Critical Review

Understanding Fibromyalgia: Lessons from the Broader Pain Research Community

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Abstract: Fibromyalgia (FM) is a chronic pain condition marked by centrally mediated augmentation of pain and sensory processes. Skepticism has marked the history of this condition, but more recent study has identified neurobiological underpinnings supporting many of the symptoms associated with this condition. Early research in FM had unprecedented latitude within the rheumatology community to borrow heavily from theory and methods being applied in chronic pain research more generally. These insights facilitated rapid advances in FM research, not the least of which was the abandonment of a peripheral focus in favor of studying central mechanisms associated with central augmentation. Currently, rapid-paced discovery is taking place in FM genetics, patient assessment, new therapeutic targets, and novel methods of treatment delivery. Such insights are not likely to be limited in application just to FM and could have relevance to the broader field of pain research as well.

Perspective: This manuscript reviews the history of FM and its diagnosis, evidence supporting central augmentation of pain in FM, potential mechanisms of central augmentation, current approaches to integrated care of FM, and areas of active collaboration between FM research and other chronic pain conditions.

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Key words: Fibromyalgia, central sensitization, treatment, stress, sensory augmentation, nonpharmacological.

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Clinicians often see patients with pain and other somatic symptoms that defy explanation when based upon the degree of damage or inflammation noted in peripheral tissues. In fact, medically unexplainable symptoms are among the most common concerns for which individuals seek medical attention.99 When a patient presents with pain, an evaluation is usually performed looking for the cause of the pain. If none is found, patients are often given a diagnostic label that merely connotes chronic pain in a region of the body, without an underlying mechanistic cause (eg, chronic low back pain, headache, temporomandibular disorder [TMD], etc.). In other cases, the diagnostic label alludes to putative underlying mechanisms that may be responsible for the individual’s pain (eg, facet syndrome).

Fibromyalgia (FM) is merely the current term given to individuals with chronic widespread musculoskeletal pain, for which no alternative cause can be identified. Gastroenterologists often see the same class of patients but focus on gastrointestinal complaints, and use terms such as functional GI disorder, irritable bowel syndrome (IBS), nonulcer dyspepsia, or esophageal dysmotility to explain the symptoms.99 Neurologists see similar individuals for their headaches and/or unexplained facial pain, urologists see individuals for unexplained pelvic pain and urinary symptoms (using labels such as interstitial cystitis, chronic prostatitis, vulvodynia, and vulvar...
vestibulitis), and dentists see similar individuals calling the condition TMD.

Until recently these unexplained pain syndromes perplexed researchers, clinicians, and patients, and were thought to be completely separate clinical entities. However, emerging evidence now suggests the following:

- Often, individuals (and their family members) with one of these entities have several of these conditions.1,2,8 Many terms have been used to describe these coaggregating syndromes and symptoms, including functional somatic syndromes, somatization disorders, allied spectrum conditions, chronic multisymptom illnesses, medically unexplained symptoms, and so on.1,6,51,79,154
- Women are more likely to have these disorders than men, but the sex difference is much more apparent in clinical samples (especially tertiary care) than in population-based samples.1,2,47
- Individuals with these conditions (eg, FM, IBS, headache, TMD, etc) display diffuse hyperalgesia (increased pain to normally painful stimuli) and/or allodynia (pain to normally nonpainful stimuli).59,61,97,115,117 This abnormality across conditions suggests that these individuals have a fundamental problem with pain or sensory processing rather than an abnormality confined to a specific region of the body where pain is perceived to originate.
- Similar types of therapies are efficacious for all of these conditions, including both pharmacological (eg, tricyclic compounds such as amitriptyline) and nonpharmacological treatments (eg, exercise or cognitive behavioral therapy). Conversely, individuals with these conditions typically do not respond to therapies that are effective when pain is due to damage or inflammation of peripheral tissues (eg, NSAIDs, opioids, injections, or surgical procedures).

Until perhaps a decade ago, these conditions were all on somewhat equal (and tenuous) scientific ground. But within a relatively short period of time, research methods in experimental pain testing, functional imaging, and genetics have led to tremendous advances in the understanding of several of these conditions, most notably FM, IBS, and TMD.

