Noncardiac Chest Pain and Fibromyalgia

Chronic widespread pain syndromes have been known for several centuries but the recognition of fibromyalgia as a distinct disorder is recent. The first description of fibromyalgia, then called fibrositis was published in 1904 by Sir William Gowers who described a syndrome of muscular regional pain, fatigue, and sleep disturbances that was characterized by the presence of increased tenderness at palpation or with the movement of affected areas, and was attributed to inflammatory patchy hyperplasia of the connective muscular fibrous tissue.1 In the 1930s and 1940s several studies reported the location and nature of the tender points.2,3 In the meantime, others focused on understanding the relationship between visceral pain and fibrositis.4 Patton and Williamson5 were the first to report a case of chest pain related to fibrositis, in a 52-year-old obese woman complaining of constricting pain in the left chest and left arm, who despite being initially managed as a myocardial infarction showed a normal electrocardiogram; the investigators later identified muscle spasm and tenderness of left erector spinae group and left trapezius as the cause of the angina-type pain. They called this entity “pseudovisceral pain,” because it was identical to referred visceral pain but differed in origin.

In the 1970s, Moldofsky and colleagues6 and Smythe and Moldofsky7 were the first to change the term fibrositis to fibromyalgia (FM), to denominate a syndrome characterized by chronic musculoskeletal pain and tender points associated with non–rapid eye movement (REM) sleep disturbance. In 1990, the American College of Rheumatology (ACR) published the current accepted classification criteria for this entity, based on the results of a multicenter study comparing 293 patients diagnosed with fibromyalgia and 265 patients with other causes of chronic pain.8 The World Health
Organization acknowledged fibromyalgia as an independent entity with the Copenhagen declaration in 1992.9

Recently, the diagnostic criteria for FM have been reconsidered, especially because the diagnosis may often be made in the absence of the requisite number of tender points.10–12 It has been argued that existing tender point criteria bias prevalence statistics toward female patients.12 Thus, Wolfe and colleagues13 have undertaken to revise the diagnostic and severity criteria for FM, particularly to reconsider the usefulness of the tender point examination and to include other clinical features that better capture the complexity of this condition.

Epidemiology

To date, descriptive epidemiologic data for FM have largely relied on the established 1990 ACR classification criteria. The ancillary population-based study performed by Wolfe and colleagues14 in Wichita (USA) estimated an overall prevalence of FM of 2% for both genders, 3.4% for women and 0.5% for men. According to a more recent study, FM is the third most common rheumatic disease after low back pain and osteoarthritis, affecting up to 5% of women in the United States.15 Studies throughout the world report variable prevalence data: from 0.05% in China,16 0.22% in Cuba,17 1.4% in Mexico18 and France,19 2.4% in Spain,20 3.3% in Canada21 to 4.4% in Bangladesh.22 FM more commonly affects middle-aged (usually more than 50 years old) women, living in rural areas, divorced with reduced household income, and lower educational level.14,20 If the criteria are broadened, however, the prevalence certainly increases. Estimates of chronic widespread pain in the United Kingdom indicate a prevalence rate of 11% at any given time,23 confirming that these conditions are common in the general population.

Coexistence of Fibromyalgia and Noncardiac Chest Pain

Functional chest pain

Patients with FM usually present symptoms of other unexplained medical conditions, such as chronic fatigue, bowel dysfunction, or mood disorders, leading to the proposal that FM is just 1 member of a broader family of conditions, the central sensitization syndromes, all of which may share a common underlying pathophysiology (Fig. 1).24 This family of syndromes may include, but is not limited to, regional pain disorders such as myofascial pain syndrome and chronic fatigue syndrome. The relationship between FM and functional gastrointestinal disorders (FGID) is believed to be strong according to the increased number of digestive complaints referred by FM patients25,26 but also by the number of studies documenting such association.25–30

