

Diagnosing and Treating Fibromyalgia:

Present and Future Considerations

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Fibromyalgia is a common cause of chronic widespread pain characterized by myofascial tender points and associated symptoms that include fatigue and depression. The nonspecific nature of fibromyalgia symptoms and a lack of objective findings on physical examination have led to skepticism regarding its diagnosis and treatment. As a result, patients with fibromyalgia often go undiagnosed and find little help in managing their pain.

The medical community is now recognizing the significant impact that fibromyalgia has on patients' lives. For these individuals, an early diagnosis of fibromyalgia can result in decreased pain, improved function, and a vastly enhanced quality of life. This review will discuss the diagnosis and epidemiology of fibromyalgia, recent findings about its pathogenesis, and advances in the clinical treatment of fibromyalgia syndrome (FMS) and its associated symptoms.

Definition and Epidemiology

Widespread pain can develop from a variety of medical conditions, including chronic arthritis conditions, diseases of the endocrine system, subacute infections, and cancer. Whereas the term *fibromyalgia* was originally used to denote the pain of patients who failed to meet the criteria for medical syndromes that were better understood, the diagnostic criteria for FMS that were proposed by the American College of Rheumatology (ACR) in 1990 have been generally accepted. This has improved the credibility and uniformity of the diagnosis, as well as the quality of research on the syndrome.¹ The criteria—which are 81% sensitive and 88% specific—distinguish patients with fibromyalgia from those with widespread pain caused by other rheumatologic disorders (eg, systemic lupus erythematosus and rheumatoid arthritis).

According to ACR criteria, patients with FMS must report a history of generalized body pain (ie, in at least 3 of 4 body quadrants) lasting for at least 3 months and with at least 11 of 18 specific tender points, based on painful palpation on physical examination. In addition to their reports of pain, patients with fibromyalgia are estimated to have a 2- to 7-fold greater risk for depression, anxiety, headache, irritable bowel syndrome, chronic fatigue syndrome, systemic lupus erythematosus, and rheumatoid arthritis compared with healthy individuals.²

Fibromyalgia affects about 2% of adults, predominantly women. Based on data from national registries, an estimated 5 million adults in the United States have fibromyalgia.³ Although it is often perceived as a disease of young women, FMS typically affects adults between 35 and 60 years of age.⁴

Pathogenesis

The implementation of a standard diagnosis for fibromyalgia has led to research to determine which factors influence the development and perpetuation of the symptoms. As with many types of chronic nonmalignant pain, most studies on FMS have suggested an important role for the abnormal processing of pain in the peripheral nervous system and the central nervous system, with both peripheral and central sensitization. A variety of neuroendocrine and biochemical abnormalities are believed to contribute to the development and perpetuation of neural sensitization.

PERIPHERAL TISSUE ABNORMALITIES

In earlier studies of patients with fibromyalgia, there was a failure to consistently show abnormalities in peripheral tissues. However, a reexamination of this aspect has uncovered differences in muscle samples between patients with FMS and healthy controls. One difference is the presence of higher levels of nitric oxide in the muscles of patients with FMS, which may increase cell death.⁵⁻⁷ Other muscle abnormalities in such patients include lower phosphorylation potential and oxidative capacity, as evidenced by lower levels of muscle phosphocreatine and adenosine triphosphate and increased levels of substance P and interleukin-1, DNA fragmentation, and perfusion deficits.⁸ Although the exact meaning of such abnormalities is unclear, the findings suggest an underlying difference in muscle metabolism with fibromyalgia. Further study is needed to establish a relationship between these findings and the pain and fatigue reported by patients with fibromyalgia.

Recent studies have also suggested that important changes occur in neural structures in the skin. *N*-methyl-D-aspartate (NMDA) receptors play a critical role in temporal summation or wind-up, a key mechanism in the development of chronic pain. Glutamate, an important pain modulator, binds to NR2 subunits of NMDA. NMDA receptors are present in the dorsal root ganglia and skin.

Kim and colleagues evaluated NMDA receptor subtypes in the skin of 11 female patients with fibromyalgia and 8 healthy matched controls. NR2D receptors were more prevalent in the patients with FMS (159 vs 100; $P=0.016$), with receptor expression correlated to disease duration ($P=0.046$).⁹ In a more recent study, Kim et al evaluated skin biopsies from 13 patients with fibromyalgia and 5 controls. Although skin appearance under normal light microscopy was similar between the 2 groups, electron microscopy of unmyelinated neurons in patients with FMS showed Schwann cell ballooning, axon peripheralization, smaller axon size, and simplified folding structures.¹⁰

Researchers at the University of Zurich in Switzerland have likewise identified important changes in pain-related receptors in 25 patients with fibromyalgia compared with 10 healthy controls.¹¹ Although opioid-receptor messenger RNA in muscle is similar in patients with fibromyalgia and controls, skin samples show an upregulation of both δ - and κ -opioid receptors; concentrations are significantly higher in patients with FMS than in controls ($P<0.01$).