Chronic pain has been thought of as being a disease having common underlying central mechanisms that are operative in these idiopathic or functional pain syndromes regardless of whether the pain is present throughout the body (eg, in FM) or localized to the low back, the bowel, or the bladder. Despite the term central being historically defined somewhat narrowly as referring to damage within the nervous system, it is an appropriate term to describe conditions such as FM, IBS, TMD, vulvodynia, and many other entities needing to imply that the pathology leading to the experience of pain is coming from the CNS rather than inflammation or damage within the periphery.1,2

The review regarding fibromyalgia below focuses on our current understanding of this disorder as a prototypical central pain syndrome using the term as described above.

Fibromyalgia: Early Conceptualizations

During the late 19th and early 20th centuries, many clinicians were intrigued by the ability of anesthesia and narcotic analgesics to eliminate acute pain from injuries and medical procedures. Believing that the pathophysiology of pain was largely understood, pain that resisted these conventional means and/or exceeded observable tissue damage was considered to emanate from psychiatric illness.111 Early conceptualizations of FM were not immune to this type of thinking.

Sir William Gowers coined the term fibrositis in 1904 to describe the muscular pain commonly seen in clinics of his time. The term fibrositis suggested inflammation of the fibrous muscle tissue as being the cause of this condition. Other clinicians of the time were less certain about the pathophysiology of this condition and instead attributed the complaint to muscle tension (a functional problem) or to psychogenic rheumatism (suggesting a psychiatric origin). The term fibromyalgia was not applied to this clinical presentation until the mid-1970s.138 The change in nomenclature from fibrositis to fibromyalgia reflected the increasing lack of evidence for any inflammation in the connective tissues of individuals presenting with this condition. Thus, within the fibrous tissues there was -algia (ie, pain) but no -itis (ie, inflammation). Researchers needed a means of quantifying the pain experience in these patients and chose to quantify tender points (regions of extreme tenderness). With this choice to include tender points, FM became a condition of both chronic pain and tenderness. FM was also associated with disturbances in deep and restorative sleep,113 Yunus et al114 later reported on the major clinical manifestations of patients with FM seen in rheumatology clinics. In 1990, the American College of Rheumatology (ACR) established its research criteria characterizing FM as a condition of both pain and tenderness.116

While the ACR criteria has succeeded in promoting research on groups of individuals possessing common qualifying criteria, these criteria may not be sufficiently broad as to capture the totality of the illnesses as experienced by patients. The use of these criteria in clinical settings to diagnose individuals, an unintended use of the criteria, has led to a number of misconceptions regarding FM (eg, FM being solely a chronic-pain condition, FM being a discrete illness of the peripheral muscle, and FM always being associated with psychiatric illness).

The inclusion of tender points in the ACR criteria suggested that there was some unique significance to the locations of tender points. In fact, the term “control points” was coined to describe areas of the body that should not be tender in FM. Individuals were assumed to have a psychological cause for their pain if they were tender in control regions. Empirical work has since found that the tenderness in FM extends throughout the entire body—there are no control points. The forehead and thumbnail (ie, former control regions) are just as tender as active tender points for individuals with FM as well as for healthy controls.38,67,125
The tender point requirement in the ACR criteria also misrepresents the nature of the tenderness in this condition (ie, local rather than widespread), and strongly influences the demographic and psychological characteristics of FM. For example, women are only 1.5 times more likely than men to experience Chronic Widespread Pain (CWP; ie, pain in all 4 quadrants of the body but not assessed by tender points), but are 10 times more likely than men to have 11 or more tender points. Thus, the addition of tender points to a diagnosis of CWP is largely responsible for women being 10 times more likely to meet ACR criteria for FM than men.

Another unintended consequence of requiring both CWP and at least 11 tender points for the diagnosis of FM is that individuals with FM are likely to be distressed. The distress in this case appears to be associated with the requirement of 11 tender points rather than CWP. Population-based studies find that CWP is only modestly associated with distress, whereas tender points show a much stronger association. Requiring tender points for a diagnosis of FM selects for women (who are generally more tender than men), and distressed individuals who are more commonly seen in tertiary-care centers (where many of the early FM studies were conducted).

