Differential diagnosis of fibromyalgia

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INTRODUCTION — The cardinal feature of fibromyalgia (FM) is chronic, widespread pain that is not explained by another rheumatic or systemic disorder. Explicit in this definition is the exclusion of other conditions that can present with widespread pain. Thus, although the differential diagnosis of FM may potentially become quite complicated, it should actually be relatively simple [1,2].

Rather than worrying about every disease that can cause musculoskeletal pain, the clinician should focus on the characteristic features of FM:

● Pain above and below the waist, which is bilateral and axial for at least three months
● Somatic complaints including fatigue and sleep, mood, and cognitive disturbance

These symptoms are often present in many other diseases. However, these other conditions, such as infection, often either are transient or manifest abnormal physical and laboratory findings. In FM, the physical examination, other than tenderness in muscles and soft tissue (tender points), is unrevealing and laboratory and imaging are unremarkable.

Conditions that should be considered in the differential diagnosis of FM include other disorders that may mimic FM or that may occur as comorbid conditions, as well as a collection of common disorders that often overlap with FM [3,4]. These latter illnesses are common and can present challenges in differential diagnosis. They include myofascial pain syndrome, chronic fatigue syndrome, irritable bowel syndrome, pelvic and bladder pain disorders, and temporomandibular pain [4]. Like FM, each of these conditions is very common and controversial, since there are no objective abnormalities found on the physical, laboratory, or radiologic examinations. As a result, FM and these overlapping disorders are often termed “functional somatic syndromes.”

This topic will review the differential diagnosis of FM in adults. The clinical manifestations, diagnosis, and treatment of this condition in adults, as well as FM in children and adolescents,
are discussed in detail elsewhere. (See "Clinical manifestations and diagnosis of fibromyalgia in adults" and "Approach to the patient with myalgia" and "Initial treatment of fibromyalgia in adults" and "Treatment of fibromyalgia in adults not responsive to initial therapies" and "Fibromyalgia in children and adolescents: Clinical manifestations and diagnosis" and "Fibromyalgia in children and adolescents: Treatment and prognosis").

APPROACH TO THE DIFFERENTIAL DIAGNOSIS — The initial approach to the differential diagnosis in a patient with complaints suggestive of fibromyalgia (FM) is a thorough history and physical examination. Baseline blood tests should be limited to a complete blood count, erythrocyte sedimentation rate (ESR), standard blood chemistries, and thyroid function tests. These tests are all usually normal in patients with FM; thus, any abnormalities may suggest the presence of one of the systemic illnesses discussed below.

FM should not be a diagnosis “of exclusion,” but rather a diagnosis based upon the typical symptoms. The diagnosis should be considered quickly in any individual complaining of months of widespread pain. Hints for an early diagnosis that will help to eliminate a costly and time-consuming search for an alternative diagnosis are described in detail separately. (See "Clinical manifestations and diagnosis of fibromyalgia in adults", section on 'Diagnosis'.)

A wide variety of disorders may be associated with diffuse or localized myalgia. An overview of the approach to the evaluation of patients presenting with myalgia is presented separately. (See "Approach to the patient with myalgia").

SYSTEMIC AND RHEUMATIC DISEASES MISTaken FOR FIBROMYALGIA — Fibromyalgia (FM) may be incorrectly diagnosed as any one of a variety of systemic and rheumatic diseases.

Rheumatoid arthritis, Sjögren's syndrome, and systemic lupus erythematosus — Rheumatic diseases such as rheumatoid arthritis (RA), Sjögren’s syndrome (SS), and systemic lupus erythematosus (SLE) may present with generalized arthralgias, myalgias, and fatigue, and like FM most often affect younger women (table 1). However, characteristic features of RA, such as multiple joint swelling, or of SLE, such as facial rash and multisystemic inflammation, do not occur in FM.

A careful history and physical examination, rather than “screening” serologic blood tests, should be sufficient to differentiate FM from a connective tissue disease. Thus, unless there is strong clinical suspicion of a systemic rheumatic disorder, routine ordering of serologic tests is NOT recommended; these tests, such as antinuclear antibody (ANA) and rheumatoid factor (RF), may be positive in healthy individuals and in many other diseases. For example, approximately 10 to 15 percent of patients with FM have a positive ANA test [5]. However, 5 to 10 percent of healthy women also have a positive ANA, at least at low titer. Therefore, the predictive value of a positive ANA is poor in patients who have no signs or symptoms of SLE. If there is clinical confusion regarding the differential diagnosis of FM with SLE or with other systemic connective tissue diseases, more specific serologic tests, such as an anti-DNA antibody test, should be obtained. (See "Origin and utility of measurement of rheumatoid factors" and "Measurement and clinical significance of antinuclear antibodies").