SENSITIZATION AND PAIN AMPLIFICATION

Whereas their perception of non-pain sensations is unaltered, patients with fibromyalgia have increased sensitivity to painful stimuli. Desmeules and colleagues compared responses to cold and heat stimulation in 85 patients with fibromyalgia and 40 controls.¹² Although the temperatures required to perceive a stimulus as either cold or hot were nearly identical for the 2

groups, the temperature changes required to produce a pain perception were substantially lower in the fibromyalgia group for both the pain of cold ($P<0.001$) and of heat ($P<0.01$). These data support clinical reports by patients with fibromyalgia of increased sensitivity to stimulation and a seemingly exaggerated perception of discomfort to stimuli that would not produce pain in normal controls.

The abnormalities of peripheral and central processing of pain are well established in fibromyalgia. In the periphery, tissue sensitization results from changes in primary nociceptive afferents, increased neuronal excitability, and enlarged neuronal receptive fields. Central sensitization involves neuroplasticity in the brain and spinal cord. "Wind-up," a normal finding of increased pain sensation after repeated exposure to a painful stimulus, is an example of central sensitization. In studies of FMS, the wind-up response is exaggerated.

Staud and colleagues studied patients with fibromyalgia and healthy controls after repeated exposure to heat stimuli. Whereas both groups had higher pain ratings after repeated exposure to heat, the degree of wind-up and temporal summation was significantly greater in the fibromyalgia group.¹³ Additionally, the fibromyalgia group had more prolonged after-sensations than did controls.

NEUROENDOCRINE ABNORMALITIES

Altered activity of the hypothalamic-pituitary-adrenal axis plays an important role in stress-related disorders like fibromyalgia. Recently, Tannriverdi et al catalogued neuroendocrine abnormalities in patients with fibromyalgia that have been reported in the literature.¹⁴ Despite normally sized adrenal glands in these patients, a number of abnormalities have been documented:

- decreased response of adrenocorticotrophic hormone (ACTH) and epinephrine to hypoglycemia;
- decreased peak cortical response to ACTH; and
- decreased 11-deoxycortisol levels in the metyrapone (Metopirone, Novartis) test.

Data suggest the hypothalamic-pituitary-adrenal axis may be less resilient than normal in patients with fibromyalgia, which may contribute to the impaired response to stress that many of these patients exhibit and the role that stress can play in aggravating symptoms of the syndrome.^{15,16}

BIOCHEMICAL ABNORMALITIES

Although there are no serologic tests to assist practitioners in diagnosing FMS, a number of biochemical abnormalities have been identified in research studies. Russell et al identified lower levels of serum serotonin and norepinephrine in patients with fibromyalgia than in controls.¹⁷ However, reductions in serum serotonin are not found in all conditions involving chronic widespread pain. A comparative study of 12 patients with fibromyalgia and 12 with rheumatoid arthritis found significantly lower levels of serum serotonin in the FMS group ($P<0.05$).¹⁸

Serotonin has not been measured in the cerebrospinal fluid (CSF) of patients with fibromyalgia, although serotonin's precursor and metabolic products have been measured at significantly lower levels in the CSF of these patients compared with controls.¹⁹ Norepinephrine's metabolite, methoxyhydroxyphenylglycol, and dopamine's metabolite, homovanillic acid, are also at reduced levels in patients with fibromyalgia.²⁰ The biochemical abnormalities found with fibromyalgia are discussed in a review by Mease.²¹

Abnormal levels of nociceptive neurochemicals have also been found in patients with FMS. Several studies have found that substance P, a neuropeptide involved in pain transmission, is present at significantly higher levels in the CSF of those with fibromyalgia than in those without the disorder.²²⁻²⁵ Nerve growth factor, which promotes production of substance P, is also found to be elevated in the CSF of patients with fibromyalgia.²⁶

IMAGING OF PAIN

Functional magnetic resonance imaging (fMRI) measures regional blood flow in the central nervous system in response to various environmental stimuli; an increase in central nervous system activity corresponds to the subjective pain reported by patients with FMS. The pain threshold in these patients is substantially reduced compared with controls. In a study by Gracely et al, a 73% stronger stimulus was required to elicit the same subjective pain response in the control group compared with the fibromyalgia group. Furthermore, fMRI testing in these same patients revealed greater activation in the fibromyalgia group ($P<0.05$), confirming subjective reports of increased pain perception with objective augmentation in cerebral blood flow.²⁷

A recent study found that fibromyalgia patients had fewer mu-opioid receptors compared with control subjects in several brain regions important for pain processing. The authors suggest that this relative mu receptor deficiency may account for the reduced efficacy of opioid analgesic in fibromyalgia patients.²⁸

Another MRI study demonstrated decreased brain gray matter volume in fibromyalgia subjects compared with controls. Loss of gray matter volume was found to progress over time. The study also demonstrated that gray matter volume was equal in fibromyalgia patients and control subjects prior to the development of painful symptoms. Further, age-related loss of gray matter was 9 times as rapid in fibromyalgia subjects compared with those without fibromyalgia.²⁹

FREE RADICALS

Free radical-mediated oxidative stress and resultant cell injury has been proposed as a factor in fibromyalgia pathogenesis. A recent study demonstrated that fibromyalgia patients have significantly higher levels of serum hydrogen peroxide and higher oxidative stress indices compared with control subjects.³⁰

GENETICS

Mounting evidence points to fibromyalgia as a heritable disorder. The evidence includes familial aggregation of fibromyalgia in addition to a reduced pain threshold in the first-degree female relatives of patients with FMS—even in those without overt clinical symptoms.^{31,32} To date, studies have not determined the extent of influence from genetics versus shared environment. Researchers in Sweden evaluated pain data from the Swedish Twin Registry that had been collected on 15,950 twin pairs at least 42 years of age.³³ In general, genetics and a shared environment each explained about half of the variation in the occurrence of chronic widespread pain, suggesting a modest genetic influence.