FGID is a heterogeneous group of gastrointestinal diseases characterized by the absence of any structural or biochemical abnormality that could explain the symptoms.31,32 According to the last consensus definition of FGID, functional chest pain is characterized by episodes of unexplained chest pain that are usually midline in location and of visceral quality, and easily confused with cardiac angina and pain from other esophageal disorders.33 To our knowledge, there is only 1 study assessing the prevalence of functional chest pain in patients with FM.25 In this study, the investigators compared a randomly selected sample of 100 patients with FM and 100 matched controls from the Spanish population. Patients and controls completed the Rome II Integrative Questionnaire for Functional Gastrointestinal Disorders to evaluate the prevalence of gastrointestinal symptoms and functional syndromes and the Symptom Checklist-90 Revised (SCL-90R) to evaluate psychological distress; patients also completed the Fibromyalgia Impact Questionnaire (FIQ) to assess the
overall impact of the disease. All gastrointestinal symptoms except vomiting were more often reported in FM; chest pain as an individual symptom was significantly more frequent in patients (55%, 95% confidence interval [CI] 45.2–64.8) than in controls (8%, 95% CI 2.7–10.3) \((P < .05)\); on the other hand, the prevalence of functional chest pain was not significantly different between both groups (3%, 95% CI 0–6.3 in patients vs 1%, 95% CI 0–3 in controls). Patients with FM had higher scores for psychological distress, although the presence of functional chest pain did not correlate with additional distress in patients with FM. Moreover, those with coexisting functional chest pain and FM showed lower scores in the Positive Symptom Distress Index (PSDI), which measures the perceived intensity of symptoms, than those with FM but without functional chest pain \((P < .05)\). These data should be interpreted with caution, given the small number of patients that were diagnosed with functional chest pain \((n = 3)\). An additional limitation of this survey is the lack of formal testing, thus, it is possible that a proportion of patients complaining of chest pain may have had cardiac disorders, organic esophageal diseases such as gastroesophageal reflux, or musculoskeletal pain.

**Musculoskeletal chest pain**

Several studies have reported the prevalence of FM in patients with NCCP. In 1992, Wise and colleagues\(^{34}\) described a 5% prevalence of FM in patients with NCCP \((n = 100)\). In 1995, Mukerji and colleagues\(^{35}\) reported a prevalence rate of FM of 30% in a sample of 40 consecutive NCCP patients attending an internal medicine clinic after complete rheumatologic evaluation.

Ho and colleagues\(^{36}\) evaluated if the presence of chest wall tenderness or FM might help to distinguish between cardiac and noncardiac chest pain, comparing 2 groups of patients with chest pain who previously underwent coronary arteriography. Seven (6 women, 1 man) of 36 patients (19%) were diagnosed with FM according to the ACR criteria in the group of subjects with normal coronary angiograms, whereas only 1

![Central Sensitization Syndromes](https://example.com/central-sensitization-syndromes.png)

*Fig. 1. Central sensitization syndromes share a common etiologic mechanism of central sensitization and frequently present with overlapping epidemiologic, clinical, and psychological features. (Adapted from Yunus MB. Role of central sensitization in symptoms beyond muscle pain, and the evaluation of a patient with widespread pain. Best Pract Res Clin Rheumatol 2007;21:481–97; with permission.)*
(a man) of 35 (3%) was diagnosed with FM among those with abnormal coronary angiograms ($P = .027$). Commonly, FM associated disorders (Raynaud disease, irritable bowel syndrome, and chronic headache) and tenderness at different body sites were also significantly more frequent in the normal angiogram group. However, the differences previously found between patients with normal and abnormal angiograms were not later confirmed when the results were analyzed by gender, which led the investigators to conclude that the presence of chest wall tenderness and FM was not helpful to distinguish between cardiac and noncardiac chest pain and the differences observed were related to a higher predominance of women in the group with normal coronary angiograms.

In 2004, Dammen and colleagues$^{37}$ compared medical comorbidities in patients with chest pain of cardiac ($n = 32$) and noncardiac origin ($n = 167$). Based on the patient’s self-reported diagnosis of a previous history of FM, the investigators did not find significant differences between groups in the rate of FM diagnosis (7.2% in NCCP vs 3.1% in cardiac patients) or other rheumatologic conditions (25.3% vs 34.4%).

