THE AMERICAN JOURNAL of MEDICINE®

Fibromyalgia: An Overview

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ABSTRACT

Fibromyalgia is the diagnosis given to individuals with chronic widespread musculoskeletal pain for which no alternative cause, such as tissue inflammation or damage, can be identified. Fibromyalgia is now believed to be, at least in part, a disorder of central pain processing that produces heightened responses to painful stimuli (hyperalgesia) and painful responses to nonpainful stimuli (allodynia). Aberrations in central pain processing may also be partly responsible for symptoms experienced in several chronic pain disorders that coaggregate with fibromyalgia, which is itself a product of genetic and environmental factors. Thus, aberrational central pain processing is implicated in irritable bowel syndrome, temporomandibular disorder, chronic low back pain, and certain other chronic pain disorders. Fibromyalgia and related disorders appear to reflect deficiencies in serotonergic and noradrenergic, but not opioidergic, transmission in the central nervous system. The heightened state of pain transmission may also be owing to increases in pronociceptive neurotransmitters such as glutamate and substance P. In some cases, psychological and behavioral factors are also in play. Although the overlapping symptomatology between fibromyalgia and related disorders may present diagnostic challenges, proper examination and observation can help clinicians make an accurate diagnosis. In recent years, the vastly improved understanding of the mechanism underlying fibromyalgia and the related spectrum of diseases has fostered rapid advances in the therapy of these chronic pain disorders by both pharmacologic and nonpharmacologic interventions.
 • *The American Journal of Medicine (2009) 122, S3–S13*

KEYWORDS: Central pain syndromes; Diagnosis; Fibromyalgia; Hyperalgesia; Musculoskeletal pain; Neuroimaging

Fibromyalgia is a condition marked by chronic widespread pain and multiple symptoms, including fatigue, sleep disturbances, cognitive dysfunction, and depressive episodes.[1] Common disorders associated with fibromyalgia include chronic fatigue syndrome, irritable bowel syndrome (IBS), irritable bladder syndrome or interstitial cystitis, and temporomandibular disorder (TMD). Although patients will sometimes experience only 1 of these pain syndromes over the course of a lifetime, it is more likely that they (and their family members) will be affected by several of these related conditions.[2,3]

Women are more likely than men to have chronic pain disorders, but the sex-based difference is much more apparent in clinical settings (especially tertiary care) compared with population-based samples.[4,5] Patients with fibromyalgia and related conditions display diffuse hyperalgesia (heightened pain responses to normally painful stimuli) and/or allodynia (pain responses to normally nonpainful stimuli).[6–10] Such responses suggest that these individuals have a fundamental problem with pain or sensory processing rather than an abnormality confined to the region of the body where pain is experienced.

Until around a decade ago, fibromyalgia and other idiopathic pain conditions were all on somewhat tenuous scientific ground. However, within a relatively short time, innovations in experimental pain testing, functional imaging, and genetics have led to tremendous advances in the understanding of these conditions, most notably fibromyalgia, IBS, and TMD. Many experts in the pain field now believe that chronic pain itself is a disease and that the underlying mechanisms operative in these heretofore-considered "idiopathic" or "functional" pain syndromes may be similar, regardless of whether pain is present throughout the body, as in fibromyalgia, or localized to the low back, the bowel, or the bladder. The following overview focuses on our current understanding of fibromyalgia as a prototypical central pain syndrome.

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0002-9343/$ -see front matter
doi:10.1016/j.amjmed.2009.09.006

HISTORICAL PERSPECTIVE

Although the term "fibromyalgia" is relatively new, this condition has been described in the medical literature for centuries. Sir William Gowers coined the term "fibrositis" in 1904. During the next half century, fibrositis was considered by some to be a common cause of muscular pain, by others to be a manifestation of "tension" or "psychogenic rheumatism," and by the rheumatology community in general to be a nonentity. The current concept of fibromyalgia was established by Smythe and Moldofsky[11] in the mid-1970s, with the new term "fibromyalgia" reflecting increased evidence that this disorder represents a pain condition ("-algia") rather than inflammation of connective tissues ("-itis"). These authors identified regions of extreme tenderness (i.e., "tender points") as being a characteristic symptom of fibromyalgia and also observed that patients with fibromyalgia often experience disturbances in restorative sleep.[12] Yunus and colleagues[13] later reported on the other major clinical manifestations of fibromyalgia in patients seen in rheumatology clinics.