Studies have identified a variety of possible candidate genes linked to FMS,³⁴ such as those encoding HLA DR4 antigen, serotonin transporter, catechol-O-methyltransferase, D₂ and D₄ dopamine receptors on chromosome 11, and substance P receptor (NK1). Although these data are still preliminary—without clear genetic markers identified—the finding of genetic polymorphisms associated with fibromyalgia strengthens our understanding of it as a biological rather than psychological condition and suggests possible new areas for developing treatments.

Clinical Presentation

PATIENT HISTORY

“Pain all over” is one of the most consistent symptoms reported by patients with FMS. This is well reflected in diagrams on which patients are asked to shade painful areas of a human figure (Figure 1).³⁵ For patients with FMS, the diagrams show diffuse shading on the right and left sides of the body, as well as above and below the waist. We have observed that some of these patients shade, circle, or put an X through the entire figure. When asked to rate their pain severity, patients with fibromyalgia report moderate to severe intensity. Patients describe a wide range of painful sensations, from a deep ache to mild tenderness to intermittent dysesthesia. For most patients, the pain is present throughout the day, with the greatest intensity experienced in the morning and evening. Triggers, including stress, cold weather, illness, and unaccustomed exertion, will likely increase pain. In addition to pain, 75% of patients report stiffness, and more than 50% report a sensation of swelling.

Nonmusculoskeletal symptoms, including fatigue and difficulty in sleeping, are typical in patients with fibromyalgia (Table 1). Psychological and neuropsychological symptoms, including anxiety, mental distress, and cognitive dysfunction, are reported by 60% of patients. Thirty percent of patients report current depression, and more than 50% report a history of depression. Headaches are also common. Uncommon symptoms (<20% prevalence) include tinnitus, dizziness, and vertigo. FMS

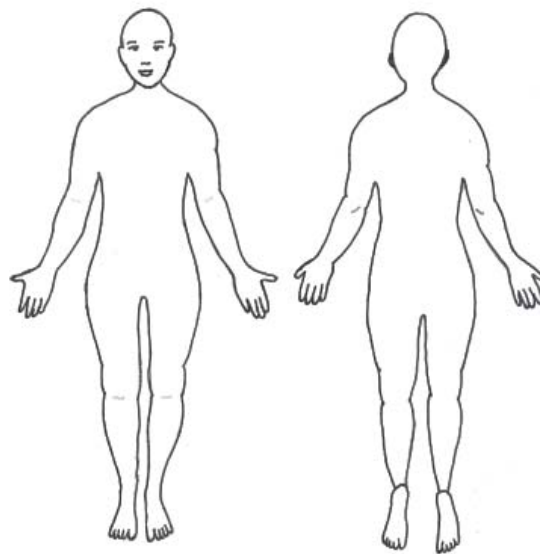


Figure 1. Drawings for recording pain.

Patients are instructed to shade all painful areas, using the following key: //// = pain; ::::: = numbness; *** = burning or hypersensitivity.

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Table 1. Symptoms Commonly Associated With Fibromyalgia

Neurologic
Difficulty concentrating (“fibro-fog”)
Dizziness
Headache (migraine, tension, chronic daily)
Psychiatric
Anxiety
Depression
Fear, anger, guilt
Gastrointestinal
Abdominal pain
Bloating
Constipation
Diarrhea
Genitourinary
Pelvic pain
Urinary burning, frequency
Constitutional symptoms
Fatigue/generalized weakness
Night sweats
Weight fluctuations