In summary, although many clinicians uniquely associate FM with women who display high levels of distress, much of this association is an artifact reflecting: 1) the ACR criteria that require 11 out of 18 tender points; and 2) the fact that most studies of FM have originated from clinical samples in tertiary-care centers, where there are higher rates of psychiatric comorbidities than in community-based samples. Thus, what was known about FM as recently as 1990 was largely predicated upon several tenuous assumptions about the nature of the condition. In fact, major advances have only occurred in understanding FM once investigators concluded that FM was not a condition caused by peripheral damage or inflammation, and began to explore the central neural mechanisms of FM.

Fibromyalgia: A Condition of Central Pain and Sensory Augmentation

Osteoarthritis and rheumatoid arthritis are examples of conditions characterized by inflammation or peripheral mechanical damage, with the pain of these conditions thought to arise predominantly via peripheral mechanisms. In contrast, early studies in FM established that there was no peripheral damage or inflammation within the muscles or tissues, and thus researchers began to search for alternative explanations for the pain of this condition. Because tenderness throughout the body was a defining feature of the illness, a number of pathophysiological processes were explored that could account for diffuse pain in the absence of peripheral damage. Investigations have focused upon central pain processing systems, hypothalamic pituitary adrenal axes, and the autonomic nervous system. To date, the accumulated evidence supports some involvement of all of these systems. However, the most fruitful area of research in FM has been the work exploring the underlying reason(s) for the allodynia (pain from normally nonnoxious stimuli) and hyperalgesia (augmented response to painful stimuli) seen in this and related central pain conditions.

The most consistent finding in FM research is increased tenderness to pressure (ie, mechanical hyperalgesia or mechanical allodynia). While skeptics have questioned the veracity of reports of increased tenderness due to a reliance on patient self-report, more sophisticated pain-testing paradigms (such as the multiple random staircase) help to rule out potential biases associated with self-report. The current data implicates central mechanisms that augment pain (eg, wind-up), or attenuate the activity in descending anti-nociceptive pathways (eg, DNIC). Augmented response to evoked painful stimuli has recently been corroborated by functional brain-imaging techniques that allow the visualization of structures purportedly involved in pain processing.

In addition to sensitivity to pressure stimuli, individuals with FM also appear to have hyperalgesia to stimuli applied to the skin and display a decreased threshold to heat, cold, and electrical stimuli. A decreased sensory threshold may not be limited to cutaneous and muscular mechanisms in FM. Decreased nociceptive thresholds also occur with auditory tones in people with FM, suggesting that these individuals may have a generalized decrease in nociceptive thresholds. A recent study by Geisser et al. used a random staircase paradigm to test both the auditory threshold and the pressure threshold in FM. This study found that individuals with FM displayed low thresholds to both types of sensory stimuli, and the shared variance between the 2 thresholds was sufficiently high as to suggest a common underlying mechanism. The notion that FM might represent generalized neurobiological amplification of sensory stimuli has some support from functional imaging studies suggesting that the insula is the most consistently hyperactive neurocortical region of the pain matrix. This region has been noted to play a critical role in sensory integration, with the posterior insula serving a purer sensory role, and the anterior insula being associated with the emotional processing of sensations.

Corroborative Neuroimaging of Central Pain Processing in FM

The primary modes of functional imaging that have been used in FM include functional Magnetic Resonance Imaging (fMRI), Single Photon Emission Computed Tomography (SPECT), and Positron Emission Tomography (PET). A summary of findings using each of these modalities in FM follows.

Single-Photon-Emission Computed Tomography

SPECT was the first functional neuroimaging technique to be used in fibromyalgia. SPECT imaging involves the introduction of radioactive compounds into the participant’s blood stream, which then decay over time,
More recently, Wood et al. used PET to show that regional cerebral blood flow between FM and controls. This study found decreased blood flow in both the caudate and the thalamus of FM patients, findings that were largely replicated in a second study. A third SPECT trial used a more sensitive radioligand (99mTc-ECD) in FM patients and pain-free controls. Guedj et al. found hyperperfusion of the radioligand within the somatosensory cortex for FM and hypoperfusion in the anterior and posterior cingulate, the amygdala, medial frontal and parahippocampal gyrus, and the cerebellum. These studies have been interpreted as providing evidence for enhanced sensory processing and reduced attentional and affect regulation in FM.

