

Fibromyalgia and Related Conditions

Daniel J. Clauw, MD

From the University of Michigan, Ann Arbor, MI.

CME Activity

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Learning Objectives: On completion of this article, you should be able to (1) understand the three underlying mechanisms of chronic pain; (2) recognize centralized pain, either as a distinct entity or as a co-morbidity with other underlying pain mechanisms; (3) treat chronic pain based on the underlying mechanisms operative in each patient rather than based on the disease that is purported to be causing the pain.

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Abstract

Fibromyalgia is the currently preferred term for widespread musculoskeletal pain, typically accompanied by other symptoms such as fatigue, memory problems, and sleep and mood disturbances, for which no alternative cause can be identified. Earlier there was some doubt about whether there was an “organic basis” for these related conditions, but today there is irrefutable evidence from brain imaging and other techniques that this condition has strong biological underpinnings, even though psychological, social, and behavioral factors clearly play prominent roles in some patients. The pathophysiological hallmark is a sensitized or hyperactive central nervous system that leads to an increased volume control or gain on pain and sensory processing. This condition can occur in isolation, but more often it co-occurs with other conditions now being shown to have a similar underlying pathophysiology (eg, irritable bowel syndrome, interstitial cystitis, and tension headache) or as a comorbidity in individuals with diseases characterized by ongoing peripheral damage or inflammation (eg, autoimmune disorders and osteoarthritis). In the latter instance, the term *centralized pain* connotes the fact that in addition to the pain that might be caused by peripheral factors, there is superimposed pain augmentation occurring in the central nervous system. It is important to recognize this phenomenon (regardless of what term is used to describe it) because individuals with centralized pain do not respond nearly as well to treatments that work well for peripheral pain (surgery and opioids) and preferentially respond to centrally acting analgesics and non-pharmacological therapies.

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Clinicians often encounter individuals who present with pain that they cannot adequately explain on the basis of the degree of damage or inflammation noted in peripheral tissues. This typically prompts an evaluation for the cause of pain. If no cause is found, these individuals are often given a diagnostic label that merely connotes that they have chronic pain in a region of the body without an underlying mechanistic cause (eg, chronic low back pain, headache, and temporomandibular joint disorder [TMJD]). In other cases, the label given alludes to an underlying pathologic abnormality that may or may not be responsible for the individual's pain (eg, endometriosis and facet syndrome). In other instances, the patients may be told that there is nothing wrong with them, advised that the disorder is “all in their head,” and given a label such as “somatizer” without being offered any treatment.

Fibromyalgia (FM) is the currently preferred term for widespread musculoskeletal pain for which no alternative cause can be identified. Every subspecialist sees the same individuals, typically because these individuals present with pain in the region of the body the subspecialist specializes in. Gastroenterologists see the very same patients and focus on their gastroenterological symptoms and often use the terms such as *functional gastrointestinal disorder*, *irritable bowel syndrome* (IBS), *nonulcer dyspepsia*, or *esophageal dysmotility* to explain the patients' symptoms. Urologists focus on their genitourinary symptoms and use terms such as *interstitial cystitis* or *chronic prostatitis*, and gynecologists use terms such as *vulvodynia*, *vulvar vestibulitis*, and *endometriosis*. Until recently these unexplained pain syndromes perplexed researchers, clinicians, and patients.

We have come to understand that although individuals sometimes have only one of these idiopathic pain syndromes over the course of their lifetime, more commonly individuals with one of these entities will have many, and their family members also have high rates of pain in many regions of the body. Many terms have been used to describe these co-occurring syndromes and symptoms, such as *functional somatic syndromes*, *somatization disorders*, *allied spectrum conditions*, *chronic multisymptom illnesses*, and *medically unexplained symptoms*. Although some of these individuals will have

comorbid psychiatric conditions, and these are often blamed by physicians as the cause of these otherwise unexplained pains, most individuals who have these conditions do not have a definable psychiatric disorder. There is now much evidence that these syndromes are clearly different and separable from depression and anxiety and have different (yet strong) genetic underpinnings. A hallmark of these conditions (eg, FM, IBS, TMJD, and headache) is that individuals display diffuse hyperalgesia (increased pain to normally painful stimuli) and/or allodynia (pain to normally nonpainful stimuli). This and many other pieces of evidence suggest that these individuals have a fundamental problem with augmented pain or sensory processing (ie, an increased gain setting) in the central nervous system (CNS) rather than a pathologic abnormality confined to the region of the body in which the person is currently experiencing pain.

Even if a practitioner has a problem with considering FM as a discrete disorder, it is critical to understand the diagnostic and therapeutic importance of centralization of pain as exemplified by a typical patient with FM. Once this phenomenon is recognized, it helps determine what types of treatments will work (centrally acting analgesics and nondrug therapies) and, just as importantly, what will not (opioids and surgery).

OVERVIEW

Fibromyalgia is generally considered to be the second most common “rheumatic” disorder, behind osteoarthritis. Depending on the diagnostic criteria used, the prevalence in the population ranges from 2% to 8%.¹⁻³ The diagnostic criteria for FM published in 1990 require chronic widespread pain plus a certain number of tender points to make the diagnosis. According to this definition, FM was an almost exclusively female disease because women have many more tender points than do men (population-based studies suggest that women are 10 times as likely to have 11 tender points as do men⁴). The new diagnostic criteria for FM published in 2010 and 2011 no longer require performing a tender point count to make the diagnosis and instead ask about the constellation of nonpain somatic symptoms that are typically present in addition to widespread pain (eg, fatigue, sleep

disturbance, memory, and mood problems). By using either of these criteria, substantially more men are diagnosed, with the female/male ratio being approximately 2:1 (instead of 9:1 with the 1990 criteria).³ This female/male ratio is similar to those seen for almost all chronic pain conditions.⁵ Fibromyalgia can develop at any age, including in childhood. It occurs in relatively equal frequency in different countries, cultures, and ethnic groups; there is no evidence that this condition occurs at increased rates in industrialized countries and cultures.²

Nearly all individuals eventually diagnosed with FM have several bouts of chronic pain in other regions of the body earlier in their life. A typical presentation is that of an individual who begins having regional pain conditions and/or somatic symptoms or syndromes earlier in life and finally progresses to having widespread pain later in life and receives this diagnosis. The prevalence of any (regional or widespread) chronic musculoskeletal pain in the population is approximately 30%, so identifying any patient who has had multiple episodes of chronic pain in different areas of their body over the course of their lifetime is an important clinical clue. This disorder often begins in childhood or adolescence, and individuals who eventually go on to develop FM are more likely to experience headaches, dysmenorrhea, TMJD, chronic fatigue, IBS and other functional gastrointestinal tract

disorders, interstitial cystitis/painful bladder syndrome, endometriosis, and other regional pain syndromes (especially back and neck pain).^{6,7} What often looks to one health care provider as a new episode of acute or subacute pain is in fact simply the latest region of the body experiencing pain.⁸ Because of this, many experts in the pain field have begun to believe that especially these “centralized” pain states are best thought of as a single lifelong disorder that begins in adolescence or young adulthood and merely tends to manifest in different regions of the body over time.⁹⁻¹¹

This knowledge might be particularly important for surgeons and proceduralists to integrate into clinical decision making because these individuals have much higher rates of surgical procedures performed to eliminate pain (eg, hysterectomy and back surgery),¹² and perhaps not surprisingly, data are beginning to emerge that this phenotype is a risk factor for individuals who fail to respond to peripherally directed procedures. Table 1 depicts that FM is the prototypical centralized pain state, differentiating it from other pain mechanisms (eg, nociceptive and neuropathic) that are typically easier to identify by clinicians.

In addition to patients with FM who have a lifetime history of chronic pain, their families often have a history of chronic pain. First-degree relatives of patients with FM are 8.5 times as likely to have this condition as do

TABLE 1. Underlying Mechanisms Operative in Chronic Pain States^a

Peripheral (nociceptive)	Neuropathic	Centralized
<ul style="list-style-type: none"> ● Pain due to inflammation or mechanical damage in tissues ● Nonsteroidal anti-inflammatory drugs and opioids are responsive ● Responds to procedures ● Classic examples <ul style="list-style-type: none"> ○ Acute pain due to injury ○ Osteoarthritis ○ Rheumatoid arthritis ○ Cancer pain 	<ul style="list-style-type: none"> ● Damage or entrapment of peripheral nerves ● Responds to both peripheral and centralized pain therapies ● Entrapment responds to surgery or injection ● Classic examples <ul style="list-style-type: none"> ○ Diabetic neuropathic pain ○ Postherpetic neuralgia 	<ul style="list-style-type: none"> ● Characterized by central disturbance in pain processing (diffuse hyperalgesia/allodynia) ● Responsive to central nervous system—acting drugs altering neurotransmitters involved in pain, sleep, and mood disturbances ● Classic examples <ul style="list-style-type: none"> ○ Fibromyalgia ○ Irritable bowel syndrome ○ Temporomandibular joint disorder ○ Tension headache

^aThere are 3 underlying pain mechanisms: nociceptive, neuropathic, and centralized. It is important to assess every patient with chronic pain for each of these mechanisms, because any of the 3 can be present in any given patient. The diseases at the bottom of the figure are classic examples of each type of pain, but we now realize that all chronic pain states are mixed pain states, in which (within each disease) any of the 3 mechanisms might be present. It is particularly common to see centralized pain co-occur with either nociceptive or neuropathic pain.

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the family members of controls and also have high rates of other chronic pain states.¹³ The strong familial predisposition to pain is shared by many chronic pain conditions, and recently there has been an expansion of knowledge about the strong predisposing role of genetic factors in leading to chronic pain states.^{11,14} Many of the genes that have been identified to date to play a role in increasing or decreasing the frequency of chronic pain states, or of pain sensitivity, are involved in regulating the breakdown or binding of neurotransmitters that modulate pain sensitivity. The facts that pain sensitivity is polygenic and that different individuals develop increased pain sensitivity because of imbalances or altered activity of many different neurotransmitters likely, in part, explain the therapeutic issue found with nearly all currently available analgesics (they work either fairly well or not at all in a given individual). Twin studies suggest that approximately 50% of the risk of developing FM and related conditions such as IBS and headache is genetic and 50% environmental.¹⁵

The environmental factors that are most likely to trigger the development of FM are various types of “stressors,” typically that involve acute pain for at least a few weeks. Fibromyalgia or similar illnesses can be triggered by certain types of infections¹⁶ (eg, Epstein-Barr virus, Lyme disease, Q fever, and viral hepatitis), trauma¹⁷ (motor vehicle collisions), or deployment to war.¹⁸ Psychological stress is but one such stressor that can trigger this complex symptom.

Fibromyalgia is also commonly seen as a comorbidity in other chronic pain conditions such as osteoarthritis, rheumatoid arthritis, and lupus. Approximately 10% to 30% of individuals with these established rheumatic disorders meet criteria for FM.¹⁹ This phenomenon had previously been termed *secondary fibromyalgia*. However, a well-accepted term used for this phenomenon is *central sensitization*, which means that these individuals have centralized their pain or have central sensitization. This term is most appropriate when CNS factors likely play a prominent role in amplifying or magnifying pain as well as in leading to other comorbid somatic symptoms such as fatigue, memory problems, and sleep and mood disturbances.¹⁹ This term does not mean that ongoing peripheral nociceptive input does not

contribute to this individual's pain (ie, central and peripheral factors are better considered to be “additive” rather than mutually exclusive). The term *central sensitization* is sometimes also used to describe this phenomenon, but many believe that this particular term should be reserved for the original and specific spinal mechanism that was identified and called by this name, rather than the more general phenomenon we now believe can result via a multitude of different spinal and supraspinal mechanisms.^{11,20} Regardless of the semantic term used, it is becoming increasingly important to identify this phenomenon because emerging evidence suggests that therapies that work best for peripheral nociceptive pain (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], opioids, injections, and surgical procedures) are less likely to be effective in these individuals.¹¹

The physiological hallmark of centralized pain, central sensitization, or FM is augmented CNS pain processing. This was originally identified in FM by noting that these patients are diffusely tender to palpation. The scientific terms for this phenomenon are *diffuse hyperalgesia* and *allodynia*. In the absence of an identifiable diffuse peripheral inflammatory process involving body tissues, diffuse hyperalgesia and allodynia strongly suggests that the CNS (ie, spinal cord and brain) is somehow augmenting pain processing. In 1990 when the original criteria for FM were first published, the feature of diffuse tenderness was incorporated into the diagnostic criteria, which required that an individual had a certain number of tender points (≥ 11), in addition to chronic widespread pain, to qualify for this diagnosis.²¹ Subsequent studies using more sophisticated measures of experimental pain testing reported that individuals with FM are more tender throughout the body, not just in the 18 regions considered to be tender points.^{22,23}

These initial observations that individuals with FM were diffusely tender led to subsequent functional, chemical, and structural brain neuroimaging studies, which gave the best “objective” evidence that the pain in FM and related pain amplification syndrome is “real.”²⁴ These methods such as functional magnetic resonance imaging clearly demonstrate that when individuals with FM are given a mild pressure or heat stimulus that most individuals would feel as “touch” rather than “pain,” they experience

pain and similar brain activation patterns in brain areas involved in pain processing.^{25,26}

A more recent advance in the use of functional magnetic resonance imaging is to look at the extent brain regions are “connected” to each other, that is, simultaneously activated (or deactivated).²⁷ Studies have shown that individuals with FM have *increased* connectivity between brain regions involved in increasing pain transmission and *decreased* connectivity to key *antinociceptive* regions.²⁸⁻³¹

Other imaging techniques have been used to identify the neurotransmitter abnormalities that may be driving the pain amplification seen in FM and other chronic pain disorders. Together with previous studies that had examined levels of neurotransmitters in the cerebrospinal fluid, these neurotransmitter plus imaging studies give us an insight into likely pathogenic mechanisms in FM and centralized pain states. Figure 1 demonstrates the neurotransmitter systems that are generally believed to exert influences on CNS

pain processing and indicates that FM increases in neurotransmitters that augment pain or sensory perception (eg, glutamate or nerve growth factor) and decreases in neurotransmitters that generally inhibit pain or sensory processing (eg, serotonin, norepinephrine, or γ -aminobutyric acid). Adjacent to each neurotransmitter are the pharmacological therapies that are thought to be working via these mechanisms.

For example, Harris and colleagues have used proton spectroscopy to probe other neurotransmitters. Several groups have shown that brain concentrations of the body’s major excitatory neurotransmitter, glutamate, increase in pain-processing regions such as the insula in FM.³² Drugs such as pregabalin and gabapentin likely work in part in FM by reducing glutamatergic activity.³³ Conversely, proton spectroscopy has recently been used to demonstrate *low* levels of one of the body’s major inhibitory neurotransmitters, γ -aminobutyric acid.³⁴ This likely accounts for the efficacy of

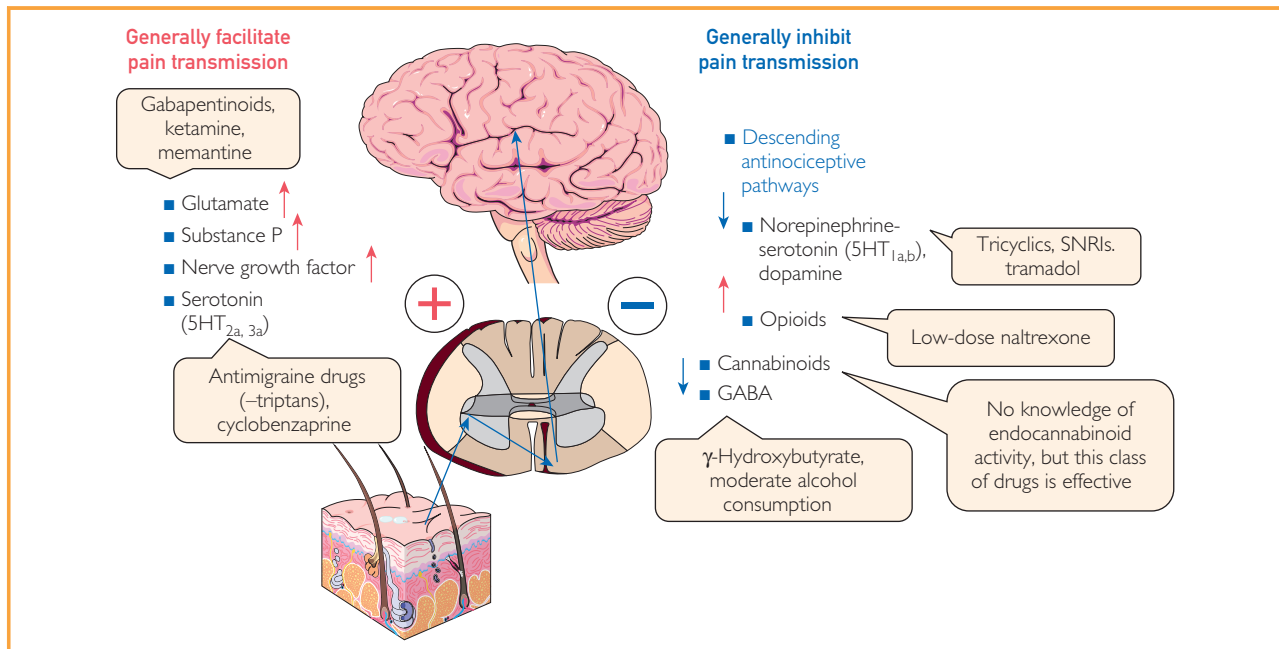


FIGURE 1. Central nervous system (CNS) neurotransmitters influencing pain. These neurotransmitters set the gain or volume control on the CNS pain processing. The CNS (spinal cord and brain) set the gain on pain processing and can act to either facilitate or inhibit pain transmission. The neurotransmitter systems on the left have a tendency to increase or facilitate pain transmission, whereas those on the right generally inhibit pain transmission. The arrows indicate the direction of the abnormality in levels of that neurotransmitter in fibromyalgia. Nearly all neurotransmitter systems that increase the gain are increased in fibromyalgia, whereas nearly all the systems that generally decrease the gain are decreased. The endogenous opioid system is the exception, with increases in endogenous opioid activity in fibromyalgia. This may be one reason why opioids appear to be less effective in fibromyalgia. Adjacent to each neurotransmitter are the drug classes that are effective in fibromyalgia and likely exert their effects at least in part via that neurotransmitter system. GABA = γ -aminobutyric acid; SNRI = serotonin norepinephrine reuptake inhibitor.

drugs such as γ -hydroxybutyrate, or even low doses of daily alcohol, in FM.^{35,36} These imbalances between excitatory and inhibitory neurotransmitters are not diffusely noted in brain structures and seem to be confined to brain regions that are known to be involved in pain or sensory processing, such as the insula,^{37,38} which is concordant with the notion that there is a global problem with sensory hyperresponsiveness that is partly responsible for the pathophysiology of FM and related conditions.^{39,40}

The same group has used positron emission tomography imaging to identify a neurotransmitter system that appears to be working paradoxically in FM: the endogenous opioid system. Although this system is generally thought to be antinociceptive, several studies suggest that endogenous opioid function might be increased in FM, with positron emission tomography showing evidence of decreased mu-opioid receptor availability in FM.^{41,42} The latter finding, as well as the results of previous studies showing increases in endogenous opioids in the cerebrospinal fluid of patients with FM, have been suggested as evidence of why opioid analgesics appear not to be efficacious in FM and why blocking endogenous opioid activity with low-dose naltrexone might be a promising therapy.⁴³

In addition to central neurotransmitter systems that are dysregulated in FM and play a role in pathogenesis, there are many other potential pathogenic mechanisms that are being actively explored. Both the hypothalamic-pituitary-adrenal and autonomic nervous systems have been shown to be abnormal in FM.⁴⁴⁻⁴⁶ However, these findings are inconsistent from study to study and may in part be driven by comorbidities common to FM such as inactivity, childhood trauma, and psychiatric disorders such as posttraumatic stress disorder and depression. Other theories regarding the pathogenesis of FM that are actively being pursued are the possible role of inflammation and/or glial cell activation,^{43,47} small fiber neuropathy,^{48,49} and viral reactivation in subsets of individuals.

Psychological, behavioral, and social issues can both contribute to the underlying pathogenesis of FM and complicate its treatment

Individuals with FM are more likely to have virtually any psychiatric disorder, including

depression, anxiety, obsessive-compulsive disorder, and posttraumatic stress disorder, likely because there are common triggers to both sets of conditions (eg, early life stress or trauma) as well as shared pathophysiology (ie, most of the neurotransmitters that affect pain transmission also affect mood, memory, fatigue, and sleep). Other potentially modifiable risk factors for developing FM include poor sleep, obesity, physical inactivity, and poor job or life satisfaction. Similarly, cognitive factors such as catastrophizing (the feeling that pain is bad and associated with a poor prognosis for recovery) or fear of movement have been shown to be poor prognostic factors in FM and other chronic pain states. Most of these issues are addressed as part of the cognitive behavioral therapy programs for FM and other chronic pain states that have been shown to be effective but are rarely used in clinical practice. Many individuals are seen in routine clinical practice with FM or FM-like syndromes who may respond well to these simple interventions (ie, reduce stress, get enough sleep, and become active and then begin exercising) and not need drug therapy.

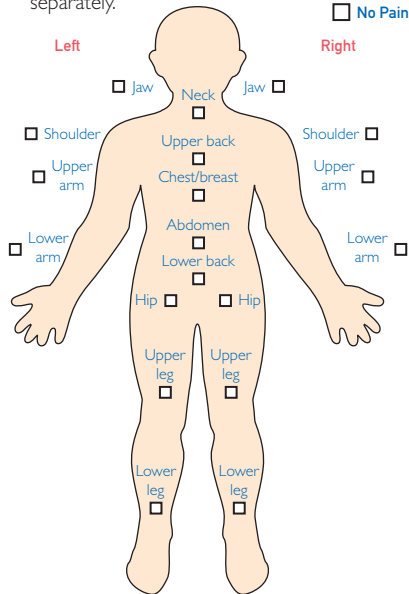
Diagnosis of FM

The original 1990 American College of Rheumatology criteria for FM were never intended to be used as strict diagnostic criteria for use in clinical practice. Many individuals who clearly have FM will not have pain throughout their entire body or may not have 11 tender points. Moreover, pain and tenderness occur across a continuum in the population, and it is impossible to know where to draw the line between an individual with symptoms and someone with an "illness."⁵⁰

For this and many other reasons, the alternative 2010 fibromyalgia criteria may represent a preferred manner of diagnosing, or thinking about, FM.⁵¹⁻⁵³ The survey criteria for FM are entirely self-reported by patients and can be administered on a single piece of paper. There is a body map with 19 areas (Figure 2) and a symptom survey that asks about the presence and severity of fatigue, sleep disturbances, memory difficulties, and mood problems. When used as a dichotomous measure with various cut points, this measure will roughly identify the same group of individuals as did the old criteria (except more men).^{52,53}

Fibromyalgia Symptoms (Modified ACR 2011 Fibromyalgia Diagnostic Criteria)

1. Please indicate below if you have had pain or tenderness over the past 7 days in each of the areas listed below. Check the boxes in the diagram below for each area in which you have had pain or tenderness. Be sure to mark right and left sides separately.



2. Using the following scale, indicate for each item your severity over the past week by checking the appropriate box.

No problem

Slight or mild problems: generally mild or intermittent

Moderate: considerable problems; often present and/or at a moderate level

Severe: continuous, life-disturbing problems

	No problem	Slight or mild	Moderate	Severe
a. Fatigue	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Trouble thinking or remembering	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Waking up tired (unrefreshed)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. During the past 6 months have you had any of the following symptoms?

	No	Yes
a. Pain or cramps in lower abdomen	<input type="checkbox"/>	<input type="checkbox"/>
b. Depression	<input type="checkbox"/>	<input type="checkbox"/>
c. Headache	<input type="checkbox"/>	<input type="checkbox"/>

4. Have the symptoms in questions 2-3 and pain been present at a similar level for at least 3 months? **No** **Yes**

5. Do you have a disorder that would otherwise explain the pain? **No** **Yes**

FIGURE 2. The 2011 survey criteria for fibromyalgia.⁵² These criteria were intended to be used in epidemiological studies, but can also be used in clinical settings to give clinicians a sense of where individuals fall on the fibromyalgia continuum. The instrument is scored by giving 1 point for each location checked on the body map (0-19), 0 to 3 points depending on the presence of fatigue, memory problems, and sleep disturbances (0-9), and 1 point each for irritable bowel, depression, and headache. Although specific cut points have been published regarding the total score that is generally indicative of fibromyalgia (12-13), it is more useful to consider this problem as a continuum rather than discrete illness and understand that in patients with chronic pain higher scores likely indicate that their pain will be less likely to respond to drugs and procedures that generally work well for nociceptive pain (surgery and opioids) and instead behave much more like fibromyalgia pain (ie, respond to centrally acting analgesics and nonpharmacological therapies). ACR = American College of Rheumatology.

However, when FM is considered more as a constellation of symptoms that helps determine where on the continuum of pain sensitivity an individual is, this survey can be used as a continuous measure (ie, degree of “fibromyalgia-ness” or the degree to which pain is centralized).⁵⁴

In clinical practice, one should suspect centralized pain or FM in individuals with multifocal pain that cannot be fully explained on the basis of damage or inflammation in those regions of the body. In most cases, musculoskeletal pain is the most prominent feature, but because pain pathways throughout the body are amplified, pain can occur anywhere. Thus, chronic headaches, visceral

pain, and symptoms of hyperresponsiveness to other sensory stimuli are common in individuals with FM.

Although the physical examination is generally unremarkable in individuals with FM, it is helpful to assess diffuse tenderness, and there are many ways that this can be done clinically other than performing a tender point count examination. For example, individuals with FM are more sensitive to the inflation of a blood pressure cuff.⁵⁵ Another way to assess the overall pain threshold is to perform a rapid examination of the hands and arms by applying firm pressure over several interphalangeal joints and adjacent phalanges and then caudally to include firm

TABLE 2. Nonpharmacological Therapies Useful in the Treatment of Fibromyalgia

Treatment	Cost	Specifics	Evidence level	Adverse effects	Clinical pearls
General recommendations					
Patient education ⁷⁸	Low	Incorporate principles of self-management including a multimodal approach	I, A		After the initial diagnosis, spend several visits (or use separate educational sessions) to explain the condition and set treatment expectations
Nonpharmacological therapies					
Graded exercise ⁷⁹	Low	Aerobic exercise has been shown to be the best, but strengthening and stretching have also been shown to be of value	I, A	Worsening of symptoms when the program begins too rapidly	Counsel patients to “start low, go slow” For many patients, focusing first on increasing daily “activity” is more helpful before actually starting exercise
Cognitive behavioral therapy (CBT) ⁸⁰	Low	Pain-based CBT programs have been shown to be effective in 1-on-1 settings, in small groups, and via the Internet	I, A	No significant adverse effects of CBT per se, but patient acceptance is often poor when they view this as a “psychological” intervention	Internet-based programs are gaining acceptance and are more convenient for working patients
Complementary and alternative medicine (CAM) therapies ⁸¹	Variable	Most CAM therapies have not been rigorously studied	I, A	Generally safe	There is emerging evidence that CAM treatments such as tai chi, yoga, balneotherapy, and acupuncture might be effective Allowing patients to choose which CAM therapies to incorporate into an active treatment program can increase self-efficacy
Central nervous system (CNS) neurostimulatory therapies ⁸²		Several types of CNS neurostimulatory therapies have been shown to be effective in fibromyalgia and other chronic pain states	Incon-sistent findings	Headache	These treatments continue to be refined as we learn about optimal stimulation targets, “dosing,” etc

palpation of the muscles of the forearm. If the individual is tender in many of these areas or just in the muscles of the forearm, the individual is likely diffusely tender (ie, have a low central pain threshold). However, if the individual is tender only in the interphalangeal joints and not the other regions, and especially if there is any swelling in these joints, one should be more concerned about a systemic autoimmune disorder leading to tenderness confined to inflamed joints.

Laboratory testing is generally not useful, except for the purpose of differential diagnosis. The intensity of the diagnostic work-up can be largely guided by the duration of time the patient has had symptoms. Individuals with long-standing symptoms and a

lifetime history of regional pain and other somatic symptoms need little testing, whereas those with acute or subacute onset of those symptoms require a much more aggressive work-up. Simple testing should be limited to complete blood cell count and routine serum chemistries, along with thyroid-stimulating hormone and erythrocyte sedimentation rate and/or C-reactive protein. Serological tests such as antinuclear antibody and rheumatoid factor assays should generally be avoided unless there are features not seen in FM.

Once a clinician rules out other potential disorders that might be causing the pain and treats potential peripheral causes of the pain, an important and at times controversial consideration to make is whether it is of

TABLE 3. Pharmacological Therapies Useful in the Treatment of Fibromyalgia

Treatment	Cost	Specifics	Evidence level	Adverse effects	Clinical pearls
Pharmacological therapies		Pharmacological therapy is best chosen on the basis of the predominant symptoms and initiated in low dose with slow dose escalation	Level 5, consensus		Some practitioners find that getting patients on a drug regimen that helps improve symptoms before initiating nonpharmacological therapies can help improve adherence
Tricyclic compounds ^{69,83}		Amitriptyline, 10-70 mg every night at bedtime Cyclobenzaprine, 5-20 mg every night at bedtime	I, A	Dry mouth, weight gain, constipation, and "groggy" or drugged feeling	When effective, they can improve a wide range of symptoms including pain, sleep, and bowel and bladder syndromes Taking these drugs several hours before bedtime improves the adverse effect profile
Serotonin norepinephrine reuptake inhibitors ⁶⁹	Duloxetine is generic, but milnacipran is not	Duloxetine, 30-120 mg/d Milnacipran, 100-200 mg/d	I, A	Nausea, palpitations, headache, fatigue, tachycardia, and hypertension	Warning patients about transient nausea, taking with food, and slowly increasing dose can increase tolerability Milnacipran might be slightly more noradrenergic than duloxetine and thus potentially more helpful for fatigue and memory problems, but also more likely to cause hypertension
Gabapentinoids ⁸⁴	Gabapentin is generic, but pregabalin is not	Gabapentin, 800-2400 mg/d in divided doses Pregabalin, up to 600 mg/d in divided doses	I, A	Sedation, weight gain, and dizziness	Giving most or all of the dose at bedtime can increase tolerability
γ -Hydroxybutyrate ³⁵	Available for treating narcolepsy and cataplexy	4.5-6.0 g every night in divided doses	I, A	Sedation, respiratory depression, and death	Shown to be efficacious but not approved by the US Food and Drug Administration because of safety concerns
Low-dose naltrexone ⁸⁵	Low	4.5 mg/d	2 small single-center randomized controlled trials		
Cannabinoids ⁸⁶	Not applicable	Nabilone, 0.5 mg poqhs to 1.0 mg bid	I, A	Sedation, dizziness, and dry mouth	No synthetic cannabinoid is approved in the United States for the treatment of pain
Selective serotonin reuptake inhibitors (SSRIs) ⁶⁹	SSRIs that should be used in fibromyalgia (see Pearls) are all generic	Fluoxetine, sertraline, and paroxetine	I, A	Nausea, sexual dysfunction, weight gain, and sleep disturbance	Older, less selective SSRIs may have some efficacy in improving pain, especially at higher doses that have more prominent noradrenergic effects Newer-SSRIs (citalopram, escitalopran, and desvenlafaxine) are less effective or ineffective as analgesics
Nonsteroidal anti-inflammatory drugs		No evidence of efficacy Can be helpful to treat comorbid "peripheral pain generators"	5, D	Gastrointestinal, renal, and cardiac adverse effects	Use the lowest dose for the shortest period of time to reduce adverse effects
Opioids		Tramadol with or without acetaminophen, 50-100 mg every 6 h No evidence of efficacy for stronger opioids	5, D	Sedation, addiction, tolerance, and opioid-induced hyperalgesia	There is increasing evidence that opioids are less effective in treating chronic pain than previously thought and that their risk-benefit profile is worse than that of other classes of analgesics

bid = twice daily; poqhs = at bedtime.

benefit to use the FM “label.” Despite editorials bemoaning that this label is typically harmful and will increase health care utilization,⁵⁶ this is not borne out of the existing evidence. The diagnosis of FM is often a tremendous source of relief for patients because they have often visited many providers before this diagnosis is made and there is an explanation for their symptoms. Several studies have shown that the diagnosis can lead to *decreased* health care utilization because of a reduction in referrals and diagnostic testing “looking for the cause of the pain.”⁵⁷

General treatment approach

The best treatment of FM involves an integrated pharmacological and nonpharmacological approach in which patients play an active role in their treatment. Fibromyalgia should generally be diagnosed and treated in a primary care setting, with referral only for individuals in whom the diagnosis is in question (eg, to rheumatology or neurology, depending on symptoms) or for patients refractory to therapy (eg, to multidisciplinary pain clinics) or with significant comorbid psychiatric issues (eg, to psychiatrist or psychologists). Creating a team of providers (either in the same setting or “virtually”) that includes individuals who can help provide education (eg, mid-level providers or nurse educators) as well as exercise (eg, physical or occupational therapists) and cognitive behavioral treatments can be extremely beneficial to both patients and providers.

The evidence for various treatments in FM has recently been comprehensively reviewed by the group publishing the Canadian Fibromyalgia Treatment Guidelines,⁵⁸ and this group’s assessment of level of evidence for each therapy is used in this review. These treatments are summarized in [Tables 2](#) (nonpharmacological therapies) and [3](#) (pharmacological therapies).

Nonpharmacological therapies. The 3 best-studied nonpharmacological therapies are education, cognitive behavioral therapy, and exercise, and all these have strong evidence (level I, A) for use in FM. In fact, the effect size of these therapies often exceeds that of drug therapies, especially for improving function, which should be the therapeutic focus in treating chronic pain.^{59,60} Another advantage of these treatments is that they can lead to sustained (eg,

>1 year) improvements. Access and adherence are the biggest issues with these therapies. These types of nonpharmacological approaches are increasingly available via websites (eg, www.fibroguide.com⁶¹) and smartphone apps to increase patient accessibility.

Complementary and alternative therapies can be a useful adjunct in the treatment of FM. As in other disorders, there are relatively few controlled trials to advocate their general use. Trigger point injections, chiropractic manipulation, tai chi, yoga, acupuncture, and myofascial release therapy all have some evidence of efficacy and are among the more commonly used modalities.⁶² There is also some evidence that the use of such alternative therapies gives patients a greater sense of control over their illness and that giving patients a choice of therapies might make it more likely that improvement via the body’s internal analgesic mechanisms (ie, the placebo response) is engendered. Thus, even in the absence of strong evidence of efficacy for all such therapies, as long as the treatment does no harm, the threshold for recommending such therapies should be low because overall treatment options for chronic pain are limited.

Although FM is still generally thought not to be due to peripheral damage or inflammation, there is emerging evidence that identifying and treating peripheral pain generators may be helpful, perhaps because peripheral nociceptive input is known to drive central sensitization. Thus, a recent study reported that individuals with FM with comorbid osteoarthritis or myofascial pain had improvement in their overall FM pain and tenderness when these were treated with local therapies.^{63,64} There is also emerging evidence that some individuals with FM exhibit a small fiber neuropathy on biopsy,⁶⁵ although the treatment implications of this finding are still not clear.

Various neurostimulatory therapies can be effective in treating musculoskeletal pain. For some time, transcutaneous electrical nerve stimulation has been used to treat peripheral musculoskeletal pain, but a new set of therapies is being developed to stimulate the CNS, and these are beginning to show promise in treating centralized pain states such as FM.^{66,67}

Pharmacological therapies. Several drugs or classes of drugs have strong evidence (level I, A)

for efficacy in FM,⁶⁸ including tricyclic compounds⁶⁹ (amitriptyline and cyclobenzaprine), gabapentinoids⁷⁰ (pregabalin and gabapentin), serotonin-norepinephrine reuptake inhibitors (duloxetine⁷¹ and milnacipran⁷²), and γ -hydroxybutyrate.³⁵ Drugs with more limited evidence of efficacy include older selective serotonin reuptake inhibitors with greater noradrenergic activity when used at higher doses (eg, fluoxetine,⁷³ paroxetine, and sertraline), low-dose naltrexone,⁴³ esreboxetine⁷⁴ (a selective norepinephrine reuptake inhibitor not available in the United States), cannabinoids, and memantine.^{75,76} Just as with treating most other chronic illnesses of a complex polygenic nature, it is often necessary to use several of these drugs with different action mechanisms in combination.

Of note are the classes of drugs that have not been found to be efficacious in FM, such as NSAIDs, opioids, and corticosteroids, because these are the mainstay of therapy in other peripheral pain states. Although there is a sense in clinical practice that the “FM drugs” do not work as well for these patients as other classes of analgesics work for other types of pain, this is simply not true. All oral analgesics are at best modestly effective in treating any type of chronic pain (ie, work well in a third of patients), including NSAIDs and opioids.⁷⁷ In fact, there is emerging concern that opioids might even be in part driving the hyperalgesia seen in FM and other centralized pain states or frequently leading to opioid-induced hyperalgesia.

CONCLUSION

Many, if not most, in the pain field now believe that FM is the prototypical centralized pain state. This can occur either in the absence of damage or inflammation of tissues or in a subset of individuals with any chronic pain condition. In the former instance, individuals will typically begin having pain in various regions of the body early in life, and then when the pain finally becomes widespread later in life, it is termed fibromyalgia. Conversely, in individuals with diseases known to be associated with damage or inflammation (eg, autoimmune disorders) or damage (eg, osteoarthritis), the same phenomenon can occur and seems to be driven by ongoing peripheral nociceptive input. If this is true, we might be able to “prevent” FM by identifying individuals with this centralized pain prone phenotype and

treating them aggressively when they have acute or subacute pain due to peripheral nociceptive input so that it does not centralize and becomes chronic. Once pain centralization occurs, regardless of the underlying “disease” that might have originally led to pain, it is likely to respond to the same types of treatments as FM. Most importantly, once centralization/FM occurs, these individuals will be less responsive to our mainstays of treating ongoing peripheral nociceptive pain (eg, opioids, injections, and surgical procedures) and more responsive to centrally acting analgesic and nondrug therapies.

Abbreviations and Acronyms: CNS = central nervous system; FM = fibromyalgia; IBS = irritable bowel syndrome; NSAID = nonsteroidal anti-inflammatory drug; TMJD = temporomandibular joint disorder

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Correspondence: Address to Daniel Clauw, MD, The University of Michigan, 24 Frank Lloyd Wright Dr, PO Box 385, Ann Arbor, MI 48105 (dclauw@med.umich.edu). Individual reprints of this article and a bound reprint of the entire Symposium on Pain Medicine will be available for purchase from our website www.mayoclinicproceedings.org.

The Symposium on Pain Medicine will continue in an upcoming issue.

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