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Practical Strategies for Improving the Diagnosis and Treatment of Fibromyalgia CME

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Goal
The goal of this activity is improve the recognition, diagnosis, and treatment of fibromyalgia.

Learning Objectives
Upon completion of this activity, participants will demonstrate the ability to:

1. Describe data on the latest concepts of the pathophysiologic underpinnings of fibromyalgia and the role of neuronal mechanisms
2. Apply knowledge of current diagnostic criteria to diagnose patients with fibromyalgia
3. Describe evidence-based data on the use of pharmacologic and nonpharmacologic treatment approaches for fibromyalgia

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Exploring the Pathophysiology of Fibromyalgia CME

Richard H. Gracely, PhD; Kirsten R. Ambrose, MS

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Fibromyalgia (FM) is characterized by an unusual distribution of chronic widespread pain. Other common clinical features of this disorder include morning stiffness, sleep disturbance, and cognitive difficulty, and comorbidid conditions such as headaches, irritable bowel syndrome, vulvodynia, temporomandibular disorder, and other related illnesses. What makes fibromyalgia complex is that afflicted persons are often hypersensitive to a number of painful and nonpainful stimulus modalities and show altered physiological responses to painful stimulation at spinal and supraspinal levels. Altered, higher levels of central nervous system (CNS) pain processing, such as temporal summation and descending inhibition, are also observed.

Despite an increasing number of studies on fibromyalgia, the mechanisms responsible for the widespread pain and other symptoms and comorbidities are poorly understood. What is understood is that mechanisms associated with fibromyalgia can be categorized into factors that predispose individuals, precipitate onset, and perpetuate symptoms.[1]

Accumulating evidence suggests that genetic and environmental factors combine to predispose individuals to develop fibromyalgia. The strongest evidence is provided by observations of familial associations that reflect both environmental and genetic factors.[2-3] Environmental insults, ranging from prebirth trauma to childhood physical or sexual abuse, may predispose individuals to FM and also serve as precipitating events. Genetic analyses have identified polymorphisms in genes involved in systems regulating serotonin, dopamine, catecholamines, apolipoprotein. and β2-adrenergic receptors.[4-12] Evidence from the related comorbid temporomandibular disorder (TMD) suggests that a haplotype in the gene encoding catechol- O-methyltransferase governs predisposition to develop TMD and influences response to treatment.[13-14] This haplotype may be associated also with fibromyalgia, although an association in relatively homogenous Spanish patients is countered by negative evidence in Mexican, British, and European populations.[15-16]

Once predisposed, fibromyalgia may be precipitated by events such as abuse, injury from motor vehicle accidents, illness including autoimmune disorders, infections, surgical procedures, and psychological stressors.[1,17-21] These events trigger processes that ultimately result in the persistent symptoms of pain and sensitivity to stimulation and physical, cognitive, and sleep dysfunction.

What processes mediate the symptoms of fibromyalgia? The finding of deep, widespread, ongoing pain and tenderness, which was emphasized in the 1990 American College of Rheumatology (ACR) criteria for the classification of fibromyalgia,[22] lead to significant tissue-oriented research involving muscle, primarily. Indeed, the "myalgia" in fibromyalgia implies muscle pathology. This focus on muscle is still actively pursued: a PUBMED search of the terms "fibromyalgia and muscle" yielded 786 publications as of March 2012.

The 1990 ACR criteria required the presence of both chronic widespread pain and tenderness, the latter assessed by the tender point count defined as the number of 18 predefined sites at which 4 kg of manual thumb pressure evokes a painful sensation. Wolfe,[23] an author of the 1990 ACR criteria, later considered that the tender point count was not a pure measure of tenderness and the examination measured a mixture of tenderness and distress. In fact, Petzke and colleagues[24] subsequently demonstrated that the tender point count was significantly associated with distress while a more sophisticated laboratory method provided a relatively pure measure of tenderness. One interesting feature of the laboratory method is that it used discrete, suprathreshold blunt pressure applied to the thumbnail bed -- a site that is devoid of muscle yet is sensitive in fibromyalgia subjects compared with control subjects.[25-26] This evidence not only helped validate the difference in pain perception between patients with fibromyalgia and healthy people, but also contributed to the growing literature that focused attention away from mechanisms of muscle pain to CNS pain processing. For example, patients with fibromyalgia are also sensitive to heat applied to the skin and to other painful modalities such as cold, electrical stimulation, and injection of hypertonic saline.[25,27-30] These findings suggest a generalized augmentation of pain sensitivity that extends beyond muscle and, has also been demonstrated for other conditions such as idiopathic low back pain[31] and vulvodynia.[32]

From Receptor to Spinal Cord

Out of this evolutionary shift from peripheral to central mechanisms emerged research exploring modalities and concepts that yielded additional evidence for CNS involvement. Several studies have used electrical stimulation of the sural nerve at the ankle to assess the nociceptive flexion reflex at the biceps femoris. The amount of electrical current needed to elicit this reflex (and the amount needed to evoke a painful sensation) was significantly lower in patients with fibromyalgia, indicating increased subjective and physiological sensitivity.[33-34] In a recent treatment trial of cognitive behavior therapy (CBT) for fibromyalgia, the amount of current needed to elicit the nociceptive reflex was higher in the CBT group in comparison with the usual care group.[35] A further analysis of data from this study found that this reflex sensitivity was associated with the magnitude of the current clinical pain in nondepressed patients but not in patients that were depressed.[36]

One interesting feature of electrical stimulation is that it bypasses the receptor to activate the primary afferent axon. Thus, the sensitivity to this stimulation is presumed to be unaffected by processes that increase the sensitivity of the pain receptor. The results from these studies that used electrical stimulation suggest that the increased sensitivity to painful stimulation observed in patients with fibromyalgia can be observed at the level of the spinal cord, a region involved in considerable modulation of sensory input. At first glance, it is not likely that the peripheral sensitization of pain receptors is the cause of increased pain sensitivity.