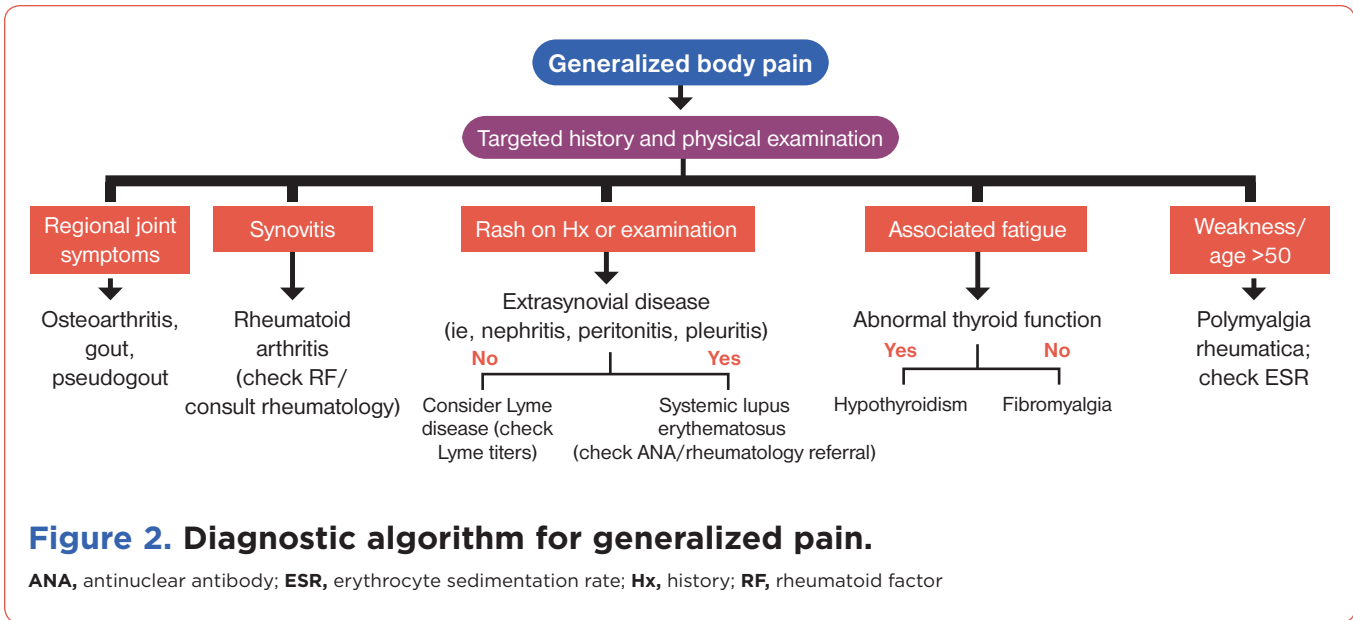


Figure 2. Diagnostic algorithm for generalized pain.

ANA, antinuclear antibody; ESR, erythrocyte sedimentation rate; Hx, history; RF, rheumatoid factor

may also coexist in 20% of patients with rheumatoid arthritis, 30% of patients with systemic lupus erythematosus, and 50% of those with Sjögren’s syndrome.²¹

Severe fatigue, a debilitating symptom, is seen in up to 80% of patients with fibromyalgia. The complaint encompasses the mental fatigue and impaired concentration commonly referred to as “fibro-fog,” postexertional fatigue, and general sleepiness. Often, patients with fibromyalgia are frustrated by a poor quality of sleep—referred to in the literature as nonrestorative sleep.

These patients awaken feeling unrefreshed, even after a full night of sleep. Other complaints include light sleep, frequent awakenings, and insomnia. Like many aspects of fibromyalgia, the cause of poor sleep and chronic fatigue is not fully known. Recent studies suggest that the fatigue stems from abnormal sleep architecture. One study reported that sleep abnormality is characterized by alpha wave intrusion into stage 4 sleep.³⁶ In patients with fibromyalgia, alpha waves typically seen in stage 1 light sleep are found in stage 4 slow-wave deep sleep.

Table 2. Common Conditions Associated With Generalized Pain

Rheumatologic/autoimmune disorders	Infectious
Ankylosing spondylitis	Hepatitis C
Fibromyalgia	HIV
Gout	Lyme disease
Mixed connective tissue disease	Nutritional
Pseudogout	Vitamin B ₁₂ deficiency
Rheumatoid arthritis	Vitamin D deficiency
Scleroderma	Neurologic disorders
Systemic lupus erythematosus	Chronic demyelinating neuropathies
Endocrinologic disorders	Multiple sclerosis
Adrenal dysfunction	Miscellaneous
Hyperparathyroidism	Occult malignancy
Hypothyroidism	Statin-induced myopathy
Musculoskeletal disorders	
Cervical/lumbar degenerative disk disease	
Osteoarthritis	

Additionally, such patients have a relative deficiency in the rapid eye movement stage of sleep compared with healthy controls.³⁷ These abnormalities, although not specific to fibromyalgia, may cause significant fatigue.

PHYSICAL EXAMINATION

When evaluating patients who report widespread chronic pain, the practitioner should be cognizant of multiple rheumatologic disorders in addition to FMS—such as generalized osteoarthritis, pseudogout, gout, rheumatoid arthritis, systemic lupus erythematosus, and polymyalgia rheumatica. Obtaining a careful history and thorough physical examination for synovial and extrasynovial findings can help differentiate these conditions from FMS. Figure 2 depicts a diagnostic algorithm that separates FMS from other common causes of generalized pain. Table 2 lists other diagnostic considerations, including hypothyroidism, vitamin D deficiency, demyelinating polyneuropathies, and paraneoplastic syndromes. Results from a targeted laboratory panel are often used to tease out these differential diagnostic considerations.

On physical examination, the characteristic finding in fibromyalgia is the presence of tender points at the specific locations outlined in Table 3. A *tender point* is defined as a spot on the body that is painful when 4 kg of pressure are applied (the amount of pressure required to blanch the examiner's thumbnail when palpating the palm of his or her own hand). Patients with fewer than 11 of the 18 tender points included in the ACR classification criteria may still be diagnosed with fibromyalgia if they have otherwise supportive clinical features (eg, sleep disturbance, fatigue, morning stiffness). Tender points may exist with a number of conditions other than FMS, including cervical and lumbosacral facet arthrosis syndrome, sacroiliitis, and chronic whiplash, and therefore a careful history and examination are key diagnostic elements.

