Fibromyalgia

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Overview of Fibromyalgia

- Fibromyalgia (FM) is a pain syndrome that has been estimated to affect 4–6% of the U.S. population.
- The cardinal symptoms of FM are widespread pain accompanied by fatigue, sleep, and memory problems. These individuals are also more sensitive to sensory stimuli. They often find bright lights, noises, and odors bothersome.
- Individuals with FM often have had one or several other Chronic Overlapping Pain Condition (COPC) diagnoses. These include irritable bowel syndrome (IBS), temporomandibular disorder (TMD), tension headache, dysmenorrhea, or interstitial cystitis/bladder pain syndrome (Maixner et al. 2016). In fact, this is one manner in which clinicians can assess for the widespread pain seen in this condition: i.e., by identifying that the individual has had chronic pain in other body regions earlier in life.
- The research identifying strong neurobiological underpinnings to conditions such as FM and other COPCs has led the international association of pain researchers to develop a new term, nociplastic pain, to identify the predominant mechanism in conditions such as FM. Nociplastic pain has previously been referred to by a number of semantic terms, including central sensitization or centralized pain.
- The most effective treatment of FM and related conditions is with an approach focusing on the importance of patient self-management, including the use of an increasing and evolving number of effective non-pharmacological therapies. These include education, many different types of activity/exercise, many different types of cognitive behavioral therapy, as well as acupuncture/acupressure, mindfulness, yoga, Tai Chi, and other integrative therapies.
- S problems may antedate and cause some of the symptoms of FM. This can first be approached using simple non-pharmacological approaches such as sleep hygiene, and then sometimes adding low nighttime doses of drugs that appear to be working in part via improving sleep (e.g., cyclobenzaprine, other tricyclic medications, gabapentinoids) or CBT for insomnia, if needed.
- The most effective drugs for nociplastic pain include non-opioid centrally acting analgesics (tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and gabapentinoids). Opioids should be avoided.
- If an individual is suffering from severe fatigue, working on getting them to slowly become more active can be very helpful. Across all fatigue states, graded exercise therapy may be the most effective available treatment.
- Encourage patients to become more active rather than to exercise more. The concept of exercise is daunting to some.

Myth *FM, in contradistinction to diseases such as rheumatoid arthritis, is not a legitimate cause of chronic pain.*

Reality: The science behind FM and other nociplastic pain conditions is now so credible that the international association of pain researchers formally voted several years ago to accept this as a third mechanism of pain. The other two types of pain are nociceptive and neuropathic. FM is the "poster child" for nociplastic pain and chronic overlapping pain conditions. Nociplastic pain as now recognized is thought to arise from the central nervous system (CNS) rather than the periphery, which is why it is defined in part by the presence of other common co-morbid CNS symptoms (fatigue, sleep, memory, mood problems), as well as hypersensitivity to other non-painful sensory stimuli (noises, odors, chemicals) (Fitzcharles et al. 2021).

In fact, this legitimization of nociplastic pain has in parallel led to a major reconceptualization of chronic pain in the ICD-11 diagnostic criteria (Treede et al. 2019). Now conditions such as FM, irritable bowel syndrome, and many forms of low back pain are now considered "chronic primary pain".

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In this context, pain is the disease. In contrast, conditions such as rheumatoid arthritis are now considered secondary chronic musculoskeletal pain.

Myth *FM occurs more commonly in industrialized countries and Western cultures.*

Reality: The prevalence of FM is just as high in rural or nonindustrialized societies as it is in "developed" countries. Individuals who have greater access to healthcare are more likely to present for care with symptoms of FM than those whose access is inferior, but FM occurs as commonly in Amish communities and Bedouin tribes as it does in the general U.S. population. In fact, the prevalence of FM is remarkably consistent in different countries and cultures. FM affects approximately 2–6% of individuals in most populations.

Myth *FM is a psychiatric disorder.*

Reality: There is a higher rate of psychiatric disorders in FM patients compared to the general population, but this is true of all chronic pain conditions and most chronic medical conditions.

Estimates of the prevalence of psychiatric disturbances among patients with FM are probably elevated artifactually because of the fact that most studies of the disorder have been performed in tertiary care centers. Community-dwelling individuals who fulfill the American College of Rheumatology (ACR) criteria for the classification of FM have a much lower rate of identifiable psychiatric conditions than those identified in tertiary health care settings.