One important spinal mechanism to note is the process of central sensitization (CS) in which persistent, focal input from pain signaling through primary afferent pathways activates a process that results in the spread of perceived pain from adjacent, normal tissue. This normal physiological effect can be observed after an injury or a simulated injury. For example, after an injection of capsaicin, the active ingredient in chili pepper, the injury (injection) causes intense spontaneous pain that extends well beyond the site of the injection. There is also a broad area of mechanical allodynia, whereby light brushing of the skin evokes a burning sensation similar to sunburn. There is an even broader region of increased pain sensitivity to pin prick. These effects cross skin dermatomes such that an injury in the territory of 1 peripheral nerve can affect the territory of a different peripheral nerve.[37-39]

The concept of central sensitization still dominates the pain literature and is perhaps inappropriately applied to fibromyalgia. After the discovery of innate analgesic mechanisms that reduce pain, the discovery of CS revealed an innate mechanism that exacerbates pain. The term CS was quickly applied to the increased pain sensitivity observed in fibromyalgia and is often used in discussions of the mechanism responsible for widespread pain and increased sensitivity to stimulation by pressure, heat, or electrical stimulation. This use of the term is inappropriate since few of the features that characterize CS are found in fibromyalgia. There are no prominent symptoms of brushing allodynia or pinprick hyperalgesia. In addition, a recent study found no evidence for the pharmacological modulation of the presumed N-methyl-d-aspartate (NMDA) mechanisms of CS in fibromyalgia.[40]

While CS may not be at play in fibromyalgia, there is clearly a heightened, centrally-mediated sensitivity to pain with mechanisms that are still not fully understood. In addition, patients with fibromyalgia experience sensory symptoms beyond pain, for example increased sensitivity to olfactory and auditory sensations that cannot be explained by spinal pain processing, which thus leads our focus to the brain.[41]

The Brain

The advent of modern neuroimaging methods has led to a plethora of studies of brain processes in health and disease. The first brain imaging studies of fibromyalgia were performed in patients at rest and more recent studies have found differences compared with control subjects in brain structure at macroscopic (voxel-based morphometry) and microscopic (diffusion tensor imaging) levels, in neurochemical concentrations (magnetic resonance imaging, positron emission tomography, and ligand binding assay) and in functional brain networks.[42-53] Another group of brain imaging studies of fibromyalgia evaluated the magnitude of the brain's response to evoked pressure or heat pain stimuli. These studies have demonstrated an increased pain sensitivity and possible modulation of brain activity by factors such as depression and catastrophizing.[26,29,54-55] These differences observed in subjects at rest and in response to stimulation provide accumulating evidence for altered neural processing in fibromyalgia.

Descending From the Brain

In addition to the findings in brain and spinal cord, a series of studies have shown that patients with fibromyalgia also show attenuated conditioned pain modulation (CPM), which is the reduction in evoked pain provoked by intense pain from a second source.[56-59] This effect has been shown to result from neural activity that descends from the brain to inhibit pain at the spinal level. The absence of CPM in fibromyalgia suggests that the pain augmentation may result from a loss of tonic inhibition. In other words,

we would all feel the pain of fibromyalgia if not for constant levels of descending pain inhibition. This hypothesis is attractive since certain types of CPM cause widespread analgesia, and the absence of CPM, hence widespread analgesia, could account for the unusual distribution of widespread pain.

There is also an alternative explanation of a saturation effect.[41,60] In this explanation, the widespread pain of fibromyalgia is the second source of pain that provokes CPM. If CPM is already turned on from an initial source, it cannot be turned on further by fibromyalgia pain. From a research perspective, CPM cannot be demonstrated using an evoked pain stimulus if it is already maximally activated. This is a novel hypothesis that approaches CPM from the other end of the spectrum; but it needs further exploration.

The Locus of Effect May not Be the Locus of Pathology

Do the differences in spinal reflexes indicate a spinal mechanism? Do the multiple findings from brain imaging indicate a problem in the brain? Unfortunately, these results do not localize the pathology, but merely indicate altered processing somewhere in the system. Effects at the spinal level may result from peripheral processes, from spinal mechanisms, or from effects of descending modulation (both inhibition and facilitation). Similarly, the supraspinal effects observed by brain imaging could be caused by altered processing at any point in the nervous system. It is a mistake to immediately assume that fibromyalgia is due to altered brain processing. This alteration may be in response to fibromyalgia and/or reflect processes at the peripheral or spinal level. And so, the evolution continues from peripheral to central mechanisms to the current consideration that both are integrally involved.

Fibromyalgia Comorbidities: Central Sensitivity Syndromes

Muhammad B. Yunus, MD[61-62] includes fibromyalgia and comorbid conditions, such as, chronic fatigue syndrome, irritable bowel disease, migraine, temporomandibular disorders, multiple chemical sensitivities, and interstitial cystitis, in a family of central sensitivity syndromes (CSS) that share features of a lack of a known structural pathology and the presence of pain augmentation, which he also refers to as "central sensitization." As we emphasize above, central sensitization in this context differs from the original use of the term to describe a spinally-mediated effect. We and other investigators in the field prefer a different term, such as pain augmentation but, ultimately, this is a matter of semantics. The main feature of the CSS concept is that this group of disorders share common features and, likely, common pathophysiological mechanisms that predispose, precipitate, and perpetuate ongoing and evoked symptoms. It also recognizes the important contributions of psychosocial factors to symptom expression. This familial view of these disorders is shared among many investigators in the field. Our group is involved in a project applying the same phenotyping/genotyping profiling to healthy control subjects and to patients with fibromyalgia, migraine, temporomandibular disorders, irritable bowel syndrome, and vulvodynia.

Fibromyalgia has often been linked to depression, which has led to support of the concept that fibromyalgia is part of a different family of "affective spectrum disorders."[17,63-64] These disorders share a number of common features; however, there is considerable evidence that fibromyalgia is a somatic condition with subgroups of patients that are also psychologically distressed.[1,55,65-70] For example, antidepressants are effective in some patients with fibromyalgia, but the effects occur at different dosages and with different time courses in fibromyalgia and depression, and are found in patients with fibromyalgia who are not depressed.[1]

Conclusion

Environmental and genetic factors predispose individuals to develop fibromyalgia, usually after a precipitating event such as injury or acute stress. The symptoms of widespread pain, sensitivity to painful and nonpainful stimulation, cognitive difficulties, and disturbed sleep are shared with other comorbid syndromes. There is an increasing recognition that these syndromes may share common mediating mechanisms. As we learn more about these poorly understood and treated disorders, new therapies will likely provide relief for patients with fibromyalgia and, also, these comorbid conditions.