Treatment

A variety of pharmacologic and nonpharmacologic interventions are available for the treatment of fibromyalgia. Anecdotally, many of these treatments are successful; however, controlled research is limited and the optimal treatment remains unknown. Limitations of available research include the short duration of studies, small sample sizes, and lack of blinding and randomization. In our treatment center, we find that an interdisciplinary approach combining pharmacologic and nonpharmacologic therapies is often best. Medications—particularly antidepressants and some antiseizure agents—may be beneficial, particularly if therapy is aimed at addressing associated symptoms such as disrupted sleep, depression, and anxiety (Table 4). For improving overall function and well-being in patients with fibromyalgia, most experts agree that nonpharmacologic therapy is a chief component of any well-formulated treatment plan.

Table 3. Location of Fibromyalgia Tender Points (Bilateral)

1. Low cervical region: anterior neck near transverse processes of C5-C7
2. Second rib: second costochondral junctions
3. Occiput: insertion of the suboccipital muscles
4. Trapezius muscles: midpoint of the upper border
5. Supraspinatus muscles: medial border of scapular spine
6. Lateral epicondyle: 2 cm distal
7. Gluteal muscle: upper outer quadrant
8. Greater trochanter: posterior to the trochanteric process
9. Knee: medial fat pad

Medications

ANTIDEPRESSANTS

Antidepressants are among the most widely studied medications for the treatment of FMS. The effects of serotonin and norepinephrine are postulated to enhance the activity of descending inhibitory pain pathways and block pain transmission from the periphery. Antidepressants may also improve the commonly comorbid disturbances in sleep and mood.

The most commonly used antidepressants in patients with FMS are the tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs). Among these classes of antidepressants, TCAs are the oldest and have the strongest evidence for efficacy in fibromyalgia. Two of the earliest placebo-controlled clinical trials demonstrated modest effectiveness of amitriptyline 25 to 50 mg at bedtime.^{38,39} Cyclobenzaprine, a muscle relaxant with structural similarity to the TCAs, has shown efficacy in several short-term clinical trials.^{40,41} A 2004 meta-analysis of the literature on cyclobenzaprine has shown its effectiveness in treating some fibromyalgia symptoms but did not show a reduction in fatigue or tender points.⁴²

Although TCAs may benefit patients with fibromyalgia, side effects may limit their use, even in low doses. The anticholinergic effects of this class are responsible for most of the adverse effects seen, including sedation, confusion, constipation, and palpitations.⁴³ Impaired mobility and falls have also been described in older adults.⁴⁴ TCAs may also prolong the QT interval, increasing the risk for torsades de pointes and even death. In older adults and in patients with a history of cardiac symptoms, an

Table 4. Medications Used in Fibromyalgia Treatment

Drug	Recommended Dose	Comments
Antiepileptic medications		
Gabapentin	100-600 mg daily; maximum dose: 1,800 mg daily	Titrate slowly; may cause sedation or dizziness; dose adjustment for renal failure
Pregabalin (Lyrica, Pfizer)	300-450 mg daily; maximum dose: 600 mg	FDA-approved for fibromyalgia; maximum dose is for the indication PHN
TCAs		
Amitriptyline	10-50 mg at bedtime	May cause sedation and confusion
Nortriptyline	10-50 mg at bedtime	Avoid using in patients with narrow-angle glaucoma. Baseline echocardiography recommended to evaluate Q-T prolongation; if present, avoid use.
SSRIs		
Citalopram	20-40 mg daily	—
Fluoxetine	20-80 mg daily	Patient tolerability of SSRIs is superior to that of TCAs.
SNRIs		
Duloxetine (Cymbalta, Lilly)	30-60 mg daily	FDA-approved for fibromyalgia; avoid using in patients with liver disease or narrow-angle glaucoma.
Milnacipran (Savella, Forest Laboratories)	100-200 mg daily (divided doses)	FDA-approved for fibromyalgia; avoid using in patients with liver disease or narrow-angle glaucoma.
Venlafaxine	75-100 mg daily ^a	Avoid using in patients with uncontrolled hypertension.
Analgesics		
Tramadol	50-100 mg every 6 hours as needed	May cause sedation and confusion. Avoid using in patients with seizures. May cause serotonin syndrome in combination with SSRIs or other antidepressants. Dose adjustment for renal failure
Muscle relaxants		
Cyclobenzaprine	5-10 mg nightly	Likely to cause sedation; side effects similar to TCAs

PHN, postherpetic neuralgia; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants

^a Doses up to 375 mg daily have been studied by MM Dwight et al (*Psychosomatics* 1998;39[1]:14-17).

electrocardiogram should be obtained before prescribing TCAs—which should be subsequently avoided if QT prolongation is observed. The secondary tricyclic amines desipramine and nortriptyline have fewer side effects but are not as well studied.