One longitudinal treatment trial used SPECT imaging to assess changes in rCBF following administration of amitriptyline in 14 FM patients. After 3 months of treatment with amitriptyline, increases in rCBF in the bilateral thalamus and the basal ganglia were observed. Since the same 2 regions had been implicated previously, these data suggest that amitriptyline may normalize the altered blood flow, thereby reducing pain symptoms.

**Functional MRI (fMRI)**

fMRI is a noninvasive brain-imaging technique that relies on changes in the relative concentration of oxygenated to deoxygenated hemoglobin within the brain in response to a stimulus (e.g., evoked pain during scanning). The first study to use fMRI in individuals with FM was performed by Gracely et al. In this study, 16 FM patients and 16 matched controls were exposed to painful pressures during fMRI scanning. During the application of stimuli considered by participants to be painful, both patients and controls demonstrated increased neural activations in the primary and secondary somatosensory cortex, the insula, and the anterior cingulate. These activations were all in cortical regions commonly observed in fMRI studies to be associated with the processing of painful stimuli. While the regions of activation were similar for the patients and controls, the groups differed with regard to the amount of stimuli needed to activate this pain matrix. For FM, this matrix was activated by less than half of the stimulus needed for healthy controls. These findings were consistent with a left-shift in the stimulus-response function, which is characteristic of centrally mediated hyperalgesia and reduced noxious threshold to sensory stimuli. Similar findings have been reported in FM using heat stimulation.

**PET Imaging**

PET has been used in several FM studies. In the first such study, Yunus et al. showed no differences in regional cerebral blood flow between FM and controls. More recently, Wood et al. used PET to show that attenuated dopaminergic activity may be playing a role in pain transmission in FM, a deficit in part manifested by deficiencies in stress-induced analgesia in FM. Harris et al. also recently used PET to demonstrate decreased mu opioid receptor availability in FM.

In summary, there is substantial evidence from neuroimaging studies suggesting that central factors are important in the processing of pain in people with FM. In addition, much of the neuroimaging work in FM is highly consistent with the work being conducted in pain more generally. These findings in aggregate suggest that individuals with FM have a narrow range of tolerance for pain (and perhaps other sensory stimuli) before it becomes noxious. Potential causes of this central augmentation of pain and sensory processing in FM will be explored next.

**Other Neurobiological, Behavioral, Psychological, and Cognitive Factors Operative in FM**

Just as in most other diseases, the underlying pathophysiological mechanisms in FM involve interactions between genetic and environmental factors that then initiate a cascade of physiological, psychological, behavioral, and cognitive factors that interact to manifest in symptoms and functional decline. In addition to the left-shift in stimulus-response function there are many other pathophysiological processes that have been extensively studied, leading to a reasonably good understanding of the biopsychosocial underpinnings of FM. These include: 1) familial and genetic predisposition; 2) environmental stressors as triggers; 3) HPA axis and autonomic nervous system dysfunction; 4) functional abnormalities in pain and sensory processing; and 5) cognitive, behavioral, and psychological factors.

**Familial and Genetic Factors in FM**

There appears to be a strong familial component to the development of FM. First degree relatives of individuals with FM display an 8-fold greater risk of developing FM than those in the general population. Family members of individuals with FM are more tender than are the family members of controls, and family members of individuals with FM are much more likely to have other disorders related to FM such as IBS, TMD, headaches, and regional pain syndromes. This familial and personal co-aggregation of conditions was originally termed affective spectrum disorder, and more recently, central sensitivity syndromes and chronic multisymptom illnesses (CMI).