How and colleagues$^{38}$ investigated the causes of musculoskeletal chest pain leading to hospital admission in 50 consecutive patients with chest pain without evidence of ischemic heart disease, respiratory disease, or gastrointestinal disease. Patients were included only when they were tender on anteroposterior chest compression, thoracic spine rotation, or firm sternal pressure. Thirteen patients (26%) had FM, 12 (24%) had inflammatory joint disease, and 25 (50%) had other regional painful conditions. Individuals with FM presented the highest scores of pain, anxiety, and depression.

Recently, Husser and colleagues$^{39}$ prospectively studied 37 consecutive patients with recurrent NCCP. Patients underwent psychiatric evaluation and completed the SCL-90R questionnaire to exclude psychiatric comorbidity; physical examination was done by an orthopedist to diagnose musculoskeletal abnormalities and a 7-day trial of a proton pump inhibitor (esomeprazole 40 mg daily) was also done to exclude pain related to gastroesophageal reflux. Twenty-one were found to have various psychiatric disorders (57%) including anxiety and depression ($n = 10$), depression ($n = 5$), panic disorder ($n = 3$), and somatization ($n = 3$). Six patients had musculoskeletal abnormalities (15%), 4 had chostochondritis (10.8%), 1 had thoracic spondylodynia (2.7%), and 1 had FM (2.7%). Sixteen patients (43%) responded to the proton pump inhibitor trial; 6 of these patients had multiple conditions (3 depression, 2 chostochondritis, and 1 FM). Table 1 summarizes the studies evaluating the prevalence of FM in patients with NCCP.

**PATHOGENESIS**

**Abnormal Pain Processing**

Work to elucidate the pathophysiology of FM and related pain syndromes has historically focused on abnormalities in muscle metabolism and joint and soft tissue structure. These investigations have not yielded adequate explanation about the cause and perpetuation of the clinical syndromes, although undoubtedly they may be valid sources of pain. Pain signals, however, seem to be misprocessed at a more central level, a pathophysiologic model that has gained increasing support in recent years. The pathogenesis of these conditions seems to involve dysregulation of pain pathways, leading to central sensitization. In addition to the hallmark pain manifestations of these syndromes, it is recognized that the frequently occurring concomitant symptoms are associated with abnormalities in the physiology of central neurotransmitters, neurohormones, and sleep.$^{40,41}$

Although the pathogenesis of FM and NCCP is not yet completely understood, both disorders seem to share a common longstanding pain hypersensitivity manifested as
allodynia (a non-noxious stimuli induces pain) and hyperalgesia (the painful response to a noxious stimuli lasts longer and has higher intensity than normal) present not only at the site of injury (primary) but also at distant or generalized sites (secondary). In FM, hyperalgesia and allodynia are indicated by the painful stimulation of tender points with a pressure of 4 kg/cm² or less, a stimulus usually non-noxious in healthy patients.

In patients with NCCP the presence of allodynia has been reported in several studies. Richter and colleagues showed that balloon distension of the distal esophagus, up to a maximum of 10 mL, induces pain more likely in patients with NCCP than in healthy controls (60% vs 20%); furthermore NCCP patients developed chest pain at lower volumes (≤8 mL) compared with controls (>9 mL).

Sarkar and colleagues compared sensory responses to electrical stimulation after acid infusion in the lower esophagus of NCCP patients (n = 7) and healthy controls (n = 19). Sensory responses were monitored in acid-exposed areas (distal esophagus), non–acid-exposed areas (proximal esophagus), and the cutaneous area of pain referral before and after acid and saline infusion. In the distal esophagus of healthy controls, acid infusion but not saline infusion decreased the pain threshold in the proximal esophagus and chest wall. Moreover, pain thresholds in the proximal esophagus of NCCP patients fell further and responses to acid infusion were significantly longer compared with healthy controls, although no differences were found in both groups after saline infusion. This study showed not only the presence of secondary allodynia in patients with NCCP but also the concurrence of visceral and somatic hypersensitivity.

Studies comparing the effect of thermal stimulus on the chest wall and electrically induced esophageal pain have shown that visceral and somatic stimuli activate similar brain areas. However, there are some differences in the central processing of somatic and visceral pain that may explain the differences in perception, behavior, and vagal response to noxious stimulation of the viscera or somatic structures.