The next advance in fibromyalgia was the development of the American College of Rheumatology (ACR) criteria for fibromyalgia, which were published in 1990.[14] These classification criteria require that an individual have both a history of chronic widespread pain and the finding of $\geq$11 of a possible 18 tender points on examination. The ACR classification criteria were intended to standardize definitions of fibromyalgia for research use, and in this regard, they have been extremely valuable. Unfortunately, many practitioners use the criteria in routine clinical practice to diagnose individual patients; this application is not consistent with the understanding of fibromyalgia as a multisymptomatic disorder with high rates of comorbidity.

Major advances in understanding fibromyalgia and related syndromes occurred after investigators realized that these conditions are not caused by peripheral damage or inflammation and instead began to explore the central neural mechanisms of these diseases.[15,16] Many terms have been used to describe these coaggregating syndromes, including "functional somatic syndromes," "somatoform disorders," and "allied spectrum conditions."[2,17-20] With the recent research indicating that fibromyalgia, IBS, and TMD are multisymptomatic disorders characterized by dysfunctions in central pain processing, other terms in current use include "central sensitivity" or "central pain" syndrome, "non-nociceptive pain," and "chronic multisymptom illness."[21–23]

ETIOLOGY OF FIBROMYALGIA

Genetic Factors

Researchers have found that fibromyalgia has a strong familial component, with first-degree relatives of individuals with fibromyalgia displaying an 8-fold greater risk of developing fibromyalgia compared with the general population.[3] In addition, family members of individuals with fibromyalgia are much more sensitive to pain than controls and are more likely to have co-occurring pain disorders such as IBS, TMD, headaches, or other regional pain syndromes.[2,24,25] Twin studies suggest that approximately half of the risk of developing chronic widespread pain is genetic while the other half is environmental.[26]

Recent studies have also begun to identify specific genetic polymorphisms associated with fibromyalgia. To date, polymorphisms in genes encoding the serotonin 5-HT2A receptor, the serotonin transporter, the dopamine D_4 receptor, and catechol-*O*-methyltransferase have been observed at elevated frequencies in individuals with fibromyalgia.[27–30] All of these identified polymorphisms influence the metabolism or transport of monoamines, which are compounds that play critical roles in the human stress response. It is likely that there are a number of genetic polymorphisms involving additional monoamines and other neuromodulators that may contribute to an individual's "set point" for pain and sensory processing.

Table 1 "Stressors" Capable of Triggering Fibromyalgia and Related Conditions

- Peripheral pain syndromes
- Infections (e.g., parvovirus, Epstein-Barr virus, Lyme disease, Q fever)
- Physical trauma (e.g., automobile accidents)
- Psychological stress/distress
- Hormonal alterations (e.g., hypothyroidism)
- Drugs
- Vaccines
- Certain catastrophic events (war, but not natural disasters)

Environmental Factors

As with most illnesses that have a genetic underpinning, environmental factors play a prominent role in triggering the development of fibromyalgia and related conditions. Environmental stressors temporally associated with the development of fibromyalgia include physical trauma (especially involving the trunk), certain infections (e.g., hepatitis C, Epstein-Barr virus, parvovirus, and Lyme disease), and emotional stress (Table 1). Of note, each of these stressors leads to chronic widespread pain or fibromyalgia in approximately 5% to 10% of affected individuals. In other words, these stressors do not act as triggers in the overwhelming majority of individuals who regain their baseline state of health after experiencing infections or traumatic events.

PATHOGENESIS OF FIBROMYALGIA

Role of Stressors

The mechanisms responsible for ongoing symptom expression in fibromyalgia and related disorders likely are complex and multifactorial. Because disparate stressors can trigger the development of these conditions, the human stress response has been closely examined for its potentially caus-

ative role. Stress responses are mediated primarily by corticotropin-releasing hormone, which is secreted from the hypothalamus and activates the locus caeruleus/norepinephrine system in the brainstem. This stress response system may be inappropriately triggered by a wide assortment of everyday occurrences that do not pose a real threat to survival, thus initiating a deleterious cascade of physiologic responses more frequently than can be tolerated.[31]