Recent studies have begun to identify specific genetic polymorphisms that are associated with a higher risk of developing FM. To date, the serotonin 5-HT2A receptor polymorphism T/T phenotype, serotonin transporter, dopamine 4 receptor, and COMT (catecholamine O-methyl transferase) polymorphisms are each seen in higher frequency in FM. All of the polymorphisms identified to date involve the metabolism or transport of monoamines, compounds that play a critical role in the human stress response, heightened pain sensitivity, and affective vulnerability.
Environmental Stressors and FM

There appear to be a number of biological stressors that are capable of either triggering or exacerbating FM and related conditions. Physical trauma, for example, has been associated with the onset of FM especially in cases involving the axial skeleton and trunk. Psychological and emotional stress, often of an interpersonal or personally relevant nature, has been associated with the onset and maintenance of FM. Other stressors include certain infections (eg, Epstein-Barr virus, parvovirus, and Lyme disease), hormonal alterations (eg, hypothyroidism), and specific types of catastrophic events where the patient is the victim of the actions of others (eg, war and auto accidents but not natural disasters). In genetically vulnerable individuals, however, single stressors or stressors in combination at a time of vulnerability may trigger the onset of FM. For others, the stressor may be a lifelong history of pain and other sensory symptoms (eg, headaches, irritable bowel and bladder, regional musculoskeletal pain, etc.) that eventually evolve into the more wholly systemic disorder characterized by FM.

HPA Axis and Autonomic Nervous System (ANS) Abnormalities

Due to the fact that disparate stressors can trigger the development of FM in genetically susceptible individuals, the human stress response has been closely examined for a causative role in FM. Recent research suggests that although this system in humans has been highly adaptive throughout history, the stress response may be inappropriately triggered in some individuals by a wide assortment of everyday occurrences (eg, non-life-threatening events). Frequent activation of a physiologic response more appropriate for threats to survival get experienced as being intolerable and can be pathogenic to the body.

The human stress systems have been studied extensively in FM and have generally demonstrated altered functioning of the HPA axis and sympathetic nervous system. However, the type of alteration has not been consistent. Studies have demonstrated both hypo- and hyper-activity of both the HPA axis and sympathetic nervous system in FM and the degree of abnormality is often small or occurs in a very small percentage of patients with substantial overlap between patients and controls. Early on, abnormalities in these axes were thought to cause the pain and other symptoms of FM. Data now suggest the opposite. Two studies examining HPA function in FM have shown that salivary cortisol levels co-varied with clinical pain levels, and that CSF levels of CRH were more closely related to an individual's clinical pain level or a history of early life trauma than to status of being someone with FM or a control. Most previous studies of HPA and autonomic function in FM failed to control for pain levels, previous history of trauma, post-traumatic stress disorder (PTSD), or other comorbid disorders that could affect HPA or autonomic dysfunction; thus, it is not surprising that a subset of patients with FM would demonstrate these HPA abnormalities.

Heart rate variability has been evaluated in patients with FM as a surrogate measure of autonomic function. Typically, individuals with FM demonstrate reduced heart-rate variability in response to a biological or environmental demand when compared to healthy controls. Several studies now suggest that whereas hyporeactive heart-rate variability may not cause the pain of FM, a history of aberrations in heart-rate variability may predispose an individual to develop FM symptoms, possibly identifying patients at risk. A recent study also showed that heart-rate variability was normalized following exercise therapy in FM, suggesting that dysregulated heart rate may be an epiphenomenon due in part to deconditioning.

Functional Abnormalities in Pain and Sensory Processing in FM

Most investigators in FM agree that there are probably multiple reasons for the augmented pain and sensory processing in this condition and for each differing mechanism, different root causes as well. Two mechanisms have very strong support: 1) a lack of descending analgesic activity, and 2) central sensitization.

Lack of Diffuse Noxious Inhibitory Control (DNIC)

In healthy humans and laboratory animals, application of an intense, painful stimulus for 2 to 5 minutes produces generalized whole-body analgesia. This analgesic effect, termed diffuse noxious inhibitory controls (DNIC), has been consistently observed to be attenuated or absent in groups of FM patients as compared to healthy controls. The DNIC response in humans is believed to be mediated partly by descending opioidergic pathways and in part by descending serotonergic-noradrenergic pathways. In fibromyalgia, the accumulating data suggests that opioidergic activity is normal or even increased, in that concentrations of cerebrospinal fluid (CSF) enkephalins are roughly twice as high in FM and idiopathic low-back-pain patients as compared to healthy controls. Moreover, PET data show that baseline mu-opioid receptor binding is decreased in multiple pain processing regions in the brains of FM patients, consistent (but not pathognomonic) with the hypothesis that there is increased release of endogenous mu-opioid ligands in FM leading to high baseline occupancy of the receptors.