Indeed, both stimuli activate secondary somatosensory and parietal cortices, thalamus, basal ganglia, and cerebellum; somatic pain produces greater activation in the anterior insula and ventrolateral prefrontal cortex, whereas visceral stimulation results in activation of bilateral inferior primary somatosensory cortex, bilateral primary motor cortex, and a more rostral region of the dorsal anterior cingular cortex.

 Syndromes of widespread pain, including FM, all share neuropathophysiologic features that result in heightened pain sensitivity. Although these disorders are aptly
described as central sensitivity syndromes, mechanisms that involve abnormalities in peripheral nerve transmission, central sensory processing in the spinal cord, supraspinal mechanisms, and autonomic responses have all been described to account for many of the symptoms experienced by patients.

At the peripheral nerve level, work focusing on the role of ion-sensing channels in primary afferent neurons has elucidated the potential of certain channel species as points of pharmacologic intervention. Sluka and colleagues describes how secondary mechanical hyperalgesia fails to develop in mice knocked out for the membrane protein acid-sensing ion channel 3 (ASIC3), yet re-expression of ASIC3 in muscle tissue of ASIC3 knockout mice restores the development of hyperalgesia. The calcium channel subunit α2-δ is abnormally up-regulated in chronic pain syndromes, and serves as a binding site for drugs such as gabapentin and pregabalin. This secondary pain hypersensitivity also results from an increase in excitability of spinal cord neurons induced by activation of nociceptive C-fibers at the site of injury, leading to central sensitization. Central sensitization is also mediated by the phosphorylation of N-methyl-D-aspartate (NMDA) receptors located at dorsal horn neurons in the spinal cord by the release of neurotransmitters such as glutamate, neurokinin A, or substance P by the nociceptive presynaptic receptors. Activation of NMDA channels through the exchange of magnesium by calcium ions depolarizes the neural membrane, which increases the excitability (hyperalgesia) of neurons and amplifies the received stimulus (alldynia). This observation has been experimentally reproduced in visceral and somatic tissues in humans to generate the phenomenon of temporal summation, or wind-up, by which nociceptive signals are amplified and perpetuated at the spinal cord level (Fig. 2).

Pain hyper-responsiveness has also been reported at the supraspinal level in nociceptive and affective aspects. Imaging techniques such as functional magnetic resonance imaging (fMRI) have been used to demonstrate hyperactivity in thalamic pain centers and its common projections, such as the insular cortex, which have interconnections with the amygdala, prefrontal cortex, and anterior cingulate cortex. Furthermore, relative decreases in the activity of central pain inhibitory centers, such as the rostral anterior cingulate cortex, are seen. There is, therefore, a situation of extremes whereby pain responses are permitted to be heightened and perpetuated.

In addition, hypothalamic-pituitary-adrenal axis abnormalities and autonomic dysfunction have been well described in FM, NCCP, and other related conditions, and may explain some of the accompanying visceral functional disturbances.
Increases in sympathetic outflow with decreases in parasympathetic tone result in visceral hyperactivity, which can be manifest as irritable bowel-like symptoms in the gastrointestinal tract, functional bladder abnormalities (in such syndromes as interstitial cystitis), peripheral vasospasm, interstitial peripheral edema, and inappropriate postural cardiovascular responses, among others. Decreases in central norepinephrine release with decreased sympathetic tone reduce pain inhibition in descending pathways of the central nervous system.

Total sleep time, sleep efficiency, and REM sleep are decreased and arousals are increased in patients with fibromyalgia.62 The $\alpha$-$\delta$ pattern is often observed in polysomnographic studies: intrusion of $\alpha$ (wakeful) brain activity into $\delta$ states (stage 3, or deep sleep). $\alpha$-$\delta$ sleep can be seen in patients with chronic pain of any cause, and is clinically associated with nonrestorative symptomatology, which in turn is associated with higher perceived levels of pain.63

**Psychological Comorbidity**

Psychological conditions, such as anxiety, depression, and somatization, are common in patients with NCCP and FM,14,64–66 although the role of psychological distress in the pathogenesis of these diseases is complex.