FM occurs more commonly in these systemic immune diseases than in the general population and can affect disease assessment. This is illustrated by the following examples:

• In a cohort of 173 patients with SLE, approximately 30 percent of the patients met criteria for FM [6]. There was a strong association between the number of tender points and health status.
In a large rheumatic disease database, FM was present in 22 percent of patients with SLE and in 17 percent of those with RA and other forms of arthritis [7].

In an observational study of patients with RA and FM, the presence of FM made evaluation of RA more difficult, resulting in an overestimate of disease activity using the composite measure, the Disease Activity Score in 28 joints (DAS28) [8].

The future development of FM was evaluated in 9739 patients with RA during 42,591 patient-years of follow-up [9]. Seven percent of RA patients satisfied criteria for FM at last observation, and 20 percent satisfied criteria at some point during follow-up. The incidence rate was 5.3 per 100 patients-years (95% CI 5.1-5.6); rates were similar in men and women. Multiple factors predicted the future development of FM, including psychosocial issues, depression, comorbidity, more severe RA, and greater baseline FM symptoms.

Ankylosing spondylitis — Ankylosing spondylitis or other inflammatory back conditions may present with axial skeletal pain and stiffness similar to that of FM and may be misdiagnosed as FM [10]. However, spinal motion in FM is generally normal, and there are characteristic imaging and radiologic features of ankylosing spondylitis and the other seronegative spondyloarthropathies [10]. (See "Diagnosis and differential diagnosis of ankylosing spondylitis and non-radiographic axial spondyloarthritis in adults".)

Polymyalgia rheumatica — Polymyalgia rheumatica (PMR) may mimic FM, although this disorder can be differentiated by the history and laboratory studies. (See "Clinical manifestations and diagnosis of polymyalgia rheumatica".)

The following features help differentiate PMR and FM:

- Patients with PMR tend to be older at onset and to present more with generalized stiffness than with severe, widespread pain.
- An elevated erythrocyte sedimentation rate (ESR) is present in the vast majority of patients with PMR but is normal in patients with FM.
- Patients with PMR, but not those with FM, respond extremely well to modest doses of glucocorticoids [11]. However, glucocorticoid withdrawal in PMR or any rheumatic condition may cause symptoms that are similar to those of FM.

Inflammatory myositis and metabolic myopathies — FM is distinguished from inflammatory myositis and the metabolic myopathies by the following features:

- Myositis and the myopathies cause muscle weakness and muscle fatigue but are not usually associated with diffuse pain.
- Patients with FM do not have significant muscle weakness, other than that related to pain or disuse.
- In contrast to myositis, patients with FM have normal muscle enzyme tests and normal or nonspecific histopathologic findings on muscle biopsy. Muscle biopsies should not be performed unless there is clinical evidence suggestive of an inflammatory or metabolic myopathy.

Infection — FM may mimic a chronic viral infection such as infectious mononucleosis. FM, as well as chronic fatigue syndrome (CFS), has been noted to follow or accompany well-documented infections, including human immunodeficiency virus (HIV) infection, human T-lymphotropic virus (HTLV) infection, hepatitis, and Lyme disease [12-14]. Approximately 25 to 40 percent of patients with documented Lyme disease who are treated appropriately with
antibiotics will develop persistent pain and fatigue, consistent with FM and CFS [13,15]. However, there has been no evidence of persistent microbial infection in the vast majority of these patients. Furthermore, antibiotics are not effective in this “post-Lyme” FM/CFS condition. Thus, patients should not be repeatedly treated with prolonged courses of antibiotics if they have no clinical or serologic evidence of active Lyme disease. (See "Musculoskeletal manifestations of Lyme disease", section on 'Post-lyme disease syndrome (chronic lyme disease) and fibromyalgia'.)

Hypothyroidism — Hypothyroidism may be difficult to distinguish from FM, since patients with hypothyroidism often complain of generalized aches, fatigue, and interrupted sleep. Thus, thyroid function studies (usually a serum thyroid stimulating hormone [TSH] level) should be routinely obtained during the initial evaluation of a patient with suspected FM; the vast majority of FM patients have normal thyroid tests. (See "Diagnosis of and screening for hypothyroidism in nonpregnant adults".)

FM may also be a presenting manifestation of hypothyroidism, and thyroid autoantibodies are common in patients with FM [16]. However, correcting the thyroid abnormality does not usually ameliorate the FM symptoms.