The biochemical and imaging findings supporting increased (or intact) activity of endogenous opioidergic systems in FM are consistent with the anecdotal clinical experience that opioids are generally ineffective analgesics in patients with FM. In contrast, studies have shown the opposite for serotonergic and noradrenergic activity in FM. The principal metabolite of norepinephrine, 3-methoxy-4-hydroxyphenethylene (MPH), is lower in the CSF of FM patients; similarly, patients with FM have been shown to have reduced levels of serotonin and its precursor, L-tryptophan, along with reduced levels of the principal serotonin metabolite, 5-HIAA, in
Lessons from FM and Chronic Pain

Central Sensitization

The terms central augmentation or central pain threshold are different than the term central sensitization. Although these terms have sometimes been inappropriately used synonymously, central sensitization refers to a distinct spinal mechanism wherein an initial nociceptive focus can lead to regional-pain amplification. In animal models, this finding is associated with excitatory amino acid and Substance P hyperactivity. Four independent studies have shown that patients with FM have approximately 3-fold higher concentrations of Substance P in cerebral spinal fluid (CSF) when compared with normal controls. Other chronic-pain syndromes, such as osteoarthritis of the hip and chronic low-back pain, are also associated with elevated Substance P levels. Interestingly, once elevated, Substance P levels do not appear to change dramatically, and do not rise in response to acute painful stimuli. Thus, high Substance P appears to be a biological marker for the presence of chronic pain in FM and perhaps other conditions as well.

Another important neurotransmitter in pain processing, with likely importance to FM, is glutamate. Glutamate (Glu) is a major excitatory neurotransmitter within the central nervous system, and cerebrospinal fluid levels of glutamate are twice as high in individuals with FM than in controls. Not only are these levels elevated, but a recent study using proton spectroscopy demonstrated that the glutamate levels in the insula of individuals with FM decrease in response to reductions in both clinical (ie, spontaneously reported) and experimental (ie, evoked) pain when FM patients are treated with acupuncture.

Psychological/Cognitive/Behavioral Factors

Psychological factors affecting pain can be divided into 2 types: 1) psychiatric disorders; and 2) psychosocial influences. Psychiatric disorders such as major depression, anxiety disorders, and personality disorders are diagnosable conditions that can coexist with and negatively impact pain. For example, depression has been shown to co-occur with pain 52% of the time in pain clinics, 27% of the time in primary-care clinics, and 18% of the time in population-based studies. Epidemiological studies, twin, and case-control studies show similar findings. While chronic-pain and psychiatric conditions often co-occur; they should not be confused with one another or viewed as being the same condition. Treatment of coexisting psychiatric disorders in a patient with chronic pain is highly appropriate; but is not likely to fully address the chronic-pain problem. Both conditions need to be addressed, often with different interventions. Neuroimaging studies suggest that augmented pain perception (eg., as seen in FM) occurs whether comorbid depression is present or not. This type of evidence helps to refute earlier claims that unexplainable pain is simply a manifestation of depression.

Quite independent of physiological factors, cognitive beliefs about pain have been shown to account for greater than 40% of the variance in physical functional status and around 30% of the variance in affective symptoms for patients with chronic pain. Awareness of individuals’ beliefs about pain can importantly influence adherence to treatment, treatment responsivity, and long-term outcomes to both physically and psychologically oriented treatments.

Two cognitive factors that have received a great deal of research attention are locus of pain control and catastrophizing. Beliefs in personal control are thought to evolve from multiple learning experiences where personal effort is perceived to influence outcomes. The perception of having personal control has been labeled an internal locus of control. Alternatively, an external locus of control is learned when outcomes are perceived as occurring outside of personal control. Locus of control for pain refers to patients’ perceptions about their personal ability to control pain. In studies of patients with FM, internal locus of control has been associated with better affect, reduced symptom severity, and less disability in function. Unfortunately, most individuals with FM have a more external orientation in their locus of control even in comparison with other chronic pain conditions.