Myth *FM only occurs in women.*

Reality: The original 1990 FM criteria led to over 90% of diagnosed individuals being female, and so, many individuals were taught that FM was almost an exclusively female disease. However, we now know that those criteria—which required both widespread pain and 11/18 tender points—caused an unintended gender bias because of the tender point requirement. Women are only 1.5 times more likely than men to experience chronic widespread pain, but 10 times more likely than men to have 11 or more tender points. (Wolfe et al. 1995) Thus, when the new 2011/16 FM criteria were published and then applied in the US population, the overall incidence of FM increased from 2–4% of the population to approximately 6%, and the female:male ratio changed from 10:1 to 2:1. (Vincent et al. 2013; Wolfe et al. 2016). This 2:1 female:male sex difference is very similar to that seen in nearly all chronic pain conditions, and likely occurs because women are innately more sensitive to pain and other sensory stimuli than men.

Pearl *Although there are established criteria for FM, it is better to think of different individuals having different degrees of FM ("fibromyalgianess") rather than it being present or absent, and to think of this construct in individuals whom you do not think of as having FM.*

Comment: Wolfe was the first to suggest that the degree of FM an individual experienced occurred on a continuum rather than a "black or white", "on or off", and "yes or no" basis. Nearly all biological studies of this phenomenon agree with these original observations. For example, using the 2011/16 FM Survey Criteria as a surrogate for the degree of FM, this continuous measure is shown to be strongly predictive of both decreased surgery and opioid responsiveness among individuals undergoing arthroplasty for extremity osteoarthritis (Brummett et al. 2015). The same findings of the ACR Survey criteria to predict surgery and opioid nonresponsiveness were found in women with chronic pelvic pain getting hysterectomy, and individuals with RA receiving a new biologic or DMARD (As-Sanie et al. 2021; Heisler et al. 2020).

Myth *A patient must have at least 11 tender points to be diagnosed with FM.*

Reality: None of the current criteria for diagnosing fibromyalgia requires performing a tender point count. At the time the original 1990 ACR FM criteria were formulated, it was thought that the location of tender points might have diagnostic significance. In fact, the concept of "control points" was coined to describe areas of the body that should not be tender, even in patients with FM. Individuals who were tender at such control points were assumed to have a psychological cause of their pain. Well after the 1990 criteria were published, it became clear that the tenderness in FM patients extends throughout the entire body and is not confined inevitably to specific body regions (Petzke et al. 2003). This phenomenon is referred to as diffuse hyperalgesia (increased pain to normally painful stimuli) or allodynia (pain in response to normally non-painful stimuli). These findings, combined with the finding that FM patients also display increased sensitivity to many other types of sensory stimuli (e.g., light, auditory), are among the findings that have led investigators to view FM and other nociplastic pain conditions as being, in part, disorders of augmented sensory processing.

Pearl *The laying on of hands is important. Formal tender point examinations are not.*

Comment: The recognition that an individual has tenderness that is diffuse and not confined to the joints is helpful in diagnosing FM. Clinicians should incorporate this approach into their physical examination routines, using the same degree of pressure on all patients in order to get a sense of any individual patient's pain threshold. This combines a general assessment of a patient's pain threshold with a specific examination of the joints affected in inflammatory or noninflammatory arthritis. However, the newer criteria for FM including the 2011/2016 FM Survey Criteria that this author prefers do not require performing a tender point count or assessing tenderness.

Pearl *View the plethora of symptoms seen in FM as an opportunity—not a problem.*

Comment: Many providers are flummoxed and frustrated by the myriad symptoms that some FM patients experience—but in reality, this represents a therapeutic opportunity. The common co-morbid CNS symptoms seen in FM and other nociplastic pain conditions such as sleep and memory problems, fatigue, and mood disturbances all have effective pharmacological and non-pharmacological treatments. Sleep issues should be identified and treated aggressively, since more and more studies now support the notion raised initially by Moldofsky that sleep problems may antedate and cause some of the symptoms of FM. This can first be approached using simple non-pharmacological approaches such as sleep hygiene, and then sometimes adding low nighttime doses of drugs that appear to be working in part via improving sleep (e.g., cyclobenzaprine, other tricyclics, gabapentinoids) or CBT for insomnia if needed. Similarly, if an individual is suffering from severe fatigue, working on getting them to slowly become more active can be very helpful. Across all fatigue states, graded exercise therapy may be the most effective available treatment.