The type of stress and the environment in which it occurs can have an impact on how the stress response is expressed. Animal studies have shown that the strongest physiologic responses are triggered by events that are accompanied by a lack of control or support and are perceived as inescapable or unavoidable.[32] Similarly in humans, daily hassles and personally relevant stressors may be more capable of causing symptoms than major catastrophic events that do not personally affect the individual.[33,34] Although intensely stressful events may lead to permanent changes in animal and human stress responses,[31,35] there are a number of factors that might be equally or more important than intensity of the stressor in predicting adverse health outcomes. For example, female sex, worry or expectation of chronicity, and inactivity or time off work following a stressful event are all factors that have been found to trigger the development of pain or other somatic symptoms.[36] Being exposed to a multitude of stressors simultaneously, or over a period of time, may also pose a significant risk for later somatic symptoms and/or psychological sequelae.

The theoretical link between stress and subsequent susceptibility to somatic symptoms or syndromes is supported by studies that have investigated the role of childhood physical or sexual abuse, posttraumatic stress disorder (PTSD), and other traumas.[4,37–40] Major traumatic events, however, are not the only stressors associated with chronic pain. In population studies and experiments conducted in healthy young adults, for example, it has been found that sleep deprivation or deprivation of exercise can lead to painful symptoms.[41,42] Given the overlapping effects of trauma and exercise on autonomic and neuroendocrine stress response systems, it is not surprising that in a recent study of Israeli war veterans with PTSD, those who exercised regularly were much less likely to develop chronic widespread pain or fibromyalgia than were those who did not exercise.[43]

Role of Neuroendocrine Abnormalities

Studies that investigate the link between stress and fibromyalgia generally point to alterations in the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system, although the type of abnormality reported varies from study to study.[44–49] These studies have also found that abnormal HPA or autonomic functioning only occurs in a very small percentage of patients with fibromyalgia, with a tremendous overlap between patients and controls in many instances. The inconsistency in the findings should not be surprising because most of these studies were cross-sectional in design and were conducted with the assumption that any detected HPA and/or autonomic dysfunction would be the potential cause of pain and other symptoms. Data now suggest, however, that HPA abnormalities may be the result of pain or early life stress and not vice-versa.[50,51]

Heart rate variability at baseline and in response to tilt-table testing has been evaluated in patients with fibromyalgia as a surrogate measure of autonomic function, with baseline heart rate variability[48,49,52] being a more consistent and useful measure than tilt-table testing.[53,54] Recent findings also suggest that aberrations in heart rate variability predispose an individual to developing fibromyalgia symptoms,[41,42,55] which may be useful for identifying potential at-risk patients.

It is likely that the neurobiologic alterations found in fibromyalgia are shared with other syndromes associated with HPA and/or autonomic function, such as depression or PTSD. A useful model of susceptibility to these disorders would take into account an individual's genetics and personality as potential risk factors. Such a model would recognize the critical importance of stressors in re-setting stress response systems, as well as other factors including (1) the role of behavioral adaptations to certain stressors such as cessation of routine exercise, and (2) whether the individual's environment is characterized by control or support.

PATHOPHYSIOLOGY

Augmented Pain and Sensory Processing

Two decades of psychophysical pressure pain testing in fibromyalgia have proved highly instructive for understanding the pathophysiology of pain and sensory processing. Early dolorimetry studies found that pain thresholds correlate with distress.[56–58] Other psychological factors, such as hypervigilance, catastrophizing, and external locus of pain control, may also play an important role in the expression of fibromyalgia symptoms. In order to minimize the potential psychological bias of experimental paradigms in which subjects can predictably anticipate increasing sensory stimuli,[59,60] Petzke and colleagues[61–63] performed a series of studies using more sophisticated paradigms involving randomly delivered pressures. These studies showed that (1) randomly measured pressure pain thresholds are not influenced by levels of distress; (2) patients with fibromyalgia are more sensitive to pressure even when it is randomly delivered; (3) patients with fibromyalgia are not more hypervigilant than controls; and (4) pressure pain thresholds at any 4 points in the body highly correlate with the average tenderness at all 18 tender points and 4 "control points." Other recent studies confirm that compared with tender point counts and dolorimetry, random pressure paradigms are highly sensitive measures of pain responses in patients with fibromyalgia.[64,65]

Aside from a heightened sensitivity to pressure, patients with fibromyalgia are similar to controls in their responses to other types of stimuli such as heat,[63,66–68] cold,[67,69] and electrical stimuli.[70] Gerster and Hadj-Djilani[71] were the first to demonstrate that patients with fibromyalgia also display a

low threshold to noxious auditory tones, a finding that has been subsequently replicated by other studies.[65,72]

In healthy humans and laboratory animals, application of an intensely painful stimulus for 2 to 5 minutes produces generalized whole-body analgesia. Several studies have shown that this analgesic effect, termed "diffuse noxious inhibitory controls" (DNIC), is more commonly attenuated or absent in patients with fibromyalgia compared with healthy controls.[67,73–75] It had been postulated that the DNIC response in humans is mediated in part by descending opioidergic pathways and in part by descending serotonergic-noradrenergic pathways. Recent biochemical and neuroimaging data suggest, however, that opioidergic activity is normal or increased in fibromyalgia, which is consistent with the anecdotal clinical experience that opioids are generally ineffective analgesics in patients with fibromyalgia and related conditions.[76,77] In contrast, other studies have shown that serotonergic and noradrenergic activity is attenuated in patients with fibromyalgia.[78] It has also been found that patients with fibromyalgia have reduced serum levels of serotonin and its precursor L-tryptophan and reduced cerebrospinal fluid (CSF) levels of the principal serotonin metabolite 5-hydroxyindoleacetic acid.[78,79] Consistent with these findings, compounds that simultaneously raise serotonin and norepinephrine levels (e.g., tricyclics, duloxetine, milnacipran, and tramadol) have been shown to exhibit efficacy in treating fibromyalgia and related conditions.[80–87]

"Wind-up" refers to the temporal summation phenomenon where, after an initial painful stimulus, subsequent equally painful stimuli are sensed as more intense. Pain testing studies have shown that some patients with fibromyalgia have an exaggerated wind-up response.[88,89] Consistent with findings from animal models that demonstrate wind-up to be associated with substance P hyperactivity,[90–92] several independent studies have shown that patients with fibromyalgia have approximately 3-fold higher CSF levels of substance P compared with normal controls.[93–96]

The excitatory neurotransmitter glutamate also appears to play a role in the pathophysiology of fibromyalgia. This hypothesis is supported by the elevation of CSF glutamate levels in patients with fibromyalgia[97] and by a recent proton spectroscopy study demonstrating altered glutamate levels in the insula of these patients.[64]

Abnormalities in Functional Neuroimaging

The convergent lines of neurobiologic evidence indicating fibromyalgia to be a state of heightened pain and sensory processing are further supported by functional imaging studies. The primary imaging methods that have been applied to fibromyalgia include single photon emission computed tomography (SPECT) and functional magnetic resonance imaging (fMRI).

In the first trial using SPECT imaging in patients with fibromyalgia, Mountz and colleagues[98] found decreased regional cerebral blood flow (rCBF) in the caudate and thalamus of patients with fibromyalgia compared with matched healthy controls. These findings were largely replicated in subsequent studies,[99] including those by Guedj and colleagues,[100–103] who observed hyperperfusion within the somatosensory cortex and hypoperfusion in the anterior and posterior cingulate, the amygdala, the medial frontal and parahippocampal gyrus, and the cerebellum of patients with fibromyalgia. In a longitudinal treatment trial that used SPECT imaging following administration of amitriptyline in 14 patients with fibromyalgia,[104] increases in rCBF were observed in the bilateral thalamus and the basal ganglia after treatment. These data suggest that amitriptyline may reduce pain symptoms of fibromyalgia in part by normalizing altered cerebral blood flow.

In the first study to use fMRI in patients with fibromyalgia, Gracely and colleagues[105] exposed 16 patients and 16 matched pain-free controls to painful pressures during fMRI. Increases in the blood oxygen–level dependent signal were found in patients with fibromyalgia compared with controls when stimuli of equal pressure magnitude were administered. Regions of increased activity included the primary and secondary somatosensory cortex, the insula, and the anterior cingulate, all of which are regions commonly observed to have increased activity in fMRI studies of healthy normal subjects during painful stimuli. Interestingly, similar activation patterns were observed when the pain-free controls were subjected to pressures that evoked equivalent pain ratings in the patients with fibromyalgia. These findings were entirely consistent with the "left-shift" in stimulus-response function noted with experimental pain testing, and suggest that patients with fibromyalgia experience an increased gain or "volume setting" in brain sensory processing systems.

Similar to the Gracely study, Cook and colleagues[106] evaluated painful heat stimuli during fMRI and observed that significant increases in the pain ratings of patients were associated with augmented pain processing within the contralateral insula. Other important fMRI studies in fibromyalgia include an investigation into the role of comorbid psychological factors on pain processing[107] and a study on the effect of catastrophizing on pain.[108] The results from these studies provide empirical evidence for the role of psychological factors in fibromyalgia and the value of treatments such as cognitive behavioral therapy (CBT).

Sleep in Fibromyalgia

Although disturbed sleep is a symptom commonly seen in patients with fibromyalgia, sleep abnormalities rarely correlate with other fibromyalgia symptoms. Many clinicians have anecdotally found that identifying and treating specific sleep disorders (e.g., obstructive sleep apnea, upper airway resistance, or periodic limb movement disorders) does not necessarily lead to improvements in the core symptoms of fibromyalgia.

Other Potential Pathogenic Factors

Besides augmented central processing of pain and sensory information, there are other pathogenic mechanisms that

Table 2 Mechanistic Characterization of Pain

	Primary Cause	Therapeutic Response	Behavioral Factors	Examples
Peripheral (nociceptive)	Inflammation or mechanical damage in periphery	Responds to both NSAIDs and opioids	Minor	• Osteoarthritis • Rheumatoid arthritis • Cancer pain
Neuropathic	Damage or entrapment of peripheral nerves	Responds to both peripheral and central pharmacologic therapy	Minor	• Postherpetic neuralgia • Diabetic neuropathy
Central (non-nociceptive)	Central disturbance in pain processing	Tricyclic, neuroactive compounds are the most effective	Prominent	• Fibromyalgia • Irritable bowel syndrome • Tension headache • Idiopathic low back pain • Poststroke pain

NSAID = nonsteroidal anti-inflammatory drug.
Adapted with permission from *Fibromyalgia & Other Central Pain Syndromes.*[120]

may play roles in fibromyalgia and related conditions, but their significance has not been as well studied. In addition to the autonomic and HPA issues already described, there have been many studies that have noted mild increases in proinflammatory cytokines in fibromyalgia and related conditions.[109–112] Again, the significance of these findings is not clear, because many of the cytokines that are found to be elevated are those closely connected to neural function, and no studies have suggested that treatment with classic anti-inflammatory drugs (e.g., nonsteroidal anti-inflammatory drugs, corticosteroids) is effective in these conditions.[113,114]

Behavioral and Psychological Factors

Behavioral and psychological factors are likely to play a role in symptom expression in many patients with fibromyalgia. The estimated rate of current psychiatric comorbidity in fibromyalgia patients may be as high as 30% to 60%, and the rate of lifetime psychiatric disorders is even higher.[2,115,116] Depression and anxiety disorders are the most commonly seen comorbid disorders. However, these rates may be artifactually elevated by virtue of the fact that most of these studies have been performed in tertiary care centers. Individuals meeting ACR criteria for fibromyalgia who are identified in the general population have substantially lower rates of identifiable psychiatric conditions.[5,117]

Because of the biopsychosocial nature of fibromyalgia, several investigators have attempted to identify subgroups of patients with fibromyalgia who may present differently or respond differentially to treatment.[118,119] One study described 3 subgroups that can be usefully identified: (1) patients with low levels of depression and anxiety, normal cognition regarding pain, and mild tenderness; (2) "tertiary care" patients with fibromyalgia with slightly more tenderness and higher levels of depression, who may externalize the locus of pain control and/or catastrophize their condition; and (3) patients with high degrees of tenderness who do not exhibit negative psychological or cognitive factors.[119] These findings suggest that in some resilient individuals, positive psychological and cognitive factors may buffer the neurobiologic factors that lead to pain and other symptoms in fibromyalgia.

