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Understanding Fibromyalgia: Lessons from the Broader Pain Research Community

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Abstract

Fibromaylgia (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; but 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.

Keywords

Fibromyalgia; central sensitization; treatment; stress; sensory augmentation; non-pharmacological

OVERVIEW

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.[89] When a patient presents with pain, usually an evaluation is 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

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cause (e.g., 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 (e.g., “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 gastroenterological complaints, and use terms such as functional GI disorder, irritable bowel syndrome (IBS), non-ulcer 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 Temporomandibular Disorder (TMD).

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

- Often, individuals with one of these entities, (and their family members), have several of these conditions.[10,79] Many terms have been used to describe these co-aggregating syndromes and symptoms, including functional somatic syndromes, somatization disorders, allied spectrum conditions, chronic multisymptom illnesses, medically unexplained symptoms, etc.[16,51,79,154]
- 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.[1,47]
- Individuals with these conditions (e.g., FM, IBS, headache, TMD, etc.) display diffuse hyperalgesia (increased pain to normally painful stimuli) and/or allodynia (pain to normally non-painful 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 (e.g. tricyclic compounds such as amitriptyline) and non-pharmacological treatments (e.g., exercise 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 (e.g. NSAIDs, opioids, injections, 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 (e.g. in FM) or localized to the low back, the bowel, or the bladder. Despite the term “central” being historically defined somewhat narrowly 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.[34,170]

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-1970's.[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* (i.e. pain) but no *–itis* (i.e inflammation). Researchers needed a means of quantifying the pain experience in these patients and as such 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 associated with disturbances in deep and restorative sleep.[113] Yunus and others later reported on the major clinical manifestations of patients with FM seen in rheumatology clinics[174] and in 1990 the American College of Rheumatology (ACR) established its research criteria characterizing FM as a condition of both pain and tenderness,[166]

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 lead to a number of misconceptions regarding FM (e.g., 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 (i.e. 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 (i.e., 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 Wide-spread Pain (CWP; i.e. pain in all four 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.[165] 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.[164] Requiring tender points selects for women (who are generally individuals who are more commonly seen in tertiary care centers (where many of the early FM studies were conducted).[1]

In summary, although many clinicians uniquely associate FM with women who display high levels of distress, much of this is an artifact reflecting: 1) the ACR criteria that require 11/18 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 co-morbidities 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 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 being 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. The most fruitful area of research in FM however has been the work exploring the underlying reason(s) for the allodynia (pain from normally non-noxious 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 (i.e. mechanical hyperalgesia or mechanical allodynia).[67,123] 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.[123,122,124] The current data implicates central mechanisms that augment pain (e.g., “wind-up”), or attenuate the activity in descending antinociceptive pathways (e.g. DNIC).[90,96,141] 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.[39,65]

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[54,58,90, 123], cold [91,90], and electrical stimuli.[13] Decreased sensory threshold may not be limited to cutaneous and muscular mechanisms in FM. Decreased nociceptive tones in people with FM suggesting these individuals may have a generalized decrease in nociceptive threshold.[57,104] A recent study by Geisser and colleagues used a random staircase paradigm to test both the auditory threshold and pressure threshold in FM.[55] This study found that displayed low thresholds to both types sensory stimuli, and the shared variance between the two 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.[40,41,146]

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 giving a window for the assessment of neural activity. The first study using SPECT imaging in FM compared 10 FM patients with 7 age- and education-matched healthy controls. This study found decreased blood flow in both the caudate and the thalamus of FM patients,[116] findings that were largely replicated in a second study.[93] A third SPECT trial used a more sensitive radioligand (99mTc-ECD) in FM patients and pain-free controls.[68,69,71,70] Guedj and colleagues 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.[3] After three months of treatment with amitriptyline, increases in rCBF in the bilateral thalamus and the basal ganglia were observed. Since the same two 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 non-invasive 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 and colleagues. In this study 16 FM patients and 16 FM patients and 16 matched controls were exposed to painful pressures during fMRI scanning.[65] 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.[39]