Other endocrine disorders — Other endocrine disorders that may present with symptoms similar to FM include hyperparathyroidism and Cushing’s syndrome. Hyperparathyroidism is recognized by the presence of hypercalcemia, while Cushing’s syndrome presents with characteristic facial and skin features and is associated with muscle weakness rather than pain. Adrenal insufficiency causes severe exhaustion but is not typically associated with chronic, widespread pain. Some studies, but not others, have suggested that patients with vitamin D deficiency without evidence of osteomalacia may also experience symptoms of chronic musculoskeletal pain [17-19]. A 2011 systematic review found no conclusive evidence for an association of vitamin D deficiency and FM [20]. (See "Diagnosis and differential diagnosis of primary hyperparathyroidism" and "Epidemiology and clinical manifestations of Cushing's syndrome".)

Statin-associated myopathy — At least 10 to 30 percent of subjects treated with statins will experience nonspecific muscle discomfort. Those with preexisting FM are more likely to develop statin-associated muscle pain [21,22].

Peripheral neuropathies, entrapment syndromes, and neurologic disorders — Peripheral neuropathies, entrapment syndromes (such as carpal tunnel syndrome), and neurologic disorders (such as multiple sclerosis and myasthenia gravis) may mimic FM (table 1). Multiple sclerosis and myasthenia gravis are associated with post-exercise muscle fatigue, as well as generalized fatigue. However, chronic, widespread pain is unusual.

Patients with FM are frequently mistakenly diagnosed with one of these neurologic diseases, since they may complain of numbness and tingling, often involving the neck and radiating down the arm, suggesting cervical radiculopathy. These symptoms of paresthesias, as well as subjective cognitive dysfunction, often lead to costly and invasive neurologic testing [23]. A careful neurologic examination should differentiate FM from neurologic disease. A report did find frequent objective neurologic abnormalities in patients with FM [24]. Poor balance or coordination, tingling or weakness in the arms or legs, and numbness in any part of the body correlated with appropriate neurologic examination findings in the FM group. However, unless there is evidence of associated nerve compression or of cervical or lumbar spinal stenosis,
extensive testing including plain radiographs, electromyography (EMG), nerve conduction velocities, computerized tomography (CT) scans, nuclear scans, or magnetic resonance imaging (MRI) is not generally necessary.

DIFFERENTIAL DIAGNOSIS OF OVERLAPPING SYNDROMES — The most confusing conditions in the differential diagnosis of fibromyalgia (FM) include a variety of illnesses that overlap with FM and that may be even considered to be part of the FM spectrum. These include myofascial pain syndrome; functional somatic syndromes, including irritable bowel syndrome (IBS), migraine, and chronic fatigue syndrome (CFS); and mood and sleep disorders (table 2 and table 3) \[25-36\].

Myofascial pain syndromes — Myofascial pain syndrome, sometimes termed repetitive strain syndrome, overlaps considerably with FM (table 4) \[26,28,37-39\]. Patients with myofascial pain syndrome complain of pain in one anatomic region, such as the right side of the neck and shoulder, with tenderness being confined to that area. Many of the original reports of FM actually described what would have subsequently been termed myofascial pain syndrome. Some of the confusion lies in the differentiation between trigger points and tender points.

Myofascial pain is defined by the presence of trigger points that are found in a taut band in the muscle (figure 1). A characteristic referral pain pattern is activated when pressure is applied to a trigger point \[26,28,38\]. Some experts also insist upon the presence of a local twitch response, a visible or palpable contraction of the muscle produced by a rapid snap of the examining finger to the taut band of muscle. By contrast, tender points, as seen in FM, are soft tissue sites that are excessively tender on manual palpation. However, the reliability of the trigger point examination has been questioned \[28,37,39\].

● One study, for example, employed experts in myofascial pain syndrome and FM to perform tender point examinations on three groups of patients: seven with FM, eight with myofascial pain syndrome, and eight healthy people. They found local tenderness to be common in both disease groups (65 to 82 percent), although more common in patients with myofascial pain. Active trigger points were found in 38 and 23 percent of patients with FM and myofascial pain syndrome, respectively (using a liberal definition of trigger point). Taut muscle bands and muscle twitches were common (50 and 30 percent respectively) and were found in the healthy controls as well \[37\].

● A second study of similar design found that dolorimetry and palpation were sufficiently reliable to discriminate control patients from patients with myofascial pain and FM but may not discriminate between the two diseases \[28\].