Pearl *The amount of diagnostic testing required to be comfortable that an individual has FM varies, based on both symptom presentation and the length of time the individual has had these symptoms.*

Comment: There is no “diagnostic test for FM” in serum—despite claims to the contrary. Thus, laboratory testing is to help rule out other entities. In general, the only screening tests generally recommended for FM are an erythrocyte sedimentation rate, a C-reactive protein, and a TSH. Serologic studies such as antinuclear antibody (ANA) and rheumatoid factor assays should generally be avoided, unless there are historical features or findings on physical examination that suggest diagnoses other than FM. The promiscuous use of autoantibody testing poses a major problem in clinical practice because of the high sensitivity of many autoantibody assays. “False-positive” results lead to incorrect diagnostic labels (“lupus”, “rheumatoid arthritis”, “undifferentiated connective tissue disease”), further unnecessary testing, and, perhaps most damaging, heightened patient anxiety.

Myth *Patients given the “label” of FM begin to think they have an illness. This will only make them worse.*

Reality: “Labeling” an individual with an illness always has the potential to increase illness behavior. However, the overwhelming majority of studies looking at whether this happens when an individual is diagnosed with FM suggest this does not generally occur. In fact, most studies suggest that finally getting a diagnosis after what is typically a long period of time seeing different physicians is often a relief to patients. Furthermore, studies to date in FM do not suggest that healthcare utilization is increased following the diagnosis of FM and instead see *reduced* healthcare costs in the year following the diagnosis of FM, likely because individuals stopped going from doctor to doctor and from test to test (Annemans et al. 2008).

Pearl *Attempting to establish links between the diagnosis of FM and possible “etiologies” can be counterproductive.*

Comment: Clinicians should avoid linking the diagnosis of FM to putative causes, such as an injury or exposure to an environmental toxin. In the overwhelming majority of cases, causal associations are speculative. All too often, the affirmation of such an association leads to blame, inactivity, a sense of being victimized, and litigation. Patients often establish links in their own minds about previous exposures and the development of FM, usually long before they see a rheumatologist.

Myth *All FM patients should be seen and managed by rheumatologists.*

Reality: FM is far too common for it to be managed primarily by rheumatologists, and in this regard is similar to other common musculoskeletal conditions such as osteoarthritis. Instead, the primary management of FM should be by primary care providers or pain clinics, even if they, too, feel poorly equipped to manage these patients. It is important for rheumatologists to be available to see patients for a single consultative visit to be certain the individual does not have an autoimmune disorder, if that is in question. As FM has become a more legitimate diagnosis in some settings, individuals with autoimmune disorders or other conditions that may mimic FM are not being thoroughly evaluated for these other problems before the diagnosis of FM is made.

Myth *There is no reasonable pathophysiologic explanation that accounts for the multitude of symptoms in FM.*

Reality: There is substantial evidence that FM is associated with abnormalities in neural pain and sensory processing, as if someone turned up the volume control on the processing of all sensory information (Sluka and Clauw 2016). Functional imaging studies indicate that the insula is the most consistently hyperactive/hyperconnected brain region in patients with FM. Not surprisingly, the insula plays a critical role in interoception and sensory integration (Craig 2003; Segerdahl et al. 2015). The anterior insula is linked with the emotional processing of sensations. The posterior insula has a more purely sensory role. In fact, some of the functional neuroimaging findings seen in adults with FM and nociplastic pain conditions are present before a child develops fibromyalgia, suggesting an identifiable diathesis in pain and sensory processing (Kaplan et al. 2021).

Pearl *When considering the diagnosis of FM, ask patients if they are sensitive to noises, odors, or have multiple side effects of drugs. All of these may indicate a generalized disturbance in processing all sensory stimuli.*

Comment: FM patients are hyperresponsive not only to painful stimuli, but also to other sensory stimuli. In fact, Yunus coined the term "central sensitivity syndrome" to describe illnesses such as FM, irritable bowel syndrome, tension headache, and other disorders than tend to cluster in the same patients (Yunus 2008). Functional MRI (fMRI) studies show reproducible abnormalities in the processing of many types of sensory stimuli. One study that used machine learning and artificial intelligence to probe the ability of fMRI responses to multiple sensory stimuli to differentiate FM patients from controls demonstrated both a sensitivity and specificity of 90% for the identification of FM patients (Lopez-Sola et al. 2017).

Pearl *Patients with FM can understand their disorder as one of "increased volume control" in which their CNS processes pain and other sensory stimuli in an altered (don't say aberrant!) manner.*

Comment: Pain and sensory processing are physiological processes in which large differences exist among individuals across the population. In this way, pain and sensory processing are similar to blood pressure, glucose metabolism, or any other physiological process. The fundamental neurobiological problem in FM and related syndromes is that patients perceive more pain from a certain amount of pressure or heat applied to their skin than do individuals without FM. As noted above, this sensitivity extends to other sensory processes. Patients should be informed that pain and other sensory symptoms do not relate necessarily to something "wrong" with the symptomatic part of their body, but rather to their underlying sensitivity.

Myth *FM is an intractable illness and carries a poor prognosis. There is no effective therapy.*

Reality: The medical literature often depicts FM as an intractable illness for which very limited therapeutic options exist. On the contrary, many patients diagnosed with FM in the community often have spontaneous remission of their symptoms. Nearly 50% of FM patients in primary care no longer had symptoms of FM 1 year after the initial diagnosis. Even in tertiary referral clinics dedicated to FM, most patients continue to work full-time and nearly two-thirds report feeling well or very well.

The notion that FM carries a poor prognosis whether diagnosed in the community or in specialty clinics contributes to pessimism on the part of both patients and clinicians. In the majority of patients, FM responds favorably to a combination of pharmacologic and non-pharmacologic therapy.

Pearl *Emphasize the importance of having the patient take an active role in their or his management, and create a virtual interdisciplinary environment that offers the patients access to many different types of providers and integrative therapies. Then ask the patient to try 2–3 new therapies of their choosing.*

Comment: One of the biggest advances in the management of chronic pain has been the increased evidence base for a wide variety of non-pharmacological therapies—many of which originated in Eastern medicine and have been referred to as alternative or complementary therapies. Because the evidence base for treatments such as acupuncture/acupressure, Tai Chi, chiropractic manipulation, massage therapy, mindfulness, and yoga has increased so dramatically over the past decade, these therapies are now referred to as *integrative* therapies rather than alternative therapies. They should be considered first line-therapies because of both their safety and effectiveness.

The fact that so many of these therapies have recently been shown to be effective is very helpful in managing chronic pain patients—many of whom feel as though they have "tried everything" and nothing has worked. These therapies are increasingly available via websites, smartphone apps, or via Zoom classes. It is reasonable to suggest that patients pursue several non-pharmacological approaches they have not yet tried. If they are not willing to do so, it is then reasonable to ask them how they expect to get better if they do not try new treatments.

Myth *Antidepressants work in FM because most FM patients are depressed.*

Reality: Although several classes of anti-depressants show analgesic activity (e.g., tricyclics, serotonin-norepinephrine reuptake inhibitors [SNRIs]), the aggregate literature do not suggest that these drugs are working as antidepressants to reduce pain. Instead, it is likely that the shared neurotransmitters of norepinephrine and serotonin are involved in both types of conditions. Norepinephrine might be the more important in FM, because pure norepinephrine reuptake inhibitors are effective in FM but pure serotonin reuptake inhibitors are not. These classes of drugs are just as effective in FM patients without depression as they are in those with depression.

Pearl *Cognitive behavioral therapies (CBT) can be quite effective in the treatment of FM, and there are now many variations of CBT that may help different subgroups of patients.*

Comment: Classic pain CBT (CBT-P) is efficacious in both FM and a broad range of other chronic pain conditions. Other variations of CBT might be beneficial in subsets of chronic pain patients. Acceptance and Commitment Therapy (ACT) is one such version. ACT aims at getting pain patients to accept that they will have pain and focus on the moment and accept thoughts and feeling without judgment. Emotional awareness therapy, also sometimes called neural reprocessing therapy, has been shown to have overall effects similar to those of CBT, but it can be nearly curative in subsets of patients in whom trauma is playing a significant role in their pain.

Another type of CBT that may be helpful in FM patients is CBT for insomnia (CBT-I), which has been recently shown to have effect sizes similar to CBT-P in several chronic pain populations. Nearly all of these therapies are also available via websites or smartphone apps. Websites that give patients general guidance and self-management (www.PainGuide.com) can also be very helpful.

Pearl *Start low and go slow when initiating new therapy for FM.*

Comment: Patients with FM are much more likely to experience adverse effects of drugs than patients without FM, perhaps because of FM patients' generalized sensory hypersensitivity. Thus, it is often quite helpful to begin at very low doses of drugs and to escalate the dose slowly.

Pearl *Describe exercise as a "drug" to patients. Consider using the term "activity" rather than exercise for patients that are sedentary.*

Comment: Exercise likely works in part in FM by raising levels of serotonin and norepinephrine. This intervention is most effective if administered in low, frequent doses several times a week rather than high doses taken intermittently. Clinicians caring for patients with FM need to mount the exercise soapbox and ask patients continually how much activity and exercise they undertake. Patients often resist beginning exercise programs for years, but perseverance on the part of the clinician pays off. Once patients become "sick and tired of being sick and tired" and begin to exercise, they usually continue this as part of their treatment program.

Exercise should be considered like any medication and explained to the patient in detail. Make a show of writing the patient a prescription for activity/exercise. Referral of the patient to a physical therapist can be helpful, especially for patients who are reluctant to begin an exercise program.

Pearl *Avoid using opioids in FM patients. Rather than not making FM and nociplastic pain better, opioids may make them WORSE.*

Comment: No opioid is approved for use in chronic pain in the US. Nevertheless, beginning in the 1990s, opioid manufacturers and their accomplices suggested that opioids should be used to treat chronic nonmalignant pain. Thought leaders in FM have consistently recommended against the use of opioids in this condition (Goldenberg et al. 2016) and this position now has scientific justification. Neuroimaging and biochemical studies suggest that the endogenous opioid system is hyperactive in FM and related conditions. This might be the reason that lowdose naltrexone can be an effective treatment for FM (Baraniuk et al. 2004; Schrepf et al. 2016). It is entirely possible that FM and nociplastic pain are driven in part by excessive endogenous opioid production and the subsequent development of *endogenous* opioid-induced hyperalgesia (OIH)(Clauw 2017). If so, we would expect opioids to make individuals with FM worse—and opioid antagonists to be effective. The first long-term study of opioids in chronic nonmalignant pain was not published in 2018 (Krebs et al. 2018)! That study not only showed that opioids are no more effective than NSAIDs and acetaminophen in treating chronic musculoskeletal pain over 1 year, but one little-noted result was that opioids led to a statistically significant WORSENING of pain during that time, as would be expected if OIH occurred with chronic opioid therapy.

Pearl *Ask patients if they were active before developing FM. Suggest that they become more "active" rather than that they exercise more, as the latter term is often daunting.*

Comment: Several studies suggest that FM patients have higher levels of premorbid activity and exercise than do controls. These data suggest that individuals learned early in life that being active and performing regular exercise made them feel better. Pointing this out to patients often assists in getting individuals to begin an exercise program, but simply increasing daily activity can be helpful so often that is a good place to start. Activity and exercise also have a salutatory effect on other symptoms such as fatigue. Patients may notice improvements in fatigue even before their pain improves.

Myth *When patients experience a flare of their FM symptoms, switch them to a new drug.*

Reality: FM flares occur most often because of stressors such as psychological pressure, infections, trauma, and other events. In these settings, the discontinuation of current therapies, especially drugs that may be overall effective, can be counterproductive. However, when patients are consistently doing poorly, it is reasonable to consider switching medications or adding a different drug.

But instead of switching drugs when an FM patient comes in for a return visit and is doing poorly, tell them that the most likely way for them to improve is to try several new nondrug therapies. Although there are only a few classes of drugs that are effective in FM, many nondrug therapies can be effective. Patients will be far more likely to improve if they try new nondrug therapies. These nondrug therapies also only work well in about one-third of individuals (the same is true for drug therapies). Nevertheless, a clinician can reassure a patient that if they try three new nondrug therapies within the next year, they are likely to find that at least one of these therapies is helpful and worth continuing. Trying new nondrug therapies and then incorporating those that are effective into a long-term treatment program is the best path to successful treatment in FM and other chronic pain states.

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