Thank you for participating in the CME activity. Please take a few moments to read and complete the questions that follow to help us assess the effectiveness of this medical education activity.

Which of the following is included in the 1990 American College of Rheumatology (ACR) criteria for diagnosis of fibromyalgia (FM) but is not required in the 2010 ACR proposed clinical case definition?

- Assessment of tender points by physical examination
- Assessment of patient report of body parts with pain
- Assessment of severity of fatigue
- Assessment of severity of cognitive dysfunction

According to the 2010 ACR diagnostic criteria, which of the following somatic symptoms may be considered in the assessment of FM?

- Chest pain and joint swelling
- Constipation and morning stiffness
- Headaches and chest pain
- Headaches and joint swelling

Which of the following has been shown in studies to precipitate fibromyalgia in predisposed individuals?

- Coronary artery disease
- Motor vehicle accident injury
- Cigarette smoking
- High fat diet

Newer hypotheses about the pathophysiology of FM focus on which of the following as being a mechanism mediating the symptoms of FM?

- Systemic inflammation
- Injury to joints
- Injury to muscles
- Altered central nervous system (CNS) pain processing

You are seeing a 52-year-old woman whom you have given a diagnosis of fibromyalgia. You had previously started her on amitriptyline, 10 mg at night, which she feels is helping her with her sleep. However, she now has significant anhedonia in addition to chronic widespread pain and unrefreshing sleep. She complains that she cannot get out of bed in the morning because she says she "has nothing to look forward to." Besides screening her for depression, which of the following would you add to her current medication regimen?

- Corticosteroids
- Cyclobenzaprine
- Serotonin and norepinephrine reuptake inhibitor (SNRI)
- Opioid

- In 2010 the ACR accepted a clinical case definition that did not include a physical or tender point examination, but required that other disorders that would otherwise explain the patient's pain be ruled out.

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ACR = American College of Rheumatology
BMI = body mass index
CBT = cognitive behavioral therapy
CNS = central nervous system
CPK = creatine phosphokinase
CPM = conditioned pain modulation
CRP = C-reactive protein
CS = central sensitization
CSS = central sensitivity syndrome
DAS = Disease Activity Score
ESR = erythrocyte sedimentation rate
FM = fibromyalgia
FDA = Food and Drug Administration
IP =proximal interphalangeal joint
NMDA = N-methyl-d-aspartate
NSAIDS = nonsteroidal anti-inflammatory drugs
RA = rheumatoid arthritis
SLE = systemic lupus erythematosus
SNRI = serotonin and norepinephrine reuptake inhibitor
SS = Symptom Severity scale
SSRI = selective serotonin reuptake inhibitor
TMD = temporomandibular disorder
TSH =Thyroid stimulating hormone
ULN = upper limit of normal
WPI = Widespread Pain Index

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Enhancing the Diagnosis and Assessment of Fibromyalgia CME

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Fibromyalgia (FM) is a common chronic widespread pain disorder that has a worldwide prevalence of between 0.5% and 5%.[1-2] Although common, fibromyalgia may be difficult to diagnose. In a study by Choy and colleagues, patients with fibromyalgia reported that it took an average of 2.3 years and assessment by an average of 3.7 physicians before they received a diagnosis of fibromyalgia.[3] Patients with fibromyalgia are often referred to multiple specialists and undergo several investigations before a diagnosis of fibromyalgia is established.[3,4]

Because of the growing number of patients requesting an evaluation for fibromyalgia, it has become important to develop strategies to help clinicians identify fibromyalgia and commonly associated conditions and to differentiate fibromyalgia from other chronic pain disorders. The goal is to identify fibromyalgia and initiate treatment as early as possible, even if further evaluation is needed to diagnose comorbidities that may also require management. Early identification and treatment of fibromyalgia may help prevent the potentially debilitating effects of the disorder.[4-5]

Diagnostic Criteria for Fibromyalgia

The establishment of the 1990 American College of Rheumatology (ACR) criteria for the classification of fibromyalgia helped to increase the recognition of the disorder and stimulate research.[6] The ACR criteria required at least 3 months of widespread pain defined as axial pain and pain above and below the waist and on the right and left sides of the body. In addition, the criteria required pain in 11 of 18 tender point sites determined by digital palpation with an approximate force of 4 kg, which usually results in a whitening of the examiner's nail bed. Although the ACR criteria made no exclusions for the presence of concomitant radiographic or laboratory abnormalities, it was implicit that clinical examination and judgment be used to exclude other causes of chronic widespread pain.

In 2010, the ACR accepted a clinical case definition that did not include a physical or tender point examination, but required that other disorders that would otherwise explain the pain be ruled out.[7] The proposed criteria take into account other fibromyalgia symptoms besides pain and are intended to also assess fibromyalgia symptom-related severity (Table 1).[7]

Table 1. 2010 ACR Diagnostic Criteria for FM[a]

Criteria			
A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met:			
1. Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5 or WPI 3-6 and SS scale score ≥9.			
2. Symptoms have been present at a similar level for at least 3 months.			
3. The patient does not have a disorder that would otherwise explain the pain.			
Ascertainment			
1. WPI: Note the number areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19.			
Shoulder girdle, left	Lower arm, right	Lower leg, left	Abdomen
Shoulder girdle, right	Hip (buttock, trochanter), left	Lower leg, right	Upper back
Upper arm, left	Hip (buttock, trochanter), right	Jaw, left	Lower back
Upper arm, right	Upper leg, left	Jaw, right	Neck
Lower arm, left	Upper leg, right	Chest	
2. SS scale score:			
Fatigue	Waking unrefreshed	Cognitive symptoms	
For the each of the 3 symptoms above, indicate the level of severity over the past week using the following scale:			
0 = no problem	1 = slight or mild problems, generally mild or intermittent	2 = moderate, considerable problems, often present and /or at a moderate level	3 = severe: pervasive, continuous, life-disturbing problems
Considering somatic symptoms in general, indicate whether the patient has [b]:			
0 = no symptoms	1 = few symptoms	2 = a moderate number of symptoms	3 = a great deal of symptoms
The SS scale score is the sum of the severity of the 3 symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score is between 0 and 12.			

[a] From Wolfe F, MA, et al. *Arthritis Care Res (Hoboken)*. 2010;62:600-610. Republished with permission.
[b]Somatic symptoms that might be considered: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.