● Most importantly, there is no accepted reference standard for the diagnosis of trigger points, and data on the reliability of physical examination for trigger points are conflicting. A systematic review concluded that the physical examination cannot be recommended as a reliable test for the diagnosis of trigger points \[39\].

Myofascial pain syndromes may include other common regional pain disorders such as tension headaches, idiopathic low back and cervical strain disorders, repetitive strain syndromes, occupational overuse syndrome, cumulative trauma disorder, work-related musculoskeletal disorder, and temporomandibular joint (TMJ) syndrome \[27,29,30\]. In the head and neck, the pain may be associated with unexplained dizziness and with neurocognitive disturbances. The etiology of these complaints is not understood, although some neurovestibular abnormalities are often found in patients with TMJ and myofascial pain of the head. These poorly understood pain
disorders are also associated with fatigue, sleep abnormalities, and mood disturbances, suggesting that myofascial pain may be just a localized or regional form of FM.

Chronic, unexplained pelvic and urethral pain, sometimes termed the female urethral syndrome, is often considered to be a variation of myofascial pain. Considered together with the disorders discussed above, myofascial pain syndrome may be one of the most common causes of chronic pain.

Myofascial pain is generally treated similarly to FM (see "Initial treatment of fibromyalgia in adults"). Myofascial pain may respond well to local treatment methods such as application of a cold spray and passive stretch of the involved muscle. Trigger point injections, using dry needling, saline, or botulinum toxin, have been effective in clinical trials [26,27,30]. This type of treatment is not felt to be as successful in FM.

Functional somatic syndromes — FM is often present in patients together with other common functional somatic syndromes, including CFS, IBS, migraine, and TMJ disorder, as well as chronic bladder and pelvic pain syndromes [25,31-33,40,41]. The prevalence of FM in each of these disorders varies from 20 to 50 percent [42,43].

Demographic, clinical, and potential pathophysiologic characteristics of CFS, IBS, and other functional somatic syndromes are very similar to those of FM. Each of these conditions is diagnosed when other diseases have been excluded, and they tend to be controversial because of the absence of a specific diagnostic test or of objective pathophysiologic abnormalities. (See "Pathogenesis of fibromyalgia".)

Simple questions to screen for each of the common functional somatic syndromes have been suggested that can be useful in determining whether additional evaluation is warranted [40]:

- **CFS** – Have you had unexplained, persistent, or relapsing fatigue for at least six months? (See "Clinical features and diagnosis of chronic fatigue syndrome".)
- **IBS** – Have you had abdominal discomfort or pain accompanied or affected by constipation or diarrhea for three or more months in the past year? (See "Clinical manifestations and diagnosis of irritable bowel syndrome in adults".)
- **Temporomandibular disorders** – Have you had recurrent facial/jaw pain and/or limitation in jaw opening occurring in the past six months? (See "Temporomandibular disorders in adults".)
- **Tension and migraine headache** – Have you had recurrent headaches (at least five for migraine, at least 10 for tension-type) lasting 30 minutes occurring in the past six months? (See "Overview of chronic daily headache").
- **Interstitial cystitis** – Have you had symptoms for over nine months of bladder pain, urinary urgency and frequency (voiding more than eight times during the day or more than two times during the night), and a negative urine culture? (See "Pathogenesis, clinical features, and diagnosis of interstitial cystitis/bladder pain syndrome").

Each of these illnesses causes pain, although the primary area of pain varies (for example, chronic, widespread pain in FM, abdominal pain in IBS, and jaw pain in temporomandibular disorder). Fatigue, cognitive disturbances, and generalized allodynia and hyperalgesia are characteristic of FM, IBS, and CFS [2,4,44-46]. Furthermore, imaging studies in these functional pain disorders reveal similar changes related to augmented pain perception in the central nervous system [45-47].
Mood disorders — Since many symptoms of FM, including depression, fatigue, lack of energy, and sleep disturbances, are characteristic of mood disturbances, many clinicians believe that FM is primarily a psychiatric illness. However, observations suggest that FM is not a psychiatric illness but that mood disturbances are important in the expression and outcome of this condition. Mood disorders are more prominent in FM than in rheumatic diseases, such as rheumatoid arthritis (RA). Approximately 25 percent of patients with FM have concurrent major depression, and 50 percent have a lifetime history of depression [1,2,45,46,48]. The greater incidence of mood disorders is especially striking in tertiary referral patients [46]. An informal evaluation of mood should be part of the initial evaluation of any patient with FM, with a more formal assessment by a mental health professional in selected patients.