Pain catastrophizing, or responses to pain that characterize it as being awful, horrible, and unbearable, is increasingly recognized as an extremely important contributor to the experience of pain. Studies have found catastrophizing to be associated with pain and pain-related disability independent of the influence of depression. Burton et al observed that catastrophizing alone accounted for 47% of the variance in predicting the development of chronic pain from an episode of acute pain. Although the precise mechanisms
by which catastrophizing influences the experience of pain are not known, it is thought that this cognitive style influences the attentional focus on painful events. Persons who catastrophize have more difficulty shifting their focus of attention away from painful or threatening stimuli and appraise stimuli as being more threatening or harmful generally. In as much as cognitions modulate cortical pain processing, both external locus of control and catastrophizing are likely to contribute to an augmentation of pain. Corroborative evidence from fMRI studies of catastrophizing in FM support this observation.66

Emotional stress/distress also influences pain modulation, but like stressors in general, emotional influences on FM pain processing are quite varied. Several studies, however, suggest that personally relevant stressors play a more salient role in symptom exacerbation in FM than do more global stressors. For example, at the time of the 9/11 terrorist attacks, 2 studies examining daily diary monitoring in FM, were being conducted in both New York and Washington, DC.128,161 In both studies, symptoms on the days immediately before, during, and following the terrorists’ attacks were compared. Both studies failed to find any relationship between the terrorists’ attacks and symptom worsening; rather, symptoms were more strongly related to personal activities and personally relevant stressors.

In summary, it is likely that there are many interrelated factors that combine to produce the symptoms of FM. It is likely however that the balance of factors (eg, psychological, DNIC, excitatory influences) tend to cluster into groups of individuals having a common presentation of FM.

One subtyping study in FM focused upon varying responses to a coping instrument (eg, the MPI148). This study suggested that there were 3 groupings of individuals with FM each requiring treatments to be tailored to their respective coping responses for FM. A second subtyping study based subtypes upon the relative predominance of the 3 dimensions of pain145 as well as functional response (ie, [a] sensory dimensions (evoked measures of tenderness, self-reported clinical pain); [b] affect (trait depression and anxiety); [c] cognitions about pain (catastrophizing and control over pain); and [d] functional status). In the latter study, cluster analytic methods revealed that the largest group of patients displayed moderate influences from each domain. A second group displayed strong influences from affective and cognitive dimensions while the third group, being the most tender, displayed relatively little affective influence but possessed positive cognitive influences (ie, greater perceived control over pain).62 Although different in their approaches, both of these subtyping studies underscore the importance of treating FM in a tailored manner and from multiple perspectives.

**Fibromyalgia: Approaches to Treatment**

Evidence-based treatment of FM advocates a multifaceted program emphasizing education, certain medications, exercise, and cognitive therapy.64 Once a physician rules out other potential disorders, an important and at times controversial step in the management of fibromyalgia is asserting the diagnosis. Despite some assumptions that being labeled with fibromyalgia may adversely affect patients, a study by White et al155 indicated that patients had significant improvement in health satisfaction and symptoms after being labeled. Regardless of whether a diagnosis is rendered, patients presenting with CWP should receive education about their condition and the role that they can play in its management. For some individuals with FM, this can be an effective and sufficient intervention.64

**Pharmacological Approaches to FM Management**

The most frequently studied pharmacologic therapy for FM has been low doses of tricyclic antidepressant (TCA) compounds. Most TCAs increase the concentrations of serotonin and noradrenaline (noradrenaline) by directly blocking their respective reuptake. The effectiveness of TCAs, particularly amitriptyline and cyclobenzaprine, in treating the symptoms of pain, poor sleep, and fatigue associated with FM is supported by several randomized, controlled trials.8,119 Tolerability is a problem but can be improved by beginning at very low doses, giving the dose a few hours before bedtime, and very slowly escalating the dose.

Because of a better side-effect profile, newer antidepressants, ie, selective serotonin reuptake inhibitors (SSRIs), are frequently used in FM. The SSRIs fluoxetine, citalopram, and paroxetine have each been evaluated in randomized, placebo-controlled trials.6,31,32,35,64,118 In general, the results of studies of SSRIs in fibromyalgia have paralleled the experience in other pain conditions. The newer, “highly selective” serotonin reuptake inhibitors (eg, citalopram) seem to be less efficacious than the older SSRIs, which have some noradrenergic activity at higher doses.50

Dual receptor inhibitors such as serotonin-NE and NE-serotonin reuptake inhibitors (SNRIs and NSRIs) may be of more benefit than pure serotonin drugs.50 These drugs are pharmacologically similar to some TCAs in their ability to inhibit the reuptake of both serotonin and NE, but differ from TCAs in being generally devoid of significant activity at other receptor systems. This selectivity results in diminished side effects and enhanced tolerability. The first available SNRI, venlafaxine, has data to support its use in the management of neuropathic pain, and retrospective trial data demonstrate that this compound is also effective in the prophylaxis of migraine and tension headaches.6 Two studies in FM have had conflicting results, with the one using a higher dose showing efficacy.