At this point, the evidence is modest for the efficacy of SSRIs and SNRIs in the treatment of fibromyalgia. These newer antidepressants may have fewer side effects than the TCAs. The SSRIs increase serotonin levels at lower doses, and increase both serotonin and norepinephrine levels at higher doses. The first double-blind, randomized placebo-controlled trial to study the use of fluoxetine to treat FMS failed to show any benefit compared with placebo.⁴⁵ A subsequent crossover study found improved pain relief, function, and overall well-being after treatment with fluoxetine 20 mg daily or amitriptyline 25 mg daily, compared with placebo. The results from a combination of both drugs were superior compared with either drug alone.⁴⁶ The newer SSRI, citalopram, has been evaluated in 2 studies.

Whereas 1 of the studies failed to show a benefit of citalopram, a study by Anderberg and colleagues demonstrated relief from depression and improved overall well-being in patients with fibromyalgia who were treated with citalopram (20-40 mg) compared with the placebo group.⁴⁷

Other studies have examined the dual SNRIs for the treatment of fibromyalgia. Although venlafaxine was found to be beneficial in open-label studies, in a randomized placebo-controlled trial with low-dose venlafaxine (75 mg daily) no benefits were found over placebo.⁴⁸ Duloxetine (Cymbalta, Lilly) was approved in 2008 for the treatment of fibromyalgia, based in part on data from a multicenter, randomized placebo-controlled trial using 60 mg of duloxetine twice daily. After 12 weeks, 30% of the women in the duloxetine group had a 50% improvement from baseline function as measured by Fibromyalgia Impact Questionnaire (FIQ) scores, compared with 16% of women in the placebo group ($P=0.035$). Women who received

duloxetine also had fewer tender points on examination and reported less pain interference compared with the placebo group.⁴⁹

Milnacipran (Savella, Forest Laboratories), an SNRI first available in Europe and Asia, is now the third fibromyalgia medication approved by the FDA. Reduction in fibromyalgia pain was seen after one week of treatment.⁵⁰ Initial doses of 12.5 mg daily are recommended with titration to 50 mg twice daily over the first week of treatment. Maximum doses of 200 mg daily have been used. Like duloxetine, the most common side effect of milnacipran is nausea.⁵⁰

ANTIPILEPTICS

Antiepileptic medications have been used to treat a wide range of centrally mediated pain syndromes, and there is support for the use of these medications in patients with fibromyalgia. Although the mechanisms of action of newer antiepileptic drugs are largely unknown, it is believed that they reduce neuronal excitability, decrease ectopic neuronal discharge, and modulate the levels of a variety of neurotransmitters.

Pregabalin (Lyrica, Pfizer), an antiepileptic drug that binds to the $\alpha_2\delta$ subunit of voltage-gated calcium channels, was the first FDA-approved medication for the treatment of FMS. Several large studies of pregabalin have demonstrated efficacy in reducing pain and improving function at doses between 300 and 450 mg daily.⁵¹ After 14 weeks of treatment, a 30% pain reduction was achieved in 42% and 50% of subjects taking 300 and 450 mg of pregabalin, respectively. This was significantly higher than in the placebo group ($P<0.05$). A 50% pain reduction was seen in 27% of those treated with pregabalin at 450 mg, compared with 15% of subjects in the

placebo group ($P<0.05$). Pain relief began in the first few weeks of treatment and lasted at least 6 months.⁵²

ANALGESICS

With the exception of tramadol, there are no data that demonstrate the efficacy of analgesics for the treatment of FMS. Tramadol, a weak Q-receptor agonist with dual inhibition of serotonin and norepinephrine reuptake, is unique in its mechanism of action. It was shown to be effective in 3 randomized controlled trials.⁵³⁻⁵⁵ Similar to other opioids, the prolonged use of tramadol may be linked to abuse and dependence and should be considered judiciously. Because of the sometimes refractory nature of pain in fibromyalgia, patients are not infrequently treated with more potent opioids; this can lead to a number of adverse effects including dysmobility and falls, delirium, increased depression, sedation, nausea, and vomiting. Research also suggests that the prolonged and excessive use of opioids in patients with FMS may result in increased pain, referred to as opioid hyperalgesia. If treatment with opioids is being considered, an evaluation by a pain specialist is often helpful.

HORMONAL SUPPLEMENTS AND OTHER AGENTS

Studies on the use of hormonal supplements for patients with fibromyalgia have had mixed results. A 9-month study of subcutaneous growth hormone showed benefit in patients with fibromyalgia who had low levels of insulin-like growth factor.⁵⁶ Because this medication is quite costly (\$1,500 per month) and the study results cannot be broadly generalized (most patients with FMS do not have low levels of insulin-like growth factor), the routine use of this agent cannot be recommended.

Based on anecdotal evidence, other hormonal

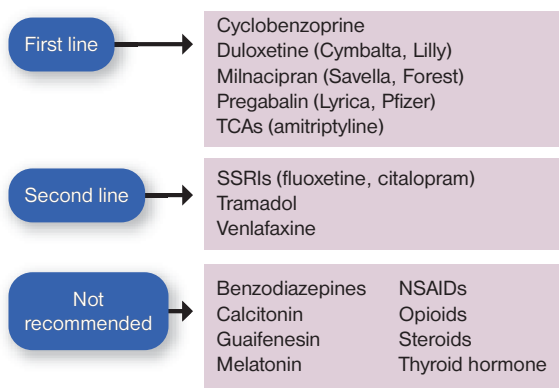


Figure 3. Pharmacologic treatments for fibromyalgia.⁶⁸

NSAIDs, nonsteroidal anti-inflammatory drugs; **SSRIs**, selective serotonin reuptake inhibitors; **TCAs**, tricyclic antidepressants

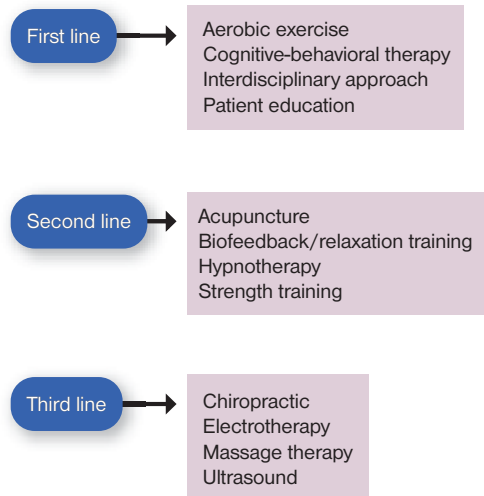


Figure 4. Nonpharmacologic treatments for fibromyalgia.⁶⁸

supplements have been tried, including thyroid hormone, dehydroepiandrosterone, and calcitonin. However, the absence of randomized controlled trials precludes recommending these agents for the treatment of FMS. Similarly, nutritional supplements, herbal medications, and vitamin therapy are not accompanied by rigorous data to support their use. Some studies and anecdotal reports have suggested a benefit from guaifenesin; however, a

12-month randomized controlled trial with this medication showed no reduction in pain or symptoms.⁵⁷

Sodium oxybate, a medication approved for the treatment of narcolepsy, improves pain and overall function in FMS. A recent randomized, double-blind, placebo-controlled trial showed sodium oxybate improved sleep quality and reduced pain scores in fibromyalgia patients, with minimal side effects.⁵⁸

Question 1. Rate how frequently you were able to perform each of the following tasks during the past week. If you would not normally perform one of these tasks, mark N/A for not applicable.

	Always, 0	Mostly, 1	Occasionally, 2	Never, 3	N/A
Do shopping					
Do laundry with washer and dryer					
Prepare meals					
Wash dishes/cooking utensils by hand					
Vacuum a rug					
Make beds					
Walk several blocks					
Visit friends or relatives					
Do yard work					
Drive a car					
Climb stairs					

Question 2. In the past week, how many days did you feel good? (Circle a number from 0 days to 7 days.)

0 1 2 3 4 5 6 7

Question 3. How many days in the past week did you miss work (including housework) because of your fibromyalgia? (Circle a number from 0 days to 7 days.)

0 1 2 3 4 5 6 7

Question 4. For each question below, circle the number on each scale that best describes how you felt overall during the past week.

A. When working (including housework), how much did pain or other fibromyalgia symptoms interfere?

0 1 2 3 4 5 6 7 8 9 10
 No problem with work Great difficulty with work

B. How bad has your pain been?

0 1 2 3 4 5 6 7 8 9 10
 No pain Very severe pain

C. How tired have you been?

0 1 2 3 4 5 6 7 8 9 10
 No tiredness Very tired

D. How have you felt when you got up in the morning?

0 1 2 3 4 5 6 7 8 9 10
 Awoke well-rested Awoke very tired

E. How bad has your stiffness been?

0 1 2 3 4 5 6 7 8 9 10
 No stiffness Very stiff

F. How nervous or anxious have you felt?

0 1 2 3 4 5 6 7 8 9 10
 Not anxious Very anxious

G. How depressed or blue have you felt?

0 1 2 3 4 5 6 7 8 9 10
 Not depressed Very depressed

Scoring the FIQ: Possible score ranges from 0 (no impact) to 100 (severe impact).

Question 1: Add the numbers for each checked item in question 1, and divide by the number of scored items. Number of scored items will be 11 unless some are not applicable. Multiply this average score by 0.33.

Question 2: Score items in question 2 in reverse order: 7=0, 6=1, 5=2, etc. Multiply the score for the selected item by 1.43.

Question 3: Multiply selected number by 1.43.

Question 4: Add all circled numbers together.

Add the numbers obtained from scoring questions 1 through 4 for the total FIQ score. Scores >70 represent severe impact.

Figure 5. The Fibromyalgia Impact Questionnaire (FIQ).

Adapted from reference 69. Reprinted with permission from reference 35.

Studies of tropisetron, an intravenous 5-HT₃ antagonist, demonstrate pain relief in fibromyalgia patients. Researchers propose that tropisetron's analgesic effect results from binding to ascending nociceptive pain fibers and inhibitory dorsal horn neurons.^{59,60}

A recent study demonstrated that pramipexole, a dopamine agonist, improved pain, function and global satisfaction when used in combination with other traditional fibromyalgia medications (antiepileptics, anti-inflammatories, antidepressants, or analgesic agents).⁶¹

Improving the quality of sleep and treating fatigue are often difficult. An emphasis on sleep hygiene to encourage regular sleep schedules, eliminate daytime naps, establish a restful sleep environment, and promote caffeine avoidance is helpful for many patients. The long-term use of benzodiazepines is not recommended because of their addictive qualities and tendency to disrupt normal sleep cycles. The use of nonaddictive sedative medications such as cyclobenzaprine and tizanidine can often improve sleep quality and decrease pain.

Nonpharmacologic Therapies

Nonpharmacologic therapies for FMS include cognitive-behavioral techniques, exercise, acupuncture, balneotherapy (ie, bathing), and massage. Aerobic exercise programs have been shown to reduce pain and improve function and well-being. The development of individual programs, based on a patient's abilities and symptoms, is best. During pain flares, which may occur after physical exertion, programs should be modified but not stopped. In our experience, water aerobics is an excellent exercise option, especially for those with concomitant arthritis. Some studies have found that patients with FMS are as much as 30% weaker than control subjects; thus, strength training may be beneficial for deconditioned patients.^{62,63}

Most data support the benefits of an interdisciplinary program—exercise coupled with educational sessions and cognitive-behavioral techniques. Both inpatient and outpatient interdisciplinary programs have been found to be beneficial. Cognitive-behavioral therapy is useful for patients who tend to characterize their painful symptoms as “catastrophic.” Using cognitive-behavioral techniques, patients can learn to alter their perception of pain and manage pain flares through coping skills and relaxation.

The benefits of local therapies and complementary techniques for the treatment of fibromyalgia have also been evaluated. A randomized controlled trial showed that tai chi was effective for improving both physical and psychological distress in fibromyalgia patients. In the 12-week trial, patients were randomized to group sessions of tai chi or stretching and wellness education. The tai chi group demonstrated significantly greater improvements in function, sleep quality, depression and health status compared with the control group.⁶⁴

Transcranial electromagnetic stimulation has been

evaluated as a potential treatment for fibromyalgia patients. Transcranial direct current stimulation, repetitive magnetic stimulation, and complex neural pulse stimulation have been demonstrated to reduce pain and improve well-being in fibromyalgia patients. While preliminary studies show some promise for transcranial stimulation devices, further controlled studies are needed.⁶⁵⁻⁶⁷

Several randomized controlled trials of acupuncture have shown effectiveness for relieving fibromyalgia symptoms. The data are encouraging, given the overall safety of this treatment modality. Weak evidence supports the use of chiropractic treatment, massage therapy, interferential current, and ultrasound for FMS. Further studies are needed to determine the potential impact of these modalities, and identify potential long-term treatment benefits.

Designing a Treatment Plan

Most pain practitioners agree that the most effective treatment for fibromyalgia includes both pharmacologic and nonpharmacologic approaches. When choosing among available medications, it is helpful to consider the most troubling symptoms and comorbidities of patients. If depression and poor sleep are significant concerns, a sedating antidepressant may address both symptoms, and thus prevent polypharmacy—which can result from treating each symptom with different medications. Patients with significant cognitive dysfunction should use antiepileptic medications with caution; initially, low doses are recommended. A slow, stepwise increase in dosing will help patients adjust to the dizziness and drowsiness that can occur as side effects.

Finally, the clinician should reinforce to patients that although medications may reduce some of their symptoms, they are likely to be more effective if taken in conjunction with exercise, stretching, and stress management techniques. Figures 3 and 4 illustrate the most effective pharmacologic and nonpharmacologic treatments for fibromyalgia.⁶⁸

Assessing Response to Treatment

Noting patients' responses to pain and additional symptoms may help the physician assess treatment for fibromyalgia. Pain can be measured using standard pain assessment tools, such as a visual analog scale, as well as by monitoring the tender point count (number of painful tender points) and tender point number (sum of severity scores from 0 [no pain or only pressure] to 10 [excruciating pain] for all 18 tender points). A reduction in global pain score, tender point count, and tender point number are all useful assessments for evaluating treatment response in both research trials and clinical practice. A comprehensive, fibromyalgia-specific, validated tool for measuring disability is the 20-question FIQ.⁶⁹ The FIQ takes only minutes to complete and quantifies physical function, painful symptoms, and emotional well-being, specifically in patients with FMS (Figure 5).

Conclusion

Adopting standardized diagnostic criteria has permitted a more thorough understanding of the epidemiology of fibromyalgia, the contributing pathophysiologic factors, and treatment response. Medical practitioners are becoming increasingly adept at diagnosing and treating FMS. Fibromyalgia is generally accepted as representing a centrally mediated pain syndrome, often linked with other central sensitization syndromes such as chronic headache and irritable bowel. Optimal treatment combines pharmacologic therapies with exercise, stretching, and techniques for cognitive-behavioral modification. Antidepressants and muscle relaxants are often helpful for relieving pain and improving mood and sleep quality. More recently, good responses have been noted in studies done with pregabalin and duloxetine.

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