Sleep disturbance — Most patients with FM have nonrestorative sleep. Sleep disturbances are also very common in patients with FM, although the most common is a nonspecific interruption in stage 4 sleep [49]. However, primary sleep disturbances, including sleep apnea, restless leg syndrome, and repetitive leg movement disorders are quite common [50]. Thus, a careful sleep history should be obtained in patients with FM symptoms. Patients with possible sleep apnea or nocturnal myoclonus should be referred to a sleep clinic for further evaluation and treatment.

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

●Beyond the Basics topics (see "Patient information: Fibromyalgia (Beyond the Basics)"

SUMMARY AND RECOMMENDATIONS

●The initial approach to the differential diagnosis in a patient with complaints suggestive of fibromyalgia (FM) is a thorough history and physical examination. In FM, the physical examination is unrevealing other than tenderness in muscles and soft tissue. Baseline blood tests should be limited to a complete blood count, erythrocyte sedimentation rate (ESR), standard blood chemistries, and thyroid function tests. These tests are all usually normal in patients with FM; thus, any abnormalities may suggest the presence of a systemic illnesses other than FM. (See ‘Approach to the differential diagnosis’ above.)

●A careful history and physical examination, rather than serologic testing, should be sufficient to differentiate FM from most rheumatic diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and Sjögren’s syndrome (SS). Selected laboratory or imaging findings, in addition to the history and physical examination, may be useful in distinguishing FM from ankylosing spondylitis, polymyalgia rheumatica, inflammatory or metabolic myopathies, hypothyroidism, and other endocrine disorders. (See 'Systemic and rheumatic diseases mistaken...
Peripheral neuropathies, entrapment syndromes (such as carpal tunnel syndrome), and neurologic disorders (such as multiple sclerosis and myasthenia gravis) may mimic FM (table 1). Multiple sclerosis and myasthenia gravis are associated with post-exercise muscle fatigue, as well as generalized fatigue. However, chronic, widespread pain is unusual. A careful neurologic examination should differentiate FM from neurologic disease. Unless there is evidence of associated nerve compression or of cervical or lumbar spinal stenosis, extensive testing including plain radiographs, electromyography (EMG), nerve conduction velocities, computed tomography (CT) scans, nuclear scans, or magnetic resonance imaging (MRI) is not generally necessary. (See 'Peripheral neuropathies, entrapment syndromes, and neurologic disorders' above.)

● The most confusing conditions in the differential diagnosis of FM include a variety of illnesses that overlap with FM and that may be even considered to be part of the FM spectrum. These include myofascial pain syndrome; functional somatic syndromes, including irritable bowel syndrome (IBS), migraine, and chronic fatigue syndrome (CFS); and mood and sleep disorders (table 2 and table 3). (See 'Differential diagnosis of overlapping syndromes' above.)

● Myofascial pain syndrome, sometimes termed repetitive strain syndrome, overlaps considerably with FM (table 4). Patients with myofascial pain syndrome complain of pain in one anatomic region, with tenderness being confined to that area. Some of the confusion lies in the differentiation between trigger points and tender points. Myofascial pain is defined by the presence of trigger points that are found in a taut band in the muscle (figure 1). A characteristic referral pain pattern is activated when pressure is applied to a trigger point. (See 'Myofascial pain syndromes' above.)

● FM is often present in patients together with other common functional somatic syndromes, including CFS, IBS, migraine, and temporomandibular joint (TMJ) disorder, as well as chronic bladder and pelvic pain syndromes. Demographic, clinical, and potential pathophysiologic characteristics of CFS, IBS, and other functional somatic syndromes are very similar to those of FM. Simple questions to screen for each of the common functional somatic syndromes have been suggested that can be useful in determining whether additional evaluation is warranted. (See 'Functional somatic syndromes' above.)

● Mood disorders are common in FM. Approximately 25 percent of patients with FM have concurrent major depression, and 50 percent have a lifetime history of depression. An informal evaluation of mood should be part of the initial evaluation of any patient with FM, with a more formal assessment by a mental health professional in selected patients. (See 'Mood disorders' above.)

● Sleep disturbances are common in patients with FM, including a nonspecific interruption in stage 4 sleep and primary sleep disturbances, such as sleep apnea, restless leg syndrome, and repetitive leg movement disorders. A careful sleep history should be obtained in patients with FM symptoms. Patients with possible sleep apnea or nocturnal myoclonus should be referred to a sleep clinic for further evaluation and treatment. (See 'Sleep disturbance' above.)

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REFERENCES