Two new SNRIs, milnacipran and duloxetine, have undergone recent multicenter trials and were shown to be effective in a number of outcome variables, and both have recently been approved by the U.S. for FM.9,152 In the study evaluating milnacipran, statistically significant differences were noted in overall improvement, physical functioning, level of fatigue, and degree of reported physical impairment. In the trial of duloxetine compared to placebo, participants treated with
A large number of fibromyalgia patients use nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. Although numerous studies have failed to confirm their effectiveness as analgesics in FM, there is limited evidence that patients may experience enhanced analgesia when treated with combinations of NSAIDs and other agents. This phenomenon may be a result of concurrent peripheral-pain (ie, due to damage or inflammation of tissues) in certain conditions (eg, osteoarthritis, rheumatoid arthritis) that may be present, and/or that these co-morbid peripheral-pain generators might lead to worsening of central pain.

**Nonpharmacologic Management of FM**

The 2 best-studied nonpharmacological therapies for FM are cognitive behavioral therapy (CBT) and exercise. Both of these therapies are efficacious in the management of FM and are well supported by systematic reviews. Both of these treatments can lead to sustained (ie, greater than 1 year) improvements, and can be quite effective in adherent individuals.

Aerobic exercise has been demonstrated to be effective at improving outcomes for a wide range of chronic medical conditions. Recent systematic reviews of the exercise literature suggest that in FM, aerobic exercise programs improve overall symptoms as well as pain. In an especially well-conducted study involving a 20-week, supervised, cardiovascular-fitness training program, 18 FM patients yielded statistically significant improvement in cardiovascular-fitness scores, and clinically and statistically significant improvements in pain-threshold scores. A second study demonstrated a short-term benefit of aerobic exercise in FM patients when compared to a group that received stress management. The reason for the apparent beneficial effect of exercise on symptoms in these conditions is likely multifactorial. Aerobic exercise may influence endogenous analgesic systems while also increasing a sense of well-being and control. To reduce the pain associated with exercise, nonimpact exercises such as walking, swimming, or stationary cycling are often recommended. Investigators have found a gradual progression in exercise intensity and a focus on adherence to a lifelong program to be most effective.

Behavioral therapy (BT) and cognitive-behavioral therapy (CBT) for pain is designed to address the various aspects of the biopsychosocial model. Reviews of the BT/CBT literature suggest that these interventions as a class are quite efficacious for pain management. In specific application to FM, there are at least 17 well-conducted studies of CBT supporting its use. While the application of CBT has long been associated with outcomes of pain reduction for FM, CBT may have its greatest influence on improving physical functional status, an outcome thought to be more challenging than pain relief.

**Advances in Patient Assessment**

FM has long been thought of as being a chronic-pain condition. Patients with FM, however, report that it has
other symptoms as well that profoundly impact their quality of life. The Outcomes Measures in Rheumatology (OMERACT) organization has worked to identify the domains of relevance that should be assessed and reported upon in the context of clinical trials involving rheumatological conditions. The Fibromyalgia Task Force within OMERACT has conducted Delphi studies to obtain consensus from both clinicians and patients regarding the domains that hold the most relevance for FM. These studies suggest that in addition to pain, the assessment of FM should include the measurement of patient global impressions of well-being, fatigue, functional status, sleep, mood, tenderness/stiffness, and problems with concentration/memory (ie, dyscognition). This initiative is also focused upon validating assessment instruments that capture domains of relevance that exceed a specific focus on pain. The work of the FM OMERACT group is highly consistent with the findings and conclusions of these 3 independent groups that there was little evidence that patients with fibromyalgia syndrome. Am J Med 106:534-543, 1999

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