To administer the Widespread Pain Index (WPI) and Symptom Severity (SS) scale, the patient reports the location of pain over the prior week at 19 sites including areas of the shoulders, arms, hips, legs, jaws, chest, abdomen, back and neck. The SS scale focuses on 3 physical symptoms, as well as somatic symptoms in general. Fatigue, waking unrefreshed, and cognitive symptoms are rated based on the level of severity over the prior week.

Notably, neither the 1990 nor the 2010 ACR revised criteria provide guidance about which painful conditions to rule out or the tests to perform to rule them out. This column discusses an approach to the diagnosis of fibromyalgia that includes the collection of pertinent information from the patient history, and physical examination to identify fibromyalgia and differentiate it from other painful conditions.[8]

An Approach to Diagnosing Fibromyalgia

The patient history. Fibromyalgia is a diagnosis that is based on the disorder's clinical characteristics and is not solely a diagnosis of exclusion. The primary, hallmark symptom of fibromyalgia is chronic widespread pain of long duration greater than or equal to 3 months. The pain associated with fibromyalgia can wax and wane, and vary in intensity from day to day and by physical location. Other key symptoms suggestive of fibromyalgia along with chronic widespread pain include fatigue and sleep disturbance.[8] Other commonly associated symptoms include tenderness, stiffness, mood disturbances (eg depression and/or anxiety) and cognitive difficulties (eg, trouble concentrating, forgetfulness, and disorganized thinking).[9] Patients with fibromyalgia frequently report impairment in multiple areas of function, especially physical function.[5]

The presence of common comorbidities associated with fibromyalgia can also help identify patients with fibromyalgia. The lifetime prevalence of mood or anxiety disorders with fibromyalgia is high, with 1 study reporting anxiety disorders in 56%, major depressive disorder in 62%, and bipolar disorder in 11% of patients with fibromyalgia.[10] Underlying pathophysiologic abnormalities common to mood and anxiety disorders and fibromyalgia may account for the high level of co-occurrence of these disorders.[10]

Other common comorbid disorders in patients with fibromyalgia include regional pain syndromes that may have overlapping pathophysiologic features with fibromyalgia, such as irritable bowel syndrome, headache/migraine, interstitial cystitis, prostadynia, temporomandibular disorder, chronic pelvic pain, and others.[11] If a patient presents with 1 of these disorders, it is important to ask the patient whether the pain is limited to a region of the body or if it is more widespread, which suggests the presence of comorbid fibromyalgia.

There are risk factors for fibromyalgia that should be considered when evaluating the patient's history. Evidence suggests that fibromyalgia is familial, which is likely due to both genetic and environmental factors.[12]

The physical examination The diagnostic evaluation of fibromyalgia includes a physical examination for diffuse tenderness which is typically accomplished with the ACR tender point examination in the clinic. The physical examination also aids in the differential diagnosis of fibromyalgia by identifying associated or comorbid disorders.[8,18] The differential diagnostic examination may involve a joint examination to assess for signs of inflammation, such as swelling, tenderness, redness, and heat, as well as an assessment of range of motion and presence of crepitus. A neurological examination based on the patient's symptoms may include an evaluation for numbness, objective weakness, or other signs of neuropathy. If the history is suggestive, the physical examination may contain an evaluation for signs of connective tissue disease such as rash, skin ulcers, and alopecia or signs of other disorders such as an infectious etiology or other medical disorders.[8,18]

Laboratory testing A diagnosis of fibromyalgia can be made based on the history and physical examination with the selective use of laboratory testing to evaluate for other possible causes of the patient's symptoms. These tests include erythrocyte edimentation rate (ESR) and/or C-reactive protein (CRP), complete blood cell, comprehensive metabolic panel, and thyroid function tests. Routine testing for rheumatoid factor and/or antinuclear antibodies is not recommended unless the patient has signs or symptoms suggesting an autoimmune disorder, or if initial inflammatory indices (ie, ESR and/or CRP) are abnormal (with the recognition that some patients with RA or SLE may have normal inflammatory indices).Depending on history and physical examination, other tests may be indicated, such as ferritin, iron-binding capacity and percentage of saturation, vitamin B12, and vitamin D levels.[8,19]

Diagnostic Screening Tool for Fibromyalgia

To address the need for a valid and easy tool to help clinicians identify fibromyalgia and commonly associated conditions, Arnold and colleagues developed a diagnostic screening tool (Fibromyalgia Diagnostic Screen) for use in primary care settings to improve the assessment of patients with fibromyalgia. This screening tool was found to accurately screen for fibromyalgia in patients who present with pain duration greater than 30 days. The Fibromyalgia Diagnostic Screen was designed to guide clinicians in the differential diagnosis of fibromyalgia, focusing on the more common medical disorders that may present with symptoms that overlap with fibromyalgia.[19]

The Fibromyalgia Diagnostic Screen includes a patient self-reported questionnaire and an abbreviated physical examination with targeted laboratory tests to assist in evaluating the differential diagnosis of fibromyalgia (Table 2).[19]

Table 2. Fibromyalgia Diagnostic Screen -- Patient[a,b]

1. Pain location: Check the box next to EACH OF THE PLACES that best matches your experience with PAIN in these locations DURING THE PAST WEEK:

	0 None	1 Mild	2 Moderate	3 Severe	4 Very Severe
Area 1					
Low back	☐	☐	☐	☐	☐
Neck	☐	☐	☐	☐	☐
Upper back	☐	☐	☐	☐	☐
Chest	☐	☐	☐	☐	☐
Area 2					
Right shoulder	☐	☐	☐	☐	☐
Right upper arm	☐	☐	☐	☐	☐
Right lower arm	☐	☐	☐	☐	☐
Area 3					
Right hip	☐	☐	☐	☐	☐
Right upper leg	☐	☐	☐	☐	☐
Right lower leg	☐	☐	☐	☐	☐
Area 4					
Left shoulder	☐	☐	☐	☐	☐
Left upper arm	☐	☐	☐	☐	☐
Left lower arm	☐	☐	☐	☐	☐
Area 5					
Left hip	☐	☐	☐	☐	☐
Left upper leg	☐	☐	☐	☐	☐
Left lower leg	☐	☐	☐	☐	☐

2. Pain history: Circle YES or NO for each of the following questions:		
Duration of pain 3 months or longer?	YES	NO
Does the pain get WORSE with physical activity or exercise?	YES	NO