PET Imaging—PET has been used in several FM studies. In the first such study, Yunus and colleagues showed no differences in regional cerebral blood flow between FM and controls.[176] More recently, Wood and colleagues used PET to show that attenuated dopaminergic activity may be playing a role in pain transmission in FM[167,168] a deficit in part manifest by

deficiencies in stressinduced analgesia in FM. Harris and colleagues also recently used PET to demonstrate decreased *mu* opiod receptor availability in FM.[76]

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.[7,145] 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 pathophysiologic 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 eight-fold greater risk of developing FM than those in the general population.[10] 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 other regional pain syndromes.[10,28,85,86] This familial and personal co-aggregation of conditions was originally termed *affective spectrum disorder*,[80] and more recently, *central sensitivity syndromes* and chronic multisymptom illnesses (CMI).[51,175]

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.[22,29,27,120] 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.[45, 46]

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.[30] Psychological and emotional stress, often of an interpersonal or personally relevant nature has been associated with the onset and maintenance of FM.[73] Other stressors include certain infections (e.g. Epstein-Barr virus, parvovirus, and Lyme disease)[36] hormonal alterations (e.g. hypothyroidism) and specific types of catastrophic events where the patient is the victim of the actions of others (e.g. war and auto accidents but not natural disasters).[36] 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 (e.g. 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 (e.g. 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.[4,37,42,44,98,127] The type of alteration however has not been consistent. Studies have demonstrated both hypo- and hyperactivity 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 individuals' clinical pain level or a history of early life trauma than to status of being someone with FM or a control.[106,107] 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 co-morbid 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.[37,98,142] Several studies now suggest that whereas hypo-reactive 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,[63,100,101] 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.[84,90,94,96] The DNIC response in humans is believed to be partly mediated by descending opioidergic pathways and in part by descending serotonergic-noradrenergic pathways.[83,92,95] 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.[15] 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.[76]

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 (MPHG), is lower in the CSF of FM patients;[131] similarly, patients with FM have been shown to have reduced serum levels of serotonin and its precursor, L-tryptophan, along with reduced levels of the principal serotonin metabolite, 5-HIAA, in CSF.[131,177] Further evidence supporting deficiencies in this mechanism comes from treatment studies, where nearly any type of compound that simultaneously raises both serotonin and norepinephrine (tricyclics, duloxetine, milnacipran, tramadol) has been shown to be efficacious in treating FM and related conditions.[8,9,19,56]

These studies in aggregate suggest that for individuals with FM who demonstrate a lack of DNIC, the abnormality most likely rests with diminished serotonin and NE rather than a deficit in endogenous opioid activity. Pharmacological agents that enhance serotonin and NE likely bolster DNIC in these individuals thus reinstating an endogenous pain inhibitory mechanism that is ineffective in some individuals with FM.

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.[129,163] Demonstrating that the tenderness or hyperalgesia occurs far away from the area of pain, “central augmentation” or “central pain” are likely to be more appropriate semantic terms for what is seen in FM. Here we will explore potential mechanisms that might contribute to excitatory influences related to augmented pain experiences in FM.

Evoked experimental pain testing studies have suggested that some individuals with FM may have evidence of wind-up, a phenomena associated with temporal summation of c-fiber nociception resulting in heightened pain and indicative of central sensitization.[126,140] In animal models, this finding is associated with excitatory amino acid and Substance P hyperactivity.[169,171,173] Four independent studies have shown that patients with FM have approximately threefold higher concentrations of Substance P in cerebral spinal fluid (CSF), when compared with normal controls.[23,133,151,153] Other chronic pain syndromes, such as osteoarthritis of the hip and chronic low back pain, are also associated with elevated Substance P levels.[137] Interestingly, once elevated, Substance P levels do not appear to change dramatically, and do not rise in response to acute painful stimuli.[137] 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.[135] 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 (i.e. spontaneously reported) and experimental (i.e. evoked) pain when FM patients are treated with acupuncture.[75]

Psychological/Cognitive/Behavioral Factors

Psychological factors affecting pain can be divided into two types: (1) psychiatric disorders, and (2) psychosocial influences. Psychiatric disorders such as major depression, anxiety disorders, and personality disorders are diagnosable concerns 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.[14] Epidemiological studies, twin and case control studies show similar findings.[17,87] 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 (e.g. as seen in FM) occurs whether co-morbid depression is present or not.[60] This type of evidence helps to refute earlier claims that “unexplainable pain” is simply a manifestation of depression.[5]

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.[150] Awareness of individuals' beliefs about pain can importantly influence adherence to treatment, treatment responsively, and long term outcomes to both physical and psychologically oriented treatments.[82,143,159,160]

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,[103,121] Unfortunately, most individuals with FM, have a more external orientation in their locus of control even in comparison with other chronic pain conditions.[24,72,121]

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.[54,53,52,82,88,144] Burton and colleagues observed that catastrophizing alone accounted for 47% of the variance in predicting the development of chronic pain from an episode of acute pain. [25] 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, two 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 (e.g. 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 (e.g. the MPI[148], this study suggested that there were three groupings of individuals with FM each requiring treatments to be tailored to their respective coping responses for FM. A second subtyping study based sub-types upon the relative predominance of the three dimensions of pain[145] as well as functional response (i.e. (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 (i.e. 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 multi-faceted 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 and colleagues indicated that patients had significant improvement in health satisfaction and symptoms after being “labeled”.[155] 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/or norepinephrine (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, i.e. 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, e.g. 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 serotonergic 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.[2] 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 have both recently been approved by the U.S. 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 duloxetine had decreased self-reported pain and stiffness, and a reduced number of tender points. In both studies, benefits were shown to be independent of the drug effect on mood, thus suggesting that the analgesic and other positive effects of this class of drugs in FM is not simply due to their antidepressant effects. The most common side effects of this class of drugs include nausea (which can be reduced by taking the drug with food and/or slowly escalating the dose) and palpitations.

Alpha-2-delta ligands such as gabapentin and pregabalin also have been shown to be effective in the treatment of many different types of pain conditions, including fibromyalgia.[156] Gabapentin was shown in several studies to be efficacious in FM, and pregabalin has demonstrated efficacy in three published trials, and was approved for use in FM by the United States Food and Drug Administration (U.S. FDA) in 2007.[12; 11; 43; 109] These compounds may be better tolerated if a higher proportion of the dose (1200 – 2400mg/day of gabapentin or 300 – 450mg/day of pregabalin) is given at bedtime. The most common side effects of this class of drugs are lightheadedness, dizziness, edema, and weight gain.

Sedative-hypnotic compounds are widely used by fibromyalgia patients. A handful of studies have been published on the use of certain non-benzodiazepine hypnotics in FM, such as zopiclone and zolpidem. Reports suggest that these agents can improve the sleep and, perhaps, fatigue of FM, though they had no significant effects upon pain. On the other hand, gamma-hydroxybutyrate (also known as sodium oxabate), a precursor of GABA with powerful sedative properties, was recently shown to be useful in improving fatigue, pain, and sleep architecture in patients with FM.[136] Note, however, that this agent is a scheduled substance due to its abuse potential.

Pramipexole is a dopamine agonist indicated for Parkinson's disease that has shown utility in the treatment of periodic leg movement disorder.[18] Recent studies suggest that this compound may improve both pain and sleep in FM.[78]

Tizanidine is a centrally acting alpha-2 adrenergic agonist approved by the Food and Drug Administration for the treatment of muscle spasticity associated with multiple sclerosis and stroke. Literature suggests that this agent is a useful adjunct in treating several chronic pain conditions, including chronic daily headaches and low back pain. A recent trial improvements in several parameters in FM, including sleep, pain, and measures of quality of life.[132] Of particular interest was the demonstration that treatment with tizanidine resulted in a reduction in substance P levels within the CSF of patients with Fibromyalgia.[132]

There have been no adequate, randomized controlled clinical trials of opiates in FM, and many in the field (including the authors) have not found this class of compounds to be effective in

anecdotal clinical experience. Tramadol is a compound that has some opioid activity (weak mu agonist activity) combined with serotonin/NE reuptake inhibition. This compound does appear to be somewhat efficacious in the management of FM, as both an isolated compound and as fixed-dose combination with acetaminophen.[18]

A large number of fibromyalgia patients use non-steroidal 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 (i.e. due to damage or inflammation of tissues, e.g. osteoarthritis, rheumatoid arthritis) conditions that may be present, and/or that these co-morbid peripheral pain generators might lead to worsening of "central"pain.

Non-pharmacologic Management of FM

The two best-studied non-pharmacological therapies for FM are cognitive behavioral therapy (CBT) and exercise. Both of these therapies are efficacious in the management of FM [64] and are well supported by systematic reviews. Both of these treatments can lead to sustained (e.g. greater than one 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.[21,81,102,105,112,139] Recent systematic reviews of the exercise literature suggest that in FM, aerobic exercise programs improve overall symptoms, as well as pain.[26] 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.[20] A second study demonstrated a shortterm benefit of aerobic exercise in FM patients, when compared to a group that received "stress management." [157] The reason for the apparent beneficial effect of exercise on symptoms in these conditions is likely multifactorial. Aerobic exercise may influence endogenous analgesic systems[81] while also increasing a sense of well-being and control.[74,102,139] To reduce the pain associated with exercise, non-impact 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.[33,157]

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.[77,114] In specific application to FM, there are at least 17 well conducted studies of CBT supporting its use.[158] 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.[130,162]

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.[108,110] 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.[147] 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.[108,110] These studies suggest that in addition to pain, the assessment of FM should include the measurement of patient global impression of well being, fatigue, functional status, sleep, mood, tenderness/stiffness, and

problems with concentration/memory (i.e. 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 ongoing work of several other large organizations such as the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) focused upon identifying the domains that should be assessed in research involving chronic pain generally,[48,149] and the World Health Organization, International Classification of Functioning Disability and Health (ICF) initiative (WHO-ICF),[172] an initiative that seeks to developed a domain categorization coding system that identifies the relevant domains of functional status for medical illnesses in general. Again, the remarkable overlap in the findings and conclusions of these three independent groups suggest that at least some conditions involving chronic pain like FM, require broader assessment of patient-relevant domains if patient well-being and health is to be adequately evaluated. Broader assessment of domains beyond pain appears to have relevance not only in application with outcomes assessment but may also have utility in the context of phenotyping as well.

Exporting Mechanistic and Treatment Models to other Conditions

As mentioned, progress in FM research was sluggish until the *–itis* and even the *fibro-* (focus on the peripheral muscle) was abandoned and discovery moved to central pain and sensory processing models. Similar paradigm shifts have recently occurred in occurred in other related conditions. IBS was previously termed “spastic colitis” until the recognition that there was little *–itis* and motility changes were not the major pathological feature. Temporomandibular disorder was previously termed temporomandibular joint disorder until it was recognized that the problem was not largely within the joint.

The most recent disorders undergoing a paradigm shift in this regard are interstitial cystitis (IC) and chronic prostatitis (CP). For many years, treatments for these conditions focused upon the end organ (e.g. surgery, infection control, and reduction of inflammation). Like many other chronic pain conditions advances in these fields were progressing more slowly than desired. In 2007 the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) chose to establish a new network of institutions with expertise in FM, IBS, and CFS to help retool discovery in IC/PC by focusing more centrally. To do so required expertise from fields who had already made this paradigm shift successfully and could rapidly infuse methods of discovery to these conditions. To date, efforts along these lines have been successful.

Fibromyalgia: A Model for Studying a “Central Pain” Syndrome – Either Alone or in Combination with other Mechanistic Types of Pain

Although there are clearly some individuals who have only “central” pain as seen in fibromyalgia, in other pain syndromes there may be combinations of central, neuropathic, and peripheral pain. Focused investigations of the mechanisms underlying the augmented pain and sensory processing in FM may help shed light on the mechanisms underlying at least a subset of individuals in these other conditions or in chronic pain more generally. Several areas in which the research field of FM is already contributing to significant advances affecting other pain conditions are in the areas of patient characterization and outcomes assessment, partnership models linking researchers and patient advocacy groups, and approaches to exporting working models of central pain and sensory augmentation to other fields interested in applying this model for discovery in new conditions. Although relatively young compared to the study of other painful conditions, research in FM is advancing rapidly with discoveries and new methodologies that can help shape our understanding of related pain conditions (e.g. IBS, TMD) as well as painful conditions more generally.

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