EVALUATION OF INDIVIDUALS WITH CHRONIC WIDESPREAD PAIN

The diagnosis, evaluation, and effective management of an individual with chronic pain is a complex process because, within any given pain diagnosis, there is tremendous heterogeneity with respect to the underlying causes. In particular, individuals with chronic pain can have varying degrees of peripheral nociceptive (i.e., tissue damage, inflammation) and central non-nociceptive (i.e., pain amplification, psychological disorder) factors contributing to their pain (Table 2).[120] The differential diagnosis of chronic pain involves identifying the degree to which these factors are present in a given individual so that the appropriate pharmacologic, procedural, and psychological therapies can be administered.

A careful musculoskeletal history and examination remain the most important procedures for the diagnosis of musculoskeletal pain. Diagnostic testing technology can be confusing when applied to musculoskeletal disorders. For example, positive antinuclear antibody, positive rheumatoid factor, and abnormal results of imaging studies are frequently found in healthy, asymptomatic individuals.[121–123] Moreover, diagnostic tests do not accurately represent pain severity because there is typically a significant discordance between laboratory or imaging results and the intensity of pain and other symptoms that the individual is experiencing. Therefore, a musculoskeletal history and examination must be performed in order for the clinician to make an accurate diagnosis (or at least a very narrow differential diagnosis); if necessary, further diagnostic testing can then be conducted to confirm findings.

DIAGNOSIS OF FIBROMYALGIA

It is important to note that the ACR criteria for fibromyalgia were never intended to be used as strict diagnostic criteria in clinical practice and that many individuals who clearly have fibromyalgia will not experience pain throughout their en-

tire body or at all 11 tender points.[57] Therefore, clinicians should suspect fibromyalgia in individuals who present with multifocal pain that cannot be explained on the basis of damage or inflammation in the affected regions of the body. In most cases, musculoskeletal pain is the most prominent feature, but because pain pathways throughout the body are amplified, pain can be perceived more generally. Thus, chronic headaches, sore throats, chest pain, abdominal pain, and pelvic pain are very common in individuals with fibromyalgia, and patients with chronic regional pain in any of these locations are more likely to have fibromyalgia.

Because pain is a defining feature of fibromyalgia, it is useful to focus on the features of the pain that can help distinguish it from other disorders. Fibromyalgia pain is typically diffuse or multifocal, often waxes and wanes, and is frequently migratory in nature. These characteristics are quite different from peripheral pain, where both the location and severity of pain are typically more constant. A number of seemingly unrelated symptoms also frequently develop and persist in fibromyalgia. These include fatigue, sleep difficulties, weakness, problems with attention or memory, unexplainable weight fluctuations, heat and cold intolerance, morning stiffness, and subjective swelling in the extremities.

Physical examination is often unremarkable, except for the presence of tenderness. If the patient's symptoms have persisted for several years, minimal additional testing is required, although a more aggressive strategy should be used for acute or subacute onset of symptoms. Simple testing should be limited to a complete blood count test and routine serum chemistries, along with thyroid-stimulating hormone and erythrocyte sedimentation rate and/or C-reactive protein.

Fibromyalgia may present similarly to or concurrently with a number of disorders, and this may confuse the diagnosis. The association of fibromyalgia with other chronic or autoimmune disorders[16,36,124] requires special attention because of its relevance to practicing clinicians. As many as 25% of patients correctly diagnosed with generalized inflammatory disorders such as systemic lupus erythmatosus (SLE), rheumatoid arthritis, and ankylosing spondylitis will also fulfill ACR criteria for fibromyalgia.[125] However, this comorbidity may go unrecognized in clinical practice, especially when fibromyalgia develops after the autoimmune disorder or regional pain syndrome. When comorbid fibromyalgia goes unrecognized in this setting, patients are often treated more aggressively with unnecessary toxic immunosuppressive drugs.

Functional disorders commonly associated with fibromyalgia include noncardiac chest pain, heartburn and palpitations, and the frequent comorbidity of IBS. Pelvic complaints are also common. In females, the frequent comorbid diagnoses are dysmenorrhea, interstitial cystitis, endometriosis, and sensitivity disorders like vulvar vestibulitis and vulvodynia, whereas in males these same symptoms are sometimes diagnosed as chronic or nonbacterial prostatitis. Certain dermatologic features often seen in fibromyalgia, including malar flushing, livedo reticularis, and Raynaud-like reddening of the hands, can mimic symptoms of autoimmune disorders. Such similarities sometimes result in patients with fibromyalgia being misdiagnosed as having an autoimmune disorder such as SLE.

Table 3 Ranking of Pharmacologic Therapies for Fibromyalgia Management

Strong evidence of benefit	• Tricyclics (amitriptyline, cyclobenzaprine) • Dual reuptake inhibitors (venlafaxine, duloxetine, milnacipran) • α_2-δ ligands (pregabalin, gabapentin)
Modest evidence of benefit	• Tramadol • Selective serotonin reuptake inhibitors • Dopamine agonists • γ-Hydroxybutyrate
Weak evidence of benefit	• Growth hormone • 5-Hydroxytryptamine • Tropisetron • *S*-adenosyl-L-methionine
Not shown to be effective	• Opioids • NSAIDs • Corticosteroids • Benzodiazepine and nonbenzodiazepine hypnotics • Melatonin • Guanifenesin • Dehydroepiandrosterone

NSAID = nonsteroidal anti-inflammatory drug.

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Table 4 Ranking of Nonpharmacologic Therapies for Fibromyalgia Management

Strong evidence of benefit	• Cardiovascular exercise • Cognitive behavioral therapy • Patient education • Multidisciplinary therapy
Modest evidence of benefit	• Strength training • Hypnotherapy • Biofeedback • Balneotherapy
Weak evidence of benefit	• Acupuncture • Chiropractic, manual, and massage therapy • Electrotherapy • Ultrasound
No evidence of benefit	• Tender (trigger) point injections • Flexibility exercise

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TREATMENT

Progress in the understanding of fibromyalgia has led to more therapeutic options for patients. Investigators continue to examine the utility of newer medications (Table 3[126]) and nonpharmacologic interventions (Table 4[126]) in controlled trials. Clinical evidence advocates a multifaceted program

emphasizing education, certain medications, exercise, and CBT.[126]

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) generally increase the concentrations of serotonin and/or norepinephrine by directly blocking their reuptake. The efficacy of TCAs in treating pain, poor sleep, and fatigue in patients with fibromyalgia is supported by a meta-analysis of several small, short-term, single-center, randomized controlled trials.[80] Tolerability is a problem but can be improved by initiating treatment at very low doses.

Selective Serotonin Reuptake Inhibitors

Because of a better side effect profile than TCAs, selective serotonin reuptake inhibitors (SSRIs) have been evaluated in randomized placebo-controlled trials in fibromyalgia.[127] In general, the results of studies of SSRIs in fibromyalgia have paralleled the experience in other pain conditions, where evidence regarding their efficacy has been inconclusive. The newer, highly selective SSRIs (e.g., citalopram) seem less efficacious than the older SSRIs, which have some noradrenergic activity at higher doses.[128]

Serotonin and Norepinephrine Dual Reuptake Inhibitors

Dual reuptake inhibitors of serotonin and norepinephrine are pharmacologically similar to TCAs in their ability to inhibit the reuptake of both serotonin and norepinephrine, but differ in being generally devoid of significant activity in other receptor systems. This selectivity results in diminished side effects and enhanced tolerability. The first agent of this type available for clinical investigation, venlafaxine, has data to support its use in the management of neuropathic pain and in the prophylaxis of migraine and tension headaches.[129] Venlafaxine was ineffective in the management of fibromyalgia at 75 mg/day in a randomized controlled trial, but appeared effective at higher doses in 2 case reports.[126]

Duloxetine and milnacipran are dual reuptake inhibitors of serotonin and norepinephrine approved by the US Food and Drug Administration (FDA) for the management of fibromyalgia. Recent clinical trials have shown that duloxetine is effective in the management of pain and other symptom domains of fibromyalgia.[81–83] In its preferential inhibition of serotonin reuptake, duloxetine may slightly differ from the dual serotonin and norepinephrine reuptake inhibitor milnacipran, which preferentially inhibits norepinephrine reuptake over serotonin at an approximate 3:1 ratio.[130] Milnacipran has also shown efficacy in the management of pain and other symptom domains of fibromyalgia, such as fatigue and physical functioning, in recent large multicenter trials.[86,87] The benefits of milnacipran and duloxetine in fibromyalgia management have been shown to be independent of their effect on mood, indicating that the analgesic and other beneficial effects of this class of drugs in treating fibromyalgia are not simply owing to their antidepressant effects.[81,85]

Other Central Nervous System Acting Drugs

Antiepileptic drugs are widely used in the treatment of various chronic pain conditions, including diabetic neuropathy.[131] Pregabalin, an α_2-δ calcium channel ligand, is approved for the treatment of neuropathic pain and was the first pharmacologic agent approved by the FDA for the treatment of fibromyalgia. Recent randomized, double-blinded, placebo-controlled trials demonstrated efficacy of pregabalin in improving pain, sleep disturbances and fatigue, as compared with placebo, in patients with fibromyalgia.[132–134] Gabapentin is a compound with similar pharmacology to pregabalin that has been indicated for the treatment of postherpetic neuralgia and studied in a variety of pain states, including fibromyalgia and headache prophylaxis.[131,135]

Sedative-hypnotic compounds are widely used by patients with fibromyalgia. A handful of studies published on the use of certain nonbenzodiazepine hypnotics in fibromyalgia, such as zopiclone and zolpidem, have suggested that these agents can improve the sleep and possibly the fatigue of patients with fibromyalgia, although they have no significant effects on improving pain. On the other hand, γ-hydroxybutyrate (also known as sodium oxybate), a metabolite of γ-aminobutyric acid with powerful sedative properties, was recently shown to be useful in improving fatigue, pain, and sleep architecture in patients with fibromyalgia.[136,137] Note, however, that, owing to its potential for abuse, this agent is a scheduled substance.

Other investigated medications include pramipexole, a dopamine agonist indicated for Parkinson disease that has shown utility in the treatment of periodic limb movement disorder,[113,138] and tizanidine, an α_2-adrenergic agonist approved by the FDA for the treatment of muscle spasticity associated with multiple sclerosis and stroke.[139] Results from these studies have demonstrated improvements in pain, sleep, and quality of life in patients with fibromyalgia.

Analgesics

There have been no adequate, randomized controlled clinical trials of opiates in fibromyalgia, and many practitioners in the field have not found this class of compounds to be effective. Tramadol is a compound that has some opioid activity combined with serotonin/norepinephrine reuptake inhibition. Tramadol appears to be somewhat efficacious in the management of fibromyalgia, both as a monotherapy and as a fixed-dose combination with acetaminophen.[84]

Nonpharmacologic Therapies

Two nonpharmacologic therapies, CBT and exercise, have been shown to be efficacious in the treatment of fibromyalgia (Table 4), as well as a plethora of other medical conditions.[126,140] Sustained improvements in fibromyalgia (i.e., >1 year) have been found with both of these treatments.

PROGNOSIS

The prognosis of fibromyalgia depends largely on where the individual falls on a continuum. On one end of the spectrum are the individuals with chronic widespread pain or fibromyalgia who are seen in primary care and who may respond to a single medication or a graded, low-impact exercise program.[141,142] On the other end of the spectrum are the patients with fibromyalgia in tertiary care settings who do quite poorly,[143] owing in part to their high levels of distress, lack of control over their illness, and little social support. For all patients, multimodal programs that integrate nonpharmacologic (especially exercise and CBT) and pharmacologic therapies are required.

SUMMARY

Fibromyalgia is a prototype of central pain syndromes that is exacerbated in affected individuals to varying extents by behavioral, psychological, and cognitive contributing factors. Experimental pain testing, functional neuroimaging, and recent clinical trial results have led to a better understanding of the causes and symptoms of this complicated disorder. The multidimensional symptomology of fibromyalgia warrants multidisciplinary management strategies, including concurrent pharmacologic and nonpharmacologic treatments. The coaggregation of fibromyalgia and disorders such as IBS and TMD appears to reflect a shared etiology involving heightened central pain processing, supporting the inference that similar or at least related therapeutic strategies may be effective against this spectrum of disorders.

ACKNOWLEDGMENT

Editorial assistance was provided by Prescott Medical Communications Group, Chicago, Illinois.

AUTHOR DISCLOSURES

The author of this article has disclosed the following industry relationships:

Daniel J. Clauw, MD, has served as a consultant to Cypress Bioscience, Inc., Eli Lilly and Company, Forest Laboratories, Inc., Pierre Fabre Médicament, Pfizer Inc, Procter & Gamble, and Wyeth Pharmaceuticals; has received research/grant support from Cypress Bioscience, Inc.; and has previously owned stock in Cypress Bioscience, Inc.

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