Different theories have been postulated to explain the increased relationship between psychological abnormalities and certain functional or medically unexplained diseases: first, psychological factors may cause these disorders; second, psychological distress is the result of having a chronic and painful condition; and third, that certain abnormal psychological profiles increase health care seeking.67 The current trend is to understand these syndromes as a process, resulting in different stimuli over time; thus, psychological, social, and biologic factors would be interrelated and implied in the origin, perpetuation, and expression of the patient’s symptom, a hypothesis already known as the biopsychosocial model (Fig. 3).67,68

**DIAGNOSIS**

The diagnostic algorithm of chest pain in a patient with FM is initially identical to that in a patient without FM: first exclude cardiac origin and then evaluate other potential causes of chest pain (see corresponding article in this issue).

However, once disorders of cardiovascular origin and common upper gastrointestinal conditions, such as gastroesophageal reflux or an esophageal motility disorder, have been ruled out, a well-structured and systematic anamnesis and psychological assessment should be conducted bearing in mind the possibility of FM.

**Fig. 3.** Biopsychosocial model in central sensitivity syndromes. Genetic, physiologic, psychological and social factors are all related and implied in the origin, perpetuation, and expression of symptoms in patients with central sensitization syndromes.
FM is a complex syndrome characterized not only by the presence of chronic widespread pain but also by its frequent association with unexplained symptoms from other organ systems, such as fatigue, nonrestorative sleep or insomnia, a sensation of swelling, dysesthesias, cognitive difficulties, dizziness, syncope, Raynaud phenomenon, dry mouth, headaches, digestive complaints, anxiety, or depression, among others. The overlap of these symptoms with FM is so important that some investigators have considered them as auxiliary in the diagnosis.

The classification criteria of FM established in 1990 by the ACR require the presence of chronic widespread pain and tenderness at 11 of 18 body sites; chronic widespread pain is considered as the presence of pain in the upper and lower body, axial skeletal and left and right sides, for at least 3 months, without any history of lesion or trauma that can explain the symptoms.

Systematic palpation of tender points is the most relevant physical examination maneuver of a patient with suspected FM. This examination must be performed with an approximate force of 4 kg/cm², which is equivalent to the moment when blanching of the examiner’s nail bed occurs. The 18 tender points are at 9 symmetric paired locations.

In a patient with FM and coexisting chest pain, the physical examination is of special interest, because it is common, although not specific, to find chest wall tenderness (especially at the tender points located in the anterior chest wall as the midpoint of the upper border of the trapezius and the second rib lateral to the chostochondral junction) and in some cases reproduction of the pain on palpation.

Although the ACR criteria for the diagnosis of FM are used in most clinical trials and research studies, in practice they are not easy to apply, and many clinicians make a diagnosis without the formal tender point examination. There is a belief that these points represent a marker of severity and distress, and that FM constitutes the extreme of the chronic widespread pain continuum.

In 2006, Katz and colleagues, aware of this situation, designed a study to determine the concordance among ACR criteria, clinician diagnosis, and survey criteria in 206 consecutive patients. The survey criteria were previously proposed by the investigators and were based in a score of 8 or higher in a Regional Pain Scale (RPS) and a fatigue score of 6 or higher on a visual analog scale. Among the 206 patients, 101 (49%) were diagnosed clinically with FM, 60 (29%) according to the ACR criteria and 83 (40.3%) based on survey criteria. Clinical and survey criteria were concordant in 74.8% of cases; clinical and ACR criteria in 75.2% of cases and survey criteria and ACR criteria in 72.3%. Of the patients who were diagnosed as having FM by at least 1 method, only 33% would be diagnosed by the 3 methods; 17% would be diagnosed clinically only, 12% by the survey criteria, and 2% by the ACR criteria only. The investigators concluded that given that there is no gold standard for FM and the concordance rates were moderately in agreement, all these methods might be useful in the diagnosis of FM.

