitriptyline was greater than placebo
[44]	Cyclobenzaprine vs placebo	9	20 to 40	4	Cyclobenzaprine was greater than placebo
[45]	Clomipramine vs maprotiline vs placebo	18	75 (clomipramine); 75 (maprotiline)	3	

ied in combination with ibuprofen, and did not exert any substantial beneficial effect [49]. Treatment of sleep disturbances is important in patients with fibromyalgia. Basic sleep hygiene measures help some patients enjoy better sleep. These include elimination of caffeine intake 6 hours before sleep, avoiding rigorous physical exercise in the evenings, and decreasing stimulation from TV and radio a few hours before sleep. Tricyclic agents, such as amitriptyline, improve sleep by their sedating effect [23]. Trazodone is commonly prescribed in doses of 50 to 100 mg at night. Benzodiazepines like temezepam 15 to 30 mg at night are often effective. The newer nonbenzodiazepines, zolpidem (5 to 10 mg per day) and zaleplon, are frequently very good choices, because they are devoid of the hangover effect experienced with other hypnotics and do not usually fragment sleep.

Miscellaneous agents

S-adenosylmethionine, which is a dietary supplement considered to have antidepressant and anti-inflammatory properties, has beneficial effects in the treatment of fibromyalgia [50,51]. Muscle relaxants, carisoprodol, methocarbamol, and tizanidine, are used with varying degrees of success [24••].

Dopamine agonists, such as levodopa, pergolide, and pempixole, may be helpful for comorbid restless leg syndrome [52]. Modafinil, which is approved to treat narcolepsy, has been suggested by some investigators to treat the fatigue associated with fibromyalgia, although controlled studies are lacking [53]. Case reports have also indicated the possible use of atypical antipsychotics like olanzapine [54]. Trigger point injections with local anesthetic agents, such as lidocaine, provide pain relief, and some authors have suggested using intravenous lidocaine to treat fibromyalgia [55].

Nonpharmacologic Management

There are few controlled trials for nonpharmacologic management, and the existing studies are often criticized for methodologic flaws, small sample sizes, insufficient duration of follow-up, and lack of appropriate control interventions [22••].

Nevertheless, a majority of patients with fibromyalgia use complementary therapies, such as herbs and lotions, multivitamins, spiritual healing, and dietary manipulation.

These modalities are perceived to relieve pain, stress, and physical, psychologic, and cognitive dysfunction. Many of these are patient-initiated, and maintained by encouragement from a provider. Aerobic exercise and regular physical activity reduce pain and muscle stiffness in patients with fibromyalgia [56]. The exercise should be of sufficient intensity to change the aerobic capacity, and should be conducted two to three times a week for 12 to 20 weeks.

Cognitive-behavioral therapy (CBT) techniques that include reframing of negative thoughts and behavioral relaxation have been a valuable treatment alternative in controlled trials [57•]. The beneficial effects of CBT are usually sustained, especially in patients who learn and rehearse the CBT techniques at home. For motivated patients, combination of CBT with pharmacologic treatments may improve symptom control and functioning. Electro-acupuncture reduced pain in patients with fibromyalgia compared with sham treatment, but there are few high-quality controlled studies to support its widespread use [58]. Electromyography biofeedback seems to help some patients, in particular those with no psychopathologic disturbance [22••]. It is sometimes recommended as part of a multimodal pain therapy in patients with fibromyalgia. Hypnotherapy may be worth considering in selected patients. One con-

trolled study found it superior to physical therapy in patients with fibromyalgia with refractory symptoms and greater subjective suffering [59].

Conclusions and Future Directions

Treatment of fibromyalgia is generally multidisciplinary with an emphasis on active patient participation, medications, CBT, and physical modalities. Currently, there is no consensus for the pharmacologic treatment for fibromyalgia. No single medication has been effective in controlling all symptoms, and often a rational combination of different medications is necessary to improve pain, sleep, fatigue, and other associated symptoms. Currently available medication classes include SSRIs, the serotonin norepinephrine reuptake inhibitor, tricyclic antidepressants, analgesics, hypnotic agents, and anticonvulsants. Treatment modalities should be individualized for patients based on target symptoms and impairment in functioning.

Unfortunately, there are relatively few controlled studies of newer medications in the management of fibromyalgia. As the pathogenesis of fibromyalgia unravels and more specific pharmacologic agents become available, it is likely that clinical trials will involve agents with more solid pharmacologic rationale. For example, a role for substance P inhibitors [60] has been suggested, because an imbalance of this neurotransmitter appears to play a role in central sensitization. Other potential targets for drug development include *N*-methyl-D-aspartate receptor inhibitors and serotonin-3 receptor antagonists [61,62]. Newer counseling strategies, such as motivation enhancement, that have been effective in several psychiatric disorders may also have a role in fibromyalgia. As is the case with several chronic disorders, the treatment is often prolonged and improvement may occur slowly. Patience and positive attitude on part of the physician and active involvement of patients and their families in treatment are likely to enhance improvement.

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