3. Symptoms: Check the box next to EACH OF THE SYMPTOMS that best matches your experience **DURING THE PAST WEEK:**

	0 None	1 Mild	2 Moderate	3 Severe	4 Very Severe
Tenderness to touch	☐	☐	☐	☐	☐
Tiredness or fatigue	☐	☐	☐	☐	☐
Unrefreshing sleep	☐	☐	☐	☐	☐
Memory problems or forgetfulness	☐	☐	☐	☐	☐
Sadness or depression	☐	☐	☐	☐	☐
Anxiety or worry	☐	☐	☐	☐	☐

[a]Data were derived from Arnold LM, et al. *J Womens Health (Larchmt)*. 2012;21:231-239.
[b] Scoring of the Fibromyalgia Diagnostic Screen-Patient: Positive screen for fibromyalgia if "yes" to all of the following: (1) at least mild pain in at least 1 site within at least 3 out of 5 areas of the body, (2) duration of pain 3 months or longer,(3) pain gets worse with physical activity or exercise, (4) sum of 8 or more in symptom severity.

Based on the findings of the validation study, the patient self-reported questionnaire has a sensitivity of 78% and a specificity of 78% and may be used alone to screen patients for fibromyalgia.[19] Clinician-rated items may be added to the patient-rated screen to aid in the evaluation of patients if desired by the clinician (Table 3).[19] These screening tools were developed to increase awareness of fibromyalgia and facilitate the identification of patients with fibromyalgia.

Table 3. Fibromyalgia Diagnostic Screen – Cliniciana,b

1. Tender Point Evaluation: To the 8 sites listed below, apply perpendicular pressure using the thumb pad of your dominant hand. Apply pressure slowly and steadily until your thumb nail bed whitens. Instruct the patients to state "yes" or "no" if there is any pain with the palpation. Circle the response to each site.		
Trapezius muscle (midpoint of the upper border):		
Right	Yes	No
Left	Yes	No
Supraspinatus muscle (above the scapular spine near the medial border of the scapula):		
Right	Yes	No
Left	Yes	No
Second rib (at the second costochondral junction, just lateral to the junction, on the upper surface):		
Right	Yes	No
Left	Yes	No
Gluteal muscle (in upper outer quadrant of the buttock in the anterior fold of muscle):		
Right	Yes	No
Left	Yes	No
2. Joint Evaluation: Check for swollen or boggy joints on bilateral exam. Check "yes" if there is bilateral joint swelling at the sites.		
Elbows	Yes	No
Wrists	Yes	No
Metacarpophalangeal joints	Yes	No
Proximal interphalangeal joints	Yes	No
3. Blood Tests:		
Erythrocyte sedimentation rate < 40	Yes	No
Thyroid stimulating hormone (TSH) < 1.5 times the upper limit of normal (ULN)	Yes	No

[a]Data were derived from Arnold LM, et al. *J Womens Health (Larchmt)*. 2012;21:231-239.
[b] **Scoring of the Fibromyalgia Diagnostic Screen -- Clinician:** A positive Fibromyalgia Diagnostic Screen -- Patient plus positive screen on each of the components selected for administration by the clinician. These components include a tender point evaluation (must have at least 2 out of 8 positive tender points), joint evaluation (must have negative examination for bilateral swelling), ESR (must be less than 40), and/or TSH (must be less than 1.5 times the ULN). Clinicians may select the components that they deem the most useful for aiding their diagnosis or they may administer the Fibromyalgia Diagnostic Screen -- Patient alone.

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ACR = American College of Rheumatology
BMI = body mass index
CBT = cognitive behavioral therapy
CNS = central nervous system
CPK = creatine phosphokinase
CPM = conditioned pain modulation
CRP = C-reactive protein
CS = central sensitization
CSS = central sensitivity syndrome
DAS = Disease Activity Score
ESR = erythrocyte sedimentation rate
FM = fibromyalgia
FDA = Food and Drug Administration
IP =proximal interphalangeal joint
NMDA = N-methyl-d-aspartate
NSAIDS = nonsteroidal anti-inflammatory drugs
RA = rheumatoid arthritis
SLE = systemic lupus erythematosus
SNRI = serotonin and norepinephrine reuptake inhibitor
SS = Symptom Severity scale
SSRI = selective serotonin reuptake inhibitor
TMD = temporomandibular disorder
TSH =Thyroid stimulating hormone
ULN = upper limit of normal
WPI = Widespread Pain Index

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Evidence-Based Treatment Options for Fibromyalgia CME

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There is strong evidence that altered pain processing in the central nervous system is important in driving the chronic pain and fatigue that are the central features of fibromyalgia. Multiple clinical studies, including those that look at neuroimaging, have been especially enlightening in that regard (as discussed by Dr Gracely and Ms Ambrose in the second column in this series). Therefore, it is not surprising that, for the past 3 decades, medications that primarily act on the central nervous system have been utilized for the treatment of fibromyalgia. The early studies focused on low doses of tricyclic antidepressants, such as amitriptyline and cyclobenzaprine. These were the first medications found to have some benefit in pain reduction in small, single-center, randomized clinical trials. However in the past 5 years, a number of new pharmacologic approaches have been investigated with large, international, multiclinic studies. Subsequently, 3 medications have been approved by the Food and Drug Administration (FDA) for the treatment of fibromyalgia: pregabalin, duloxetine, and milnacipran. The nonpharmacologic management of fibromyalgia has been based more on the general principles of treating chronic pain. The most effective forms of therapy have included patient education, exercise, and cognitive behavioral approaches. Most experts advocate multidisciplinary treatment in combination with carefully-tailored medications.

Medications

The initial studies of amitriptyline and cyclobenzaprine demonstrated moderate improvement compared to placebo.[1-2] These studies have typically involved small numbers of patients and controls and were carried out for 3 months or less. Nevertheless, in combining a number of these studies, there is strong evidence that doses such as 25 mg of amitriptyline at bedtime or 20 mg of cyclobenzaprine at bedtime are somewhat effective in the treatment of fibromyalgia. The utility of the tricyclic antidepressants is limited by their adverse effects and the absence of evidence from studies lasting for 6 months or longer. There have also been studies that demonstrated added improvement when low doses of tricyclic agents at bedtime were combined with low doses of selective serotonin reuptake inhibitors (SSRIs) in the morning.[3]. However, monotherapy with SSRIs has been somewhat disappointing.

There is strong evidence that the serotonin and norepinephrine reuptake inhibitors (SNRIs) can be effective in the management of fibromyalgia. Duloxetine significantly reduced pain and improved global assessment in large, randomized, controlled studies of more than 500 patients with fibromyalgia.[4] Currently, the approved dose in the United States is 60 mg once daily. The most common adverse effects include nausea, headaches, and dry mouth. Patients with concurrent depression were included in the trials and there was no difference in efficacy in patients with fibromyalgia with and without depression.[4] Milnacipran is also approved for the treatment of fibromyalgia. In large, randomized clinical trials, milnacipran improved pain, global well-being, and the composite global status score significantly more than placebo.[5] Adverse effects were similar to those seen with duloxetine. The approved dose is 100 to 200 mg daily.

The alpha-2 ligands, pregabalin and gabapentin, have proven effective in fibromyalgia in randomized, clinical trials. These drugs are calcium channel modulators and their analgesic effect may be related to blocking the release of various neurotransmitters. Pregabalin was the first drug approved in the United States for the treatment of fibromyalgia. It has been extensively studied in clinical trials and a meta-analysis of 5 placebo-controlled, randomized trials with over 3000 patients with fibromyalgia reported significant improvement in pain and quality of life.[6-7] The FDA-approved dose of pregabalin is 300 to 450 mg daily. The most common adverse effects include dizziness, sedation, lightheadedness, weight gain, and edema. Data from a single randomized clinical trial demonstrated that a generic alternative to gabapentin given at a dose of 1200 to 2400 mg daily was found to be more effective than placebo.[7]

The only analgesic that has demonstrated modest efficacy in fibromyalgia has been tramadol, either alone or in combination with acetaminophen.[8-9] The studies with tramadol have been limited by potential for adverse effects and drug-drug interactions, and their study only in short-term trials. There is no evidence that nonsteroidal anti-inflammatory drugs or opioids are effective in fibromyalgia. There is also concern that opioid use and abuse may aggravate chronic widespread pain.[10]. A number of other medications have been investigated in randomized trials and, among them, results for sodium oxybate have been especially promising[11]; however, it is currently not approved for fibromyalgia. Table 1.[12]

Table 1. Pharmacological Therapies for Fibromyalgia[a,b]

Evidence	Pharmacological Therapies
Strong Evidence	• Tricyclics – amitriptyline • SNRIs – milnacipran – duloxetine • Pregabalin
Modest Evidence	• Tramadol • Gabapentin • SSRIs • Gamma hydroxybutyrate
Weak or No Evidence	• Opioids • Corticosteroids • Nonsteroidal anti-inflammatory drugs • Benzodiazepine and nonbenzodiazepine hypnotics • Guanifenesin • Thyroid hormones

SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.
[a]Adapted from Goldenberg DL, et al. JAMA. 2004;292:2388-2395.[12]
[b]Levels of evidence are based on the author's evaluation of available evidence.

Nonpharmacologic Management

There is strong evidence to support exercise, cognitive behavioral therapy (CBT), and patient education in the management of fibromyalgia. A systematic review of controlled studies, demonstrated that cardiovascular exercise had beneficial effects on global measures of well-being and physical function, as well as possible benefits for improving pain and the pain-pressure threshold.[13] More than 2200 patients with fibromyalgia were evaluated in this review, although the quality of the studies was extremely variable. There is also some evidence for strength training as well as flexibility exercises, although that evidence is not as robust as the evidence for cardiovascular exercise. A combined exercise program may provide the optimal benefit.[14].

There is also strong evidence for cognitive behavioral therapy in the management of fibromyalgia.[15-16] This therapy has often been evaluated in a group format, but there is also evidence to support individual forms of CBT. Cognitive behavioral therapy is designed to allow subjects with chronic pain to cope better with their symptoms, which may include formal stress reduction techniques, with a focus on teaching individuals optimal self-management of chronic illness.

Patient education should focus on assuring an appropriate diagnosis has been made and explaining the nature of the disorder and treatment approaches. Formal education, for both individuals and their families, is most helpful when it is combined with approaches to self-management and exercise.[12,17]

Tai chi and yoga have shown to be effective in single-study randomized, controlled trials.[18-19] The evaluation and treatment of peripheral pain generators, often termed trigger points, has been a helpful adjunct to therapy.[20] Initial studies of transcranial magnetic stimulation demonstrated improvement in pain in patients with fibromyalgia.[21]

Table 2. Nonpharmacologic Therapy for Fibromyalgia[a,b]

Evidence	Nonpharmacologic Strategies
Strong Evidence	• Exercise – Physical and psychological benefits – Improves physical function, may increase the tender point pain pressure threshold and improve pain. Efficacy not maintained, if aerobic exercise stops • Cognitive-behavioral therapy. – Improvements in pain, fatigue, mood, and physical function – Improvement often sustained for months – Patient education/self-management – Improves pain, sleep, fatigue, and quality of life • Combination (multidisciplinary therapy)
Modest Evidence	• Strength training • Acupuncture • Hypnotherapy] • Electromyogram biofeedback • Tai-chi, yoga • Transcranial electrical stimulation
Weak or No Evidence[12]	• Chiropractic • Manual and massage therapy • Ultrasound • Trigger point injections

[a]Adapted from Goldenberg DL, et al. JAMA. 2004;292:2388-2395.[12]
[b]Levels of evidence are based on the author's evaluation of available evidence.

The initial management of fibromyalgia should begin with a prompt and accurate diagnosis. Unfortunately, many patients with fibromyalgia go months or even years before diagnosis, delaying therapy and possibly making management more difficult. Patients with fibromyalgia need to be engaged in a detailed discussion that includes discussion of their symptoms, an explanation of the pathophysiology of chronic pain, and an introduction to management principles.[10,17] This discussion is especially daunting because fibromyalgia is a disorder considered to be somewhat nebulous and controversial. Patients should be reassured that fibromyalgia is a real syndrome, similar to migraine headaches. Patient education, including educating patients' families, may take a significant amount of time and some expertise; however, it can be done effectively with a healthcare team. Clinical studies have shown improvement of symptoms and patient satisfaction when working with a team of healthcare professionals in focused programs.[22] A biopsychological framework for managing fibromyalgia is recommended. It is important that the patient understand that there is no single cause or cure, as is often the case with chronic illnesses.

Each patient should be carefully assessed in regard to his or her ability to become more active and exercise. Frequently, patients need to be referred to physical therapy or a physical medicine and rehabilitation group to obtain a structured evaluation and to begin an appropriate individualized exercise routine. Exercise should be started slowly, with an initial focus on low-impact cardiovascular fitness training.

Any patient with a possible primary sleep disturbance, such as sleep apnea or restless leg syndrome, should be referred to a sleep expert for appropriate management. If there is concern about major psychiatric illness, the patient should also have a full psychiatric evaluation prior to any other therapeutic interventions. Many patients will benefit from formal education and CBT.

Most patients should be started on a single drug and the choice of medication should be based on the predominance of their symptoms. For example, in patients with fibromyalgia who have severe sleep disturbances and chronic pain, it would be reasonable to start low doses of a tricyclic antidepressant medication or an alpha-2 ligand at bedtime. Initially the use of amitriptyline or cyclobenzaprine may be favorable because of the low cost, especially for use in low doses at bedtime. In contrast, patients with fibromyalgia with more exhaustion and anhedonia might initially be started on low doses of 1 of the SNRIs in the morning. Although it is considered off label, it is preferable to begin medication at low doses. For example, I will often begin treatment with 25 or 50 mg of pregabalin, 10 mg of amitriptyline, or 5 mg of cyclobenzaprine at bedtime. When beginning a SNRI, I initiate therapy with 20 mg of duloxetine or 25 mg of milnacipran to be taken at breakfast time each morning. These medications can be gradually increased in dosage, if tolerable. Flexible dosing should be considered. For example, treatment with duloxetine at flexible doses of 60, 90, and 120 mg/day was associated with improved symptoms and function.[23]

At times, the suggested dose of these medications may not be achieved because of adverse effects. In such situations it is appropriate to consider polypharmacy. For example, a logical approach is to use 1 of the SNRIs in the morning in conjunction with pregabalin in the evening.

Although there are 3 drugs now approved in the United Sates for the treatment of fibromyalgia, medications alone have provided only modest improvement.[1,7] Overall, in the large trials with pregabalin, duloxetine, and milnacipran, approximately 50% of subjects showed modest improvement and only 25% showed clinically significant improvement.[5,7,23] This highlights the fact that a combined nonpharmacologic and pharmacologic approach may work best. In my experience, patients who tolerate medications and report initial improvement, tend to have sustained improvement, however most of the long-term studies have only been carried out to 1 year.[24]

Multiple measures of treatment response in fibromyalgia have been used in clinical trials. Twenty-four potential fibromyalgia responder definitions were developed by expert consensus and evaluated in 12 randomized, placebo-controlled trials involving 4 medications.[25] The 2 responder definitions that performed best included greater than or equal to 30% reduction in pain and greater than or equal to 10% improvement in physical function. The definitions differed in that 1 included a greater than or equal to 30% improvement in sleep or fatigue, and the other included a greater than or equal to 30% improvement in 2 of the following symptoms: sleep, fatigue, depression, anxiety, or cognition. Going forward, using responder indices that include assessments of key symptoms and function domains may improve the sensitivity of clinical trials to identify meaningful and significant improvements for the future management of fibromyalgia.

Currently, amitriptyline, pregabalin, duloxetine, and milnacipran should be considered as first-line options for the treatment of fibromyalgia; however, only a minority of patients achieve significant improvement without intolerable adverse effects.[26] Despite this, a recent study using a systematic review and mixed treatment comparisons confirmed the therapeutic efficacy of pregabalin and the SNRIs, duloxetine and milnacipran, in the treatment of fibromyalgia.[27] Results suggest that given their different modes of action, combination therapy with pregabalin plus an SNRI should be investigated.

Indeed, treatment should be based on a combined pharmacologic and nonpharmacologic approach, which is tailored to each individual patient. To date, the optimal and most cost-effective methods to achieve this have not been completely elucidated and need to be evaluated further in clinical trials.

How has your medical knowledge and competence improved? Assess your performance in comparison with your peers by completing this brief survey.

Case #1: A 40-year-old woman presents to your rheumatology office for an initial visit. She complains of "pain all over" most of the time, general fatigue, and disturbed sleep that have negatively impacted her quality of life. She has also lost interest in activities she previously enjoyed. She notes she has been to 2 other physicians during the preceding 1.5 years with these symptoms and has been treated with non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), and opioids but has felt little symptom improvement. She takes no medications currently and denies alcohol or tobacco use. Family history is unremarkable. She expresses frustration at her persistent symptoms despite multiple previous evaluations and treatments.

Which of the following would you administer next?

- Epworth Sleepiness Scale
- Edmonton Functional Assessment
- Fibromyalgia Diagnostic
- Screen Patient Health Questionnaire-2
- None of the above

Case #1 continued: Physical examination is notable for a body mass index (BMI) of 31.2 kg/m^2 and tenderness to palpation in the neck and lower back. No evidence of joint inflammation is noted, and neurologic exam is normal. Laboratory studies reveal normal erythrocyte sedimentation rate (ESR) and thyroid function tests.

Based on the new diagnostic criteria developed by the American College of Rheumatology in 2010, which of the following is included as 1 of the 3 conditions that must be met in order to diagnose this patient with fibromyalgia?

- The presence of pain in at least 11 of 18 tender point sites determined by digital palpation
- Presence of symptoms at a similar level for at least 3 months
- Widespread pain index (WPI) ≥ 2
- Disease activity score (DAS) ≥ 5

Which of the following would you do next?

- Start a glutamate/N-methyl-D-aspartate (NMDA) receptor inhibitor and arrange for transcranial electrical stimulation
- Start a serotonin norepinephrine reuptake inhibitor (SNRI) and prescribe an exercise program
- Start an anxiolytic and evaluate her lumbar spine with a magnetic resonance imaging (MRI) study
- Start a brief course of corticosteroids and recommend cognitive behavioral therapy (CBT)

Case #1 continued: The patient is started on an SNRI and the dose is titrated upward to the recommended dose over the next several weeks. At her 3-month follow-up visit, she reports feeling some improvement in her pain. However, she continues to feel overwhelmed by having been diagnosed with fibromyalgia and has difficulty coping with stress in her life that seems to make her symptoms worse. She asks what else she can do to feel better.

Which of the following approaches would you recommend?

- *Massage therapy*
- *Phototherapy*
- *Cognitive behavioral therapy*
- *Trigger point injections*

Case #2: A 36-year-old woman was diagnosed with fibromyalgia 2 months ago following a comprehensive evaluation. She was placed on an SNRI and reports decreased pain and an improvement in her mood. However, she continues to experience disrupted sleep and daytime fatigue.

Which of the following is characteristic of this patient's condition?

- ◯ Augmented central nervous system processing of pain
- ◯ Increased levels of norepinephrine metabolites in the cerebrospinal fluid
- ◯ Altered NMDA-receptor system leading to central sensitization
- ◯ The etiology is based on genetic, rather than environmental factors

How would you manage this patient at this time?

- ◯ Start an NSAID for better pain management
- ◯ Add an alpha-2-delta ligand (e.g., pregabalin) to address ongoing symptoms
- ◯ Refer her for an electromyogram (EMG) to rule out myopathy
- ◯ Check creatine phosphokinase (CPK) level to rule out myositis

Case #2 continued: She returns a month later and has been adherent to your recommendations. Her sleep has improved and her pain is more manageable. However, she reports that she still has trouble with physical functioning.

Which of the following would you add to her regimen?

- ◯ Graded exercise therapy
- ◯ Phototherapy
- ◯ SNRI
- ◯ SSRI
- ◯ None of these

Case #3: A 44-year-old woman was diagnosed with possible fibromyalgia 4 months ago by her previous physician. She was prescribed naproxen and asked to follow-up in 1 month. Due to a change in her husband's career, she has recently relocated and now presents to your office for an initial visit. She complains of generalized pain, particularly stiffness, and reports no benefit from the naproxen. "I've been taking it every day, but I feel like I might as well be taking a sugar pill," she says. Following a comprehensive history and examination, you suspect she may indeed have fibromyalgia.

Which of the following is the best explanation for this patient's poor response to previous therapy?

- ◯ There is no evidence for efficacy of monotherapy with NSAIDs in treatment of fibromyalgia
- ◯ NSAIDs have greater efficacy when combined with nonpharmacologic therapy
- ◯ NSAIDs should be used for breakthrough symptoms only
- ◯ Only certain specific NSAIDs have demonstrated efficacy in management of fibromyalgia

Which of the following would you do next in this patient?

- Begin treatment for fibromyalgia right away using evidence-based treatments
- Exclude other causes of her chronic pain in a stepwise fashion before initiating any treatment
- Send laboratory tests recommended by the 2010 American College of Rheumatology (ACR) diagnostic criteria for fibromyalgia
- Perform trigger point injections

Case #4: A 47-year-old woman presents to your office because of difficulty sleeping. She reports waking up frequently during the night and feeling un-refreshed in the morning. The patient is a high school counselor and has recently had to take multiple days of sick leave. "I can't do what I used to do, and some days I have trouble concentrating," she tells you. A month ago she had a sleep study that ruled out sleep apnea and periodic limb movement disorder along with a basic laboratory evaluation including thyroid studies, complete blood count, and comprehensive metabolic panel that was unremarkable. Upon further discussion the patient also reports 9 months of gnawing pain "everywhere." She does not smoke or drink alcohol, and family history is positive for an anxiety disorder in the patient's mother.

Which of the following would you do next?

- Calculate Disease Activity Score (DAS)
- Calculate Expanded Disability Status Scale (EDSS) score
- Compute Fibromyalgia Pain Inventory Score (FPIS)
- Compute Symptom Severity (SS) and Widespread Pain Index (WPI) scores
- None of these

Case #4 continued: Physical examination is notable for a BMI of 32.1 kg/m^2, no evidence of joint inflammation, and normal neurologic exam. Based on your assessment, you diagnose the patient with fibromyalgia.

Which of the following would you initially prescribe for this patient?

- Alpha-2 ligand
- NMDA-receptor antagonist
- SSRI
- Low-potency benzodiazepine

Which of the following is characteristic of fibromyalgia?

- Worldwide prevalence of between 7% and 10%
- Laboratory testing is necessary before fibromyalgia can be diagnosed
- Frequently associated with a lifetime history of major mood disorder or anxiety disorder
- Peripheral mechanisms are the principal source of widespread pain

In your experience, which of the following is the most significant barrier to the optimal management of fibromyalgia?

- ◯ Presence of comorbidities and complexities
- ◯ Time required to diagnose and treat
- ◯ Lack of expertise in the diagnosis and/or management of fibromyalgia
- ◯ Lack of specialists for referral
- ◯ Frequent need to have multiple clinicians involved in coordinating care
- ◯ Difficulty distinguishing fibromyalgia from other causes of chronic pain

Please indicate how relevant this CME activity is to your practice: approximately how many patients do you see each week?

- ◯ 0
- ◯ 1-20
- ◯ 21-40
- ◯ 41-60
- ◯ 61-80
- ◯ > 80

Approximately what percentage of your patients are diagnosed with fibromyalgia?

- ◯ 0
- ◯ < 5%
- ◯ 5-10%
- ◯ 11-15%
- ◯ 16-20%
- ◯ > 20%

This article is part of a CME certified activity. The complete activity is available at:
http://medscape.org/column/fibro

ACR = American College of Rheumatology
BMI = body mass index
CBT = cognitive behavioral therapy
CNS = central nervous system
CPK = creatine phosphokinase
CPM = conditioned pain modulation
CRP = C-reactive protein
CS = central sensitization
CSS = central sensitivity syndrome
DAS = Disease Activity Score
ESR = erythrocyte sedimentation rate
FM = fibromyalgia
FDA = Food and Drug Administration
IP =proximal interphalangeal joint
NMDA = N-methyl-d-aspartate
NSAIDS = nonsteroidal anti-inflammatory drugs
RA = rheumatoid arthritis
SLE = systemic lupus erythematosus
SNRI = serotonin and norepinephrine reuptake inhibitor
SS = Symptom Severity scale
SSRI = selective serotonin reuptake inhibitor
TMD = temporomandibular disorder
TSH =Thyroid stimulating hormone
ULN = upper limit of normal
WPI = Widespread Pain Index

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