Recently, the ACR has begun the task of revising the diagnostic and severity criteria for FM, appreciating the fact that the tender point examination may not be necessary to assign a diagnosis. Wolfe and colleagues recently proposed novel criteria that largely exclude the need for tender points, although at the same time generally adhering to the concept of FM presented in the 1990 criteria. These new criteria are based largely on an index of widespread pain (WPI) and a symptom severity score (SSS), which comprises the presence of fatigue, nonrestorative sleep, cognitive disturbances, and other somatic symptoms. These criteria offer better face validity by capturing the concept of FM as a disorder of central sensitization with frequent non-musculoskeletal and constitutional symptoms. Although validation studies have yet to
be conducted, these new criteria will likely offer greater sensitivity and place the patient in the correct diagnostic arena where the principles of treatment would apply.

As the diagnosis of FM is based solely on clinical and exploratory data without clinically available biologic diagnostic markers, the value of laboratory and diagnostic tests in FM is low. The only tests recommended are a complete blood count and basic chemistry panels including thyroid hormones and those indicated based on the symptoms and physical examination findings. Markers of systemic autoimmunity and
TREATMENT

Various pharmacologic and nonpharmacologic treatments have been shown to have short-term positive effects on individual symptoms of FM: antidepressant such as amitryptiline, cyclobenzaprine, fluoxetine, duloxetine, milnacipran; opiates such as tramadol and other central nervous system acting agents such as gabapentin and pregabalin (approved by the US Food and Drug Administration); aerobic exercise; cognitive behavioral therapy; and even alternative treatments such as homeopathy, hydrotherapy, or acupuncture. However, to date the results of several meta-analysis show that none of these therapeutic interventions have been effective to control all the symptoms related to the FM syndrome or change the natural history of the disease. Given the heterogeneity of patients with FM, the better approach seems to be to individualize the treatment for every patient according to their main complaints.

Data suggest that a multimodality approach that addresses the issues of pain, fatigue, and sleep and mood disorders, and includes cognitive behavioral therapy, produces the greatest benefit in the long-term. This approach includes the use of analgesics such as nonsteroidal antiinflammatory drugs and tramadol for pain relief (but avoiding moderate to potent opiate analgesics), antidepressants, sleep aids, and atypical neuroactive agents such as pregabalin, usually in a carefully titrated, stepwise approach as chemical and drug sensitivities are common. Exercise, often with the initial assistance of a physical therapist familiar with the precepts of FM treatment, should be gradual and graded to avoid over-exhaustion and more pain, and to promote sustainability. A formal sleep evaluation, including polysomnography, is often required to diagnose treatable disorders of sleep such as obstructive apnea, restless leg syndrome, or sleep disordered breathing.

Fig. 5. Approach to the patient with NCCP and suspected FM.
Cognitive behavioral therapy may be incorporated to treat dysfunctional pain attitudes and behaviors and promote lifestyle adjustments such as goal-setting, prioritization, pacing, and building support systems. More and more specialized centers for treatment of FM using a comprehensive paradigm are being established. Referral of the patient should be considered. Table 2 summarizes current therapeutic approach in patients with NCCP and FM.

### Table 2

<table>
<thead>
<tr>
<th>Pharmacologic: Pain Control</th>
<th>Nonpharmacologic: Adjuvant Therapy</th>
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<tr>
<td>Tramadol</td>
<td>Physical therapy (gradual supervised exercise programs)</td>
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<tr>
<td>Cyclobenzaprine</td>
<td>Sleep evaluation and therapy</td>
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<td>Tricyclic antidepressants</td>
<td>Cognitive behavioral therapy</td>
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<tr>
<td>Pregabalin</td>
<td>Treatment of other coexisting conditions (psychological, gastrointestinal, and so forth)</td>
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<td>Duloxetine</td>
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SUMMARY

FM remains an enigmatic and challenging clinical entity to manage, given its wide spectrum of symptoms, chronicity, associated psychopathology, and lack of clinically available diagnostic tests. However, recent insights into the pathophysiology of FM offer hope that this condition, and all central sensitization syndromes, can be more readily diagnosed, measured, and treated. Among the manifestations of FM, NCCP seems to be frequent. The clinician should be vigilant to the possibility of FM and its important attendant comorbidities as an important contributor in these clinical situations.

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