# Fibromyalgia Syndrome

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*Editors*

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# Chapter 1
# Chronic Fatigue: Definition and Overlap with Fibromyalgia


**Galya Tanay and Yehuda Shoenfeld**

## Introduction

This chapter includes a rather simplified definition and the diagnostic criteria of fibromyalgia syndrome (FMS) and a more detailed one for myalgic encephalomyelitis/chronic fatigue syndrome (CFS). Definitions will lead to a discussion on whether CFS is the same or a different illness from FMS, since a clinical overlap indeed exists between the two syndromes, and there have been notions in the literature claiming that they are variants of the same illness—called "the unitarian hypothesis." A review of the existing literature will be presented in an attempt to delineate similarities and differences between the two syndromes.

## Definitions

### *Fibromyalgia*

(Very briefly, since it has been discussed amply in other chapters in this book).

Fibromyalgia syndrome (FMS) is defined by the World Health Organization (WHO) as a condition of chronic widespread pain accompanied by fatigue with sleep disturbance and a cognitive disorder, associated with varied additional syndromes such as irritable bowel syndrome, dry mouth, dry eyes, orthostatic intolerance, temporomandibular joint dysfunction, and many others [1–3]. Over the

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years, different rheumatological societies from different countries have proposed various definitions and diagnostic criteria for FMS. The latest set of diagnostic criteria for FMS (year 2016) is easier to use in clinical practice, requiring only multisite pain (present in 6/9 body areas), enduring at least 3 months and sleep problems OR fatigue, assessed as moderate to severe by the healthcare professional without any score [3].

The estimated prevalence of FMS is 2–4% worldwide, and the female to male ratio is 3–9:1 [4].

## *Chronic Fatigue syndrome*

Myalgic encephalomyelitis/chronic fatigue syndrome (CFS) is a disabling clinical condition, characterized by an unexplained and persistent post-exertional fatigue and widespread pain. It is accompanied by a variety of symptoms related to cognitive, immunological, endocrinological, and autonomous dysfunction. The estimated prevalence of CFS worldwide is 0.1–0.5% [5]. CFS is an enigmatic disease for the physicians, and a debilitating one for the patients, thereby becoming a significant public health problem [6]. It was estimated that between 836,000 and 2.5 million Americans suffer from CFS, causing an annual financial cost that ranges between USD17 and 24 billion per year.

It is characterized by a marked reduction of the patients' quality of life, and ability to maintain work or participate in occupational, social, and personal activities. It affects all ages, races, and socioeconomic groups and has an estimated female predominance of 3–4:1 [6–8].

**Table 1.1** Function and features and of the three main organ systems involved in chronic fatigue syndrome

| System | Organ system cell type | Characteristics |
|---|---|---|
| CNS | Neuron | Distorted and chronic noxious sensory signaling. Neuroimmune activation. A variety of neurological disturbances leading to a variable symptomatology. |
| | Glial cells | The BBB is permeable. TLR signaling induced activation. Upregulated expression of IL-1B and of 5-HTT in astrocytes. Decreased extracellular 5-HT, resulting in reduced 5-HT-R activation. |
| Immune system | Lymphocytes | A Th2 Type immune response predominance. |
| | NK cells | Reduced NK cell activity with increased tendency to infections. |
| | B cells | B cell autoreactivity and increased autoantibody production, triggered by infections. |
| Endocrine system | HPA-axis | Hypo-cortisolism induced by increase corticosteroid negative feedback. Diurnal variation is blunted. Attenuated ACTH challenge response. |

*BBB* blood–brain barrier, *5-HTT* 5-hydroxy tryptamine transporter, *5-HT-R* 5-hydroxy tryptamine receptor, *IL-1B* interleukin 1 beta, *TLR* toll-like receptors, *NK* natural killer, *HPA* hypothalamus–pituitary–adrenal axis, *Th-2* T helper type 2

The central neurological system (CNS), the immune system, and the endocrine system are the three pillars which stage the pathogenesis of ME/CFS (Table 1.1).

## The Alterations in the CNS Involve Neurons and Glial Cells

The symptomatology is related to a neuronal aberrant chronic disturbance in noxious sensory signaling and neuroimmune activation [9]. A wide spectrum of pathophysiological phenomena have been well described:

In particular, marked blood–brain barrier permeability, microglia activation through toll-like receptors (TLR) signaling, increased secretion of interleukin 1 beta (IL-1B), upregulation of 5-hydroxytryptamine (5-HT), and 5 hydroxy tryptamine transporter (5-HTT) in astrocytes have been observed. In addition, reduced extracellular 5-HT levels are found. Further, a reduced activation of 5-HT receptors is established [10].

## Indicators for the Involvement of the Immune System Are the Following

The presence of a lymphocyte Th1/Th2 imbalance shows a bias toward type 2 responsiveness [11].

Natural killer cells (NK) display a reduction of cytotoxic activity in these patients, thus leading to an increased propensity for infections [12].

B cells display a persistence of autoreactive B cells producing autoantibodies (AAb) during common infections [13].

Autoantibodies against G-protein coupled receptors (GPCR) are significantly important in CFS. High levels of AAb against M1, M3, and M4 muscarinic AChR and β2 AdR are found in CFS patients compared to controls [14, 15]. Anti-M1 AChR AAb are associated with muscle weakness [15]. Levels of anti-β2 AdR AAb correlate with levels of activated HLA-DR+ CD8+ T cells, antinuclear antibodies, anti-thyroperoxidase AAb, and IgG1–3 level [14]. It is of interest since β AdR are expressed by lymphocytes and contribute to the regulation of activation, differentiation, cytokine, and also antibody production [16]. Loebel et al. [14] reported about a significant decrease in anti-β2 AdR and anti-M4 AChR AAb in CFS patients treated with rituximab in clinical responders. In another study, immunoadsorption was shown to remove anti-β2 AdR and anti-M3/M4 AChR AAb in ME/CFS patients and was accompanied by symptom improvement [17]. In post-orthostatic tachycardia syndrome (POTS) anti-β2 AdR AAb were shown to be elevated. Since β2 AdR are the primary adrenergic receptors that mediate vasodilation, one could assume they affect vascular regulation in CFS.

## Changes Within the Endocrine System

One finds, especially in the hypothalamus–pituitary–adrenal (HPA) axis, increased corticosteroid-induced negative feedback, basal hypo-cortisolism, attenuated diurnal variation, and a reduced responsiveness to various standardized challenges [18].

## Criteria Controversies

In 1994, Fukuda formulated a clinical and workup protocol aimed at delineating and integrating the diverse approaches to study CFS [19].

According to Fukuda, fatigue in CFS is defined as a "self-reported persistent or relapsing fatigue lasting six or more consecutive months." It required a clinical evaluation to identify and rule out other possible medical or psychological conditions responsible for the symptomatology. A diagnosis required the absence of other fatigue-associated conditions, a symptomatology lasting for at least 6 months, and a minimum of four of eight minor symptoms. This overly inclusive definition had been widely criticized, but it is still used in the clinical evaluation and diagnosis of CFS. Up to 20 other clinical criteria have emerged, among which are the 2003 Canadian Criteria and an update of the 2011–2012 International Consensus Criteria [20] (Tables 1.2, 1.3, and 1.4).

**Table 1.2** Key features of chronic fatigue syndrome patients

| Symptomatology | Characterization |
|---|---|
| Fatigue | Fatigue at rest, not relieved by rest. No medical reason found. Induced by light tasks. |
| Sleep disorder | Short non-refreshing sleep. Disrupted sleep rhythms with insomnia, day time sleepiness and even day-night reversal. |
| Arthralgias | Mainly generalized aches. Can be attributed to an autoimmune co-morbid state. |
| Myalgias | Often attributed to co-morbid fibromyalgia. |
| Headache | Episodic migraine headaches and new onset intensity fluctuating headaches. |
| Cognitive dysfunction "Brain fog" | Working memory is impaired. Slowing down of mentation. Attention deficit. Missing words. Concentration deficit. Impaired multitasking. |
| Post exertional malaise | All symptoms are worsening following normal day to day activities. Prolonged recovery period, extending 24 h. |
| Autonomic imbalance | Orthostatic intolerance. Exertional intolerance. Excessive sweating. Gastrointestinal, sexual and urinary dysfunction. |
| Neuroendocrine | Anxiety. Stress intolerance. Reduced appetite. Sensation of fever. |
| Immune related | Painful lymphadenopathy. Sore throat. New onset intolerances to foods and drugs. |

**Table 1.3** Symptomatology in chronic fatigue syndrome

| Symptoms | Percentage |
|---|---|
| Fatigue | 100 |
| Headache | 90 |
| Concentration difficulty | 90 |
| Sore throat | 85 |
| Lymph nodes tenderness | 80 |
| Myalgia | 80 |
| Arthralgia | 75 |
| Deranged sleep | 70 |
| Affective disorder | 65 |
| Allergy | 55 |
| Abdominal pains | 40 |
| Loss of weight | 20 |
| Tachycardia | 10 |
| Skin rashes | 10 |
| Nocturnal sweats | 5 |
| Chest pain | 5 |
| Weight gain | 5 |

**Table 1.4** 2015 Chronic fatigue syndrome-diagnostic criteria

| *Diagnostic requirements*[a]: |
|---|
| All three must be present: |
| 1. A marked impairment, of ≥6 months in the ability to perform occupational, educational, social, or personal activities, compared to premorbid levels. Profound, new-onset fatigue should be present. The fatigue is not induced by excessive exertion. Fatigue is not ameliorated by rest. |
| 2. Post-exertional malaise: Function and symptoms become severe after a physical or cognitive stress that was tolerated in pre-morbid state. |
| In addition, one of the following manifestations must be present: |
| 1. Cognitive impairment: Exertion, physical, mental stress or time pressure exacerbate difficulties in thinking and executive functions. |
| 2. Orthostatic intolerance: Maintained upright posture induces worsening of symptoms. Reassuming lying down or feet elevation usually abolishes symptomatology. |

[a]Assessment of frequency and severity of symptoms should be done. These should be present at least half of the time with moderate, substantial, or severe intensity

## Overlap Between FMS and ME/CFS

Both FMS and ME/CFS are medically unexplained illnesses, prevalent in women, and characterized by disabling fatigue and by widespread pain with tenderness. Currently, there are no validated biomarkers for the diagnosis of these entities. Diagnosis, therefore, is based on clinical criteria. There is a considerable overlap between CFS and fibromyalgia; the majority of patients with CFS meet tender point

**Table 1.5** Clinical overlap between chronic fatigue syndrome and fibromyalgia

| |
|---|
| • Female to male ratio = 9:1 |
| • Fatigue and widespread pain >90%. |
| • Both are characterized by sleep disorders, headaches, and neurocognitive and affective impairments. |
| • Lack of medical etiopathogenesis. |
| • Normal physical findings, with tender points. |
| • Laboratory results are normal. |
| • Chronic course. |
| • Therapeutic modalities generally ineffective. |

**Table 1.6** Differences between CSF and FMS

| Distinguishing parameters | CSF | FMS | Ref |
|---|---|---|---|
| Prevalence | 0.1–0.5% | 2–4% | [5, 19] |
| Substance P in CSF | Not increased | Increased | [22] |
| Substance P, CRH, IL-6, TNF in plasma | Not increased | Increased | [23] |
| Obstructive sleep apnea | More frequent[a] | Less frequent[a] | [24] |
| Preceding viral prodrome | Double as many | Half as many | [25] |
| Tryptophan infusion[b] produced an: | Increased serotonergic response | No increased serotonergic response | [26] |
| PTSD is diagnosed in | 1.5% | 8.5% | [27] |
| Sleep architecture: | | | [28] |
| REM/wake transitions | More frequent | Less frequent | |
| slow wave/light sleep transitions | Less frequent | More frequent | |

*CFS* chronic fatigue syndrome, *FMS* fibromyalgia syndrome, *CSF* cerebrospinal fluid, *CRH* corticotropin releasing hormone, *IL-6* interleukin 6, *TNF* tumor necrosis factor, *PTSD* post traumatic stress disorder, *REM* rapid eye movement sleep stage
[a]Statistically significant, [b]Compared to FMS and healthy controls

criteria for fibromyalgia [21]. Similarly, approximately 70% of patients with fibromyalgia meet the criteria for CFS (Table 1.5) [21, 22].

However, there is a major defining difference between these two quite similar diseases. In CFS, existence of a medical condition, which can be the source of fatigue, excludes the diagnosis, whereas in FMS any comorbid medical condition is non-exclusive for the diagnosis. In the case of FMS, patients without painful comorbid conditions are defined as suffering from a primary FMS, while those with coexisting rheumatological diseases are considered as suffering from a secondary FMS. This disparity in determining the diagnosis certainly accounts for the marked difference in prevalence: with FMS ranging roughly 2–4% [23], while CFS only 0.1–0.5% (Table 1.6) [5].

Notwithstanding the dissimilar prevalence of these two syndromes, a very similar core symptom complex prevails in both: fatigue, sleep problems, and cognitive

difficulties with significant disability and comorbidity. In one study, 34% of 323 patients with CSF had also FMS [29].

Several researchers [24] keep querying to what extent and in what sense are CFS and FMS indeed distinct entities? The hypothesis that the two diseases are, in fact, one disease ("the unitarian hypothesis") can be challenged on two grounds. The first has to do with the difference between the nature of the original 1990 case definition criteria for FMS and the revised one of 2010. This 2010 definition blurred the diagnostic distinction between FMS and CSF, resulting in twice as many patients with CSF co-diagnosed with FMS, compared with the use of the former set of the definition criteria. The second challenge is concerned with the issue of determining whether or not the two syndromes share the same pathophysiological process.

However, there have been numerous pathophysiological differences found between the two entities:

1. An increase in substance P was found in the cerebrospinal fluid (CSF) of FMS patients, not found in the CSF of CFS patients [25].
2. In addition, substance P along with corticotropin-releasing hormone and proinflammatory cytokines (IL-6 and TNF) was found to be elevated in the serum of patients with FMS, implicating involvement of mast cells [26].
3. Interleukin-37 (IL-37), an anti-inflammatory cytokine, was recently suggested as a potential treatment in this inflammatory process found in FMS [27].

There are other differences that distinguish CFS patients from those with FMS:

1. In a cohort of 122 patients with obstructive sleep apnea, CFS was found significantly more frequent, compared with FMS [28].
2. In double as many patients with CSF when compared to patients with FMS, the disease is preceded by a viral prodrome [30].
3. Compared to FMS patients and healthy controls, in CFS patients, tryptophan infusion produced an increased serotonergic response [31].
4. Post-traumatic stress disorder is diagnosed substantially more frequently in FMS compared to CFS, 8.5% vs. 1.5% [32].

Another pathophysiological difference between CFS and FMS was found in a study of the sleep architecture of patients with CFS when compared with patients with CFS +FMS and normal controls [33]. Patients with CFS only had more frequent transitions from REM to wake state, while patients with CFS +FMS had a sleep disruption characterized by a higher frequency of changes from slow wave sleep to light sleep. This pattern was not seen in CFS and healthy controls.

These findings provide further support for a sharp differentiation between CFS and FMS and lend additional weight to the notion that these are two distinct diseases and not the same disorder on the same spectrum with differing severities.

## Summary

Chronic fatigue syndrome and FMS are indeed two quite similar disorders, manifesting numerous overlapping symptoms such as fatigue, widespread pain, and sleep disorder among numerous others. It has been strongly argued that notwithstanding these similarities, there are sufficient supporting data to conceptualize them as two different entities. First and foremost, the two disorders have different pathogenic mechanisms. Moreover, while FMS is a more "permissive" diagnostic entity which enables the clinician to diagnose it in the presence and/or absence of additional conditions, with the resulting distinction between primary or secondary FMS, respectively, CFS definition is a rather exclusive one, namely excluding the comorbid presence of another fatigue inducing disorder.

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# Chapter 2
# Chronic Pain as a Pathogenetic and Clinical Entity


**Elon Eisenberg**

## Acute Versus Chronic Pain

Principally, pain is a main defense mechanism of the human body, where within milliseconds from being exposed to an acute noxious stimulus (thermal, mechanical, chemical) we feel pain in the affected part of the body and withdraw it, away from the noxious source. Hence, acute pain alerts us to potential or actual damage, and by activating a withdrawal reflex, it prevents further damage. Acute pain is not always so brief, but we still regard pain which lasts for up to 3 months as an acute or subacute pain. While it is true that such pain does not evoke the withdrawal reflex anymore, it still serves as an alarm mechanism, which indicates that the healing process has not been completed (i.e., pain after osteoporotic fracture of a vertebra).

In contrast, worldwide, about 20–30% of the adult population suffer chronic pain. Chronic pain lasts for more than 3 months, often many months, years, or even lifetime, and therefore loses its alarming properties and serves no more as a protective mechanism [1–3].

Additional differences between acute and chronic pain are noteworthy. Acute pain typically accompanies an acute medical illness or condition and often associated with anxiety. Acute pain or even fear from it may have negative effects such as enhanced "postsurgical stress response," reduced mobility-related complications (deep vein thrombosis, pneumonia), avoidance of repeated painful diagnostic or therapeutic medical procedures, and increased risk for developing chronic pain. Nonetheless, most people recover from acute pain within 3 months from its causing event.

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Chronic pain differs considerably. Not only that it lasts longer, it can be adequately relieved only in a minority of the patients, regardless of the treatment they receive. It frequently interferes with daily activities including, work, home responsibilities, recreational and social activities, and sleep. It is consistently linked to depression, feelings of hopelessness, helplessness, and despair. Not surprisingly, patients with chronic pain report markedly decreased quality of life [3].

Chronic pain has additional costs: not only it affects patients; their families can be detrimentally affected as well. Impaired relationships between patients and their spouses and children and income loss due to pain interference with work are just two of many examples of the negative effects of chronic pain on families of patients with chronic pain. In the broader sense, chronic pain also has a negative societal impact as well. Studies from different parts of the world show that chronic pain affects somewhere between 20% and 30% of the adult population. This is a huge number which sums at millions and millions of patients. These figures create enormous direct and indirect socioeconomic costs including costs of direct patient care, loss of income from work, welfare payments, and so forth, adding up to expenses which reportedly exceed—at least in some countries—those estimated for heart disease, cancer, and diabetes together. Collectively, data suggest that chronic pain presents a burden at least as great, or perhaps even greater, as conditions that are conventionally prioritized as public health concerns [4].

On top of all that, another societal crisis has emerged during the past decade in quite a few Western countries such as Canada and the USA, in relation to narcotic drugs or what has been termed as a "flood of opioids" or "epidemic of prescription—opioid overuse, abuse and addiction" [5]. Prescription of opioids has increased dramatically, mainly for the treatment of chronic pain. Unfortunately, unlike their good analgesic effect for acute or cancer pain, opioids often fail to provide adequate relief for many patients with chronic pain. This has many reasons, which are beyond the scope of this lecture. However, due to poor training, knowledge gaps, and misunderstanding of the situation by both caregivers and patients, the lack of adequate analgesic response frequently led, and still leads, to repeated increments of the prescribed opioid doses. Eventually, thousands of patients with chronic pain are taking massive doses of opioids, with dependence, addiction, and still without adequate pain relief.

## Types of Pain and Their Basic Physiological Principles

When talking about pain physiology, the term "pain matrix" is often mentioned. The pain matrix consists of the central somatosensory nervous system, which includes the brain, brain stem, and spinal cord, and the peripheral somatosensory nervous system, which is made of the peripheral nerves [6].

In the case of acute pain (i.e., a pin prick), the sharp edge of the needle penetrates the skin and activates a free nerve ending, a high-threshold unmyelinated or thinly myelinated nociceptor (c-fiber and A-delta, respectively). These nociceptors are

activated by intense thermal, mechanical, and/or chemical stimuli, which have the potential to—or actually—cause tissue damage by a physiological process termed transduction. Action potentials, which result from the transduction, are conducted along the peripheral nerves, transmitted to the spinal cord, and further conducted to the thalamus and finally to multiple sites of the brain, where they are perceived as the sensation of pain. This process, which follows a pin prick, is typically short-lasting. Hence the sharp pain will subside quickly, but shortly after, a second type of pain accompanied by local sensitivity, redness, and some swelling will soon occur. This is an inflammatory pain. Notably, the inflammation itself sensitizes local nociceptors, leading to a reduction in their activation threshold. This process is called peripheral sensitization, which typically leads to ongoing spontaneous pain and hyperalgesia.

A second critically important part of the pain matrix is the substantia-gelatinosa, located in the superficial dorsal horn of the spinal cord, where the synaptic transmission from the nociceptor to second-order neurons takes place. It is a typical neurochemical synapse. However, under circumstances, such as inflammation or peripheral nerve injury, the efficacy of this synapse may be enhanced, leading to sensitization of second-order neurons in the spinal cord. This phenomenon known as central sensitization and is presented clinically by further aggravation of the pain and by allodynia (a condition where non-painful stimuli are perceived as painful).

As already mentioned the conduction of pain pathways terminates at multiple sites in the brain including the primary and secondary somatosensory cortex, insula, cingulate gyrus, amygdala, and others. The involvement of so many brain sites in pain matrix explains the complexity of pain, which has sensory, emotional, cognitive, and motivational aspects.

Thus far, acute nociceptive and inflammatory pain was discussed, but two other pain types deserve consideration. One is neuropathic pain which results from damage to or disease of the somatosensory nervous system. Peripheral neuropathic pain is more common than the central one, and can be diffuse (painful diabetic neuropathy) or isolated, acute or chronic (herpes zoster and post-herpetic neuralgia, respectively). From a physiological standpoint, the main characteristic of neuropathic pain is that it is not initiated by the classical transduction process. Rather, action potentials are created at an ectopic site, somewhere along the injured nerve. In simpler words, the somatosensory nervous system does not signal the brain about potential or actual tissue injury; it creates the pain by itself. The diagnostic criteria for neuropathic pain have been revised and published recently [7]. The second noteworthy type of neuropathic pain has recently been termed nociplastic pain, previously called dysfunctional pain [8]. Patients who suffer this type of pain may report ongoing pain, hyperalgesia, and even allodynia, although no evidence for tissue injury, inflammation, or nerve injury can be identified. Perhaps, the most well-known example of this pain is fibromyalgia. An important take-home message is that the pain matrix is subject to plasticity (sensitization). Hence, in the case of chronic inflammatory, neuropathic, and nociplastic pain, noxious stimuli are no longer required to generate pain. Indeed, pain may arise spontaneously in the absence of any stimulus [9].

## Modern Approaches to Chronic Pain Diagnosis and Therapy

The goals of pain therapy are to reduce pain intensity and to improve function.

In the case of acute pain, the main goal has traditionally been to reduce pain intensity even at the cost of temporary impaired function. One example is pain after surgery, where focus has been put on minimizing pain and thereby reducing suffering, diminishing pain-related complications, and preventing the transition from acute to chronic persistent pain. For achieving this goal, function is often temporarily compromised by anesthesia, sedation from strong analgesics, and bed rest. However, modern approaches of acute postoperative pain management continuously change and modern individually tailored approaches aimed to effectively treat pain while maintaining function are being employed. They include pre-operative risk assessment and patient education, preemptive analgesia, regional anesthesia, multimodal analgesia, and repeated postoperative close-loop pain assessments [10, 11].

Perhaps, the most common mistake in the practice of chronic pain management is the adoption of uniform algorithms, where analgesics' strength is simply adjusted to pain intensity: non-opioids for mild pain, "weak opioids" for moderate pain, and "strong opioids" for severe pain. This simplistic approach is no longer valid for the management of acute pain and certainly not for chronic pain. In fact, overuse of this approach has led to the opioid epidemics in North America and in several other countries [12].

The management of chronic pain is challenging at times for several reasons. First, chronic pain tends to become less responsive to known treatments compared to acute pain. Second, as mentioned earlier, while a temporary compromise of functionality of patients with acute pain may be acceptable, long-term conciliation of functionality of patients with chronic pain in order to reduce their pain intensity is inadequate. Third, chronic pain is frequently complexed by impaired sleep, anxiety and depression, feeling of despair and helplessness, and difficulties with performing physical and sometimes mental activities. All these have led to the understanding that a multidisciplinary team approach is necessary for comprehensive assessment and subsequently proper management of these patients [13]. The treatment of chronic pain is aimed to improve quality of life, but this can only be achieved by the combination of reducing pain and improving function. Many studies have shown that these goals are inter-related to one another and need to be addressed and treated simultaneously. Nonetheless, while in some patients this works well, the "satisfactory pain reduction" part of the equation is not always achievable. Hence, in many patients the focus of treatment has to be shifted from pain reduction to pain management or pain rehabilitation. What this practically means is that regardless of the underlying cause of pain, patients are being taught how to better manage their pain, and improve quality of life and functioning, despite having residual pain [14–16].

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# Chapter 3
# Etiology and Triggers in the Development of Fibromyalgia


**Dana Amsterdam and Dan Buskila**

## Introduction

Fibromyalgia (FM) is an intriguing cryptic disorder, categorized as a chronic pain syndrome which affects a considerable amount of the population worldwide, with prevalence between 2% and 6% [1]. FM syndrome constitutes a significant healthcare issue causing great disability, loss of employment, and psychological hardship [2].

Major manifestations of FM are chronic widespread pain, accompanied by fatigue and mood and sleep disorders which impose grave effect on quality of life. The widely accepted explanation for chronic pain in FM focuses on aberrant perception of nociceptive stimuli through a process of central sensitization resulting in erroneous interpretation and amplification of pain [2, 3].

Autonomic dysfunction is inherent to FM with descriptions of alternations in function and hypo-reactivity of the autonomic nervous system [4]. Additionally, FM causes a dysfunction of the endocrine system which manifests with alterations in the hypothalamic–pituitary–adrenal functioning which simultaneously contribute to the flawed perception and amplification of the nociceptive system [5].

However, the biological mechanism driving the stimulation of this adverse process continues to elude researchers, and some suggest rather an emotional basis that encompasses the syndrome manifestations [6].

FM is a multisystemic syndrome with a winding path: it is occasionally considered to be at the distant end of the spectrum of psychosomatic syndromes with symptoms and signs frequently misinterpreted as being of psychological or

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psychosocial origin. FM manifests both cognitively and physically, with recent research demonstrating evidence of changes in endocrine, sympathetic, and immune dysregulation [4, 6, 7]. Our understanding of FM has made significant advances over the past decade although to this day, despite extensive research, the etiology and pathogenesis of FM still remains enigmatic [8]. Thus, this syndrome of chronic widespread pain which encompasses clustering of somatic symptoms without definitive etiology gives rise to overlapping syndromes such as chronic fatigue syndrome, somatoform disorders, and chronic regional pain.

Understanding the interrelated physiological, psychological, and social processes is important in any rheumatic disease, though even more in FM due to the inherent invisibility of its symptoms combined with the absence of observable deformity and multiple overlapping psychological symptoms and history [3, 5].

FM is considered as a multifactorial disease with abundant potential triggers and a multifarious pathophysiology process. There is no evidence for a single event that "causes" FM; rather, many physical and/or emotional stressors may trigger or aggravate symptoms [9, 10]. Notable triggers include physical trauma, emotional trauma, and stress, as well as external stimuli contributors such as infections and vaccinations. In a systemic review conducted by Yavne et al., which inquired for precipitating physical and psychological traumatic events in the development of FM, a significant association was established through retrospective data between prior physical or psychological trauma and the subsequent development of chronic widespread pain and FM [3]. Greenfield et al.'s research augments this stance by depicting a high incidence of reactive FM among individuals who reported a precipitating event as trauma, surgery, or a medical illness before the onset of FM [11].

The role of these negative events in the initiation of the FM symptomology has been the center of debate and research as a means of understanding FM pathophysiology with major implications on prediction of disease development and exacerbations [2, 8, 12]. More importantly, understanding the mechanisms underlying altered pain processing characteristic of FM is crucially important in progression toward tailoring of specific treatment and production of novel strategies for therapeutic management and alleviation of care [3, 8].

## Genetics

FM is generally regarded as a noninflammatory and nonautoimmune disease with a polygenic inheritance and environmental contributors. Although it is perceived as nonautoimmune, the high proportion of female patients, a trend reflected in many autoimmune diseases, has spurred the search for an immune-mediated basis for FM. FM is common in patients with autoimmune disease, for instance SLE, with overlapping symptomatology [13, 14], while some FM patients showed evidence of autoimmunity, without meeting the criteria for a specific diagnosis.

Past research suggests genetic factors may play a role in the pathogenesis of FM. Research evolved regarding polymorphisms of genes in the serotoninergic,

dopaminergic, and catecholaminergic systems in light of their cardinal role in pain transferal variation and perception [15, 16]. H. Cohen et al. observed an association between COMT polymorphism, which is involved in the mediation of pain perception, and the number of pressure points reported, an important component of FM severity [17]. Another research performed by Seong-Kyu et al. demonstrated NO enzyme is partially responsible for pain sensitivity in the pathogenesis of FM and GCA1 gene is a potential protective component in FM susceptibility and pain sensitivity [17, 18].

Furthermore, it is presumed that certain environmental factors, especially physiologically or mentally related stress, may trigger the development of FM in already genetically predisposed individuals. Recent publications have documented increased prevalence of FM among family members of patients suffering from FM, likely representing both polygenic inheritance and environmental influence [15]. Another study demonstrated gene polymorphism inheritance in specific family clusters, which make them predisposed to suffering from FM [19]. Deciphering the genetic underpinning for the hyperalgesia in FM would constitute a major advance in understanding FM syndrome pathophysiology. The future is near with new genetic modalities such as the genome-wide association study, which offers the hope of integrating the genetic, the physiological, and ultimately the therapeutic levels for FM [20].

## Physical Trauma

Patients often report that a precipitating event, such as physical or emotional trauma, occurred before the onset of FM with a prevalence of 21–47% [21]. The precipitating event may be mechanical, including motor vehicle accidents (MVA), surgery, physical and sexual abuse, or a diagnosis of a medical illness [22–24]. In a study investigating the development of reactive FM following a preceding physical event, the patient-reported prevalence of FM was 23% [11]. These results were later reinforced by Al-Allaf et al. who investigated patient-reported physical trauma during the previous 6 months in FM patients versus controls, demonstrating that physical trauma was significantly associated with the onset of FM, with 36% report rate in FM patients compared to 24% in matched controls [25].

There is a common assumption that a diagnosis of FM occurring after a previous precipitating event carries a graver course and prognosis. Published studies comparing the severity of clinical features of FM between patients with a preceding physical trauma and patients with idiopathic presentation show conflicting results. Findings vary from no significant difference [21] to negative effects and greater disability in patients with traumatic onset compared with those with idiopathic onset [11].

Trauma has been suggested to precipitate the onset of FM by altering normal sleep patterns as well as by turning local injury sites into focuses of regional pain by causing neural plasticity [11]. It is believed that the persistent nociceptive input

from peripheral tissues following a traumatic event may lead to neuroplastic changes resulting in central sensitization and FM [5]. Further research is warranted in order to better understand which types of trauma are more likely to lead to FM and which patient characteristics are most likely associated with the development of FM after precipitating events [12].

FM development after motor vehicle collision was the center of a review which established criteria for determining causality, thus supporting causation between the two [26]. Gareth et al. reinforced their claims by demonstrating a high prevalence (11.3%) of FM development after motor traffic accidents during 4 years of follow-up, compared to the general population. In addition, it was suggested that individuals from a lower socioeconomic background may be more predisposed to develop chronic widespread pain (CWP) syndromes, including FM, following a traumatic stimulus [27, 28]. On the other hand, Wolfe et al. claim in their review that the causative model between the two is poor due to low quality of scientific evidence, depending mostly on studies which rely on patient's recall and attribution [29]. This approach was later refuted in an editorial by Jones who argued that the authors presented a very partisan argument, basing their claim on the analysis of five published studies with no evidence of systematic literature search and without a structured review [30].

Whiplash injury is a common kind of mechanical trauma which may lead to the development of FM. The interpretation of the biological association between mechanical stress, for instance chronic whiplash syndrome in regard to FM, has generated considerable controversy, due to its social and medicolegal implications and consequences, in all jurisdictions where compensation is available [3, 7, 26, 31–34]. Thus, emphasis must be placed on the differentiation between medical and legal approaches and on the need for more research to elucidate the manner of causation [10, 34].

Some studies have demonstrated a positive correlation between whiplash injury and higher prevalence of FM, the most well known by Buskila et al. which demonstrated that FM development following neck injury was 13 times more frequent than following lower extremity injury, with the same rates of insurance claims [35]. Other studies have demonstrated a negative correlation, with the same 1-year follow-up incidence of FM post-whiplash injury as in the general population. The difference may lie in the referral bias of non-recovered patients or due to malingering and personal gain [36]. In such cases, the decision regarding a diagnosis of FM and the degree of work-related disability require a systematic approach. A precaution is warranted to maintain a "divide-and-conquer" approach, on one hand, from a medical standpoint to establish a strong diagnosis and determine disability level, and on the other hand from a legal standpoint to determine the causative relation between the disease and disability [7].

Physical trauma and emotional trauma in many cases are entwined. Buskila et al. conducted a research following the course of survivors of a train crash who were exposed to the combination of physical injury and extreme stress, with a diagnosis of FM found at a high prevalence (15%) among 53 survivors in a follow-up time of

3 years. This finding is in accordance with previous data regarding the association of FM with both physical and emotional stress [35].

## Stress and Emotional Trauma

There is a long-standing debate regarding psychology versus biology for FM, one espousing psychology as the more important component and the other claiming that biology plays the greater role [37]. Nevertheless, there is no doubt that the psychological perspective is of major importance in FM. The pathophysiology mechanism linking between precipitating stress-related events and the physical manifestations of FM is yet to be understood. The deviations of the neuroendocrine stress systems in FM are the same as in healthy individuals pre-exposed to an acute stressor. This observation strengthens the assumption that FM is a stress-associated syndrome and enhances the mind–body connection narrative. However, strong evidence in favor of the arguments is lacking [5, 38, 39].

Another potential trigger for FM is emotional turmoil which can be derived from many possible circumstances, from negative experiences in early childhood, such as neglect or abuse, to traumatic adult experiences involving PTSD and sexual abuse [22]. Patients suffering from mental health issues have a higher risk of suffering from FM symptomology and being diagnosed with FM, and vice versa. The reported rate of depression among FM patients is significantly increased, at the somewhat alarming rate of up to 50–70% of patients [38, 40, 41].

There are many studies investigating the association between physical and sexual abuse and FM, with the assumption that abuse may affect the expression and perpetuation of FM syndrome in adult life [42]. Häuser et al. concluded in a meta-analysis that the association of FM with prior physical and sexual abuse could be confirmed, but that the overall low quality of evidence was a confounding factor [23]. These results were augmented by a comprehensive meta-analysis conducted by Afari et al., which demonstrated that individuals had a 2.52-fold likelihood of developing FM following exposure to trauma [43]. Edwards et al. found higher rates of traumatizing events such as sexual and emotional abuse in FM patients in comparison with rheumatologic controls, in association with disability severity, and a more treatment-refractory illness [44]. Another study performed by Haviland et al. reinforced these results, with a significant association between self-reported sexual assault and physical abuse in women and a physician-given FM diagnosis [28]. Childhood trauma was more commonly reported than adult trauma, as supported by Hellou et al.'s observation of significantly higher levels of emotional abuse and neglect in FM patients [45]. In a cross-sectional study by Häuser et al. only emotional and sexual abuse in childhood remained significantly associated with FM in comparison with healthy controls after removing the confounding factor of depression [46]. In a similar study by Yeung et al., childhood neglect was correlated with a flattened cortisol profile in FM patients [47], which is associated with pain, as

supported by previous research depicting endocrine changes related to FM syndrome [5].

Previous studies have described a high prevalence of PTSD among FM patients, which can be up to 56%, with concurrent occurrence increasing the severity of both disorders [48–51]. There is evidence that even re-traumatization of a previous traumatic event can lead to development of both PTSD and FM. When attempting to evaluate the temporal relationship of stressful events to PTSD and FM, their connection seems to be interwoven. The association between the two syndromes does not appear to be explained by a common familial or genetic vulnerability [52]. Häuser et al. have demonstrated a PTSD prevalence of 45.3% among 395 FM patients and showed that chronic widespread pain and a diagnosis of FM symptoms were antedated by the traumatic event and the diagnosis of PTSD in 66.5% of patients [49]. Another study investigated FM–PTSD comorbidity in a cohort of men following a traumatic event. Of the PTSD patients, 49% fulfilled FM diagnostic criteria, suggesting that PTSD is highly associated with FM and that the degree and impact of these disorders are closely related [53].

Two unique studies by Ablin et al. have been published regarding traumatized population that sustains the strong correlation between PTSD and FM: Firstly, a population-based survey which demonstrated a significantly elevated proportion of CWP, FM-like somatic symptoms, and depression among residents of a city targeted by missile attacks, in comparison with residents of a city which was beyond the line of fire [52]. Secondly, a research which examined holocaust survivors and documented an increased rate of FM and PTSD among this unimaginably traumatized population, in comparison with controls [54]. These works were noteworthy due to their design, which focused on uniquely traumatized populations and were able to extend previous data by demonstrating the ability of stress to induce chronic pain and FM symptoms up to decades after the initial exposure.

To conclude, stress and emotional trauma appear to have a crucial effect on the development of FM. A study conducted by Bennet et al. reinforces this claim by demonstrating a vast association between the two. In this study, emotional distress was the most common exacerbating factor, with 83% report rate and the most common triggering event with over 73% of FM patients with a prior triggering event attributing it to emotional trauma or chronic stress [55]. These findings are in accordance with other studies presented in this review, emphasizing the relationship between physical and psychological trauma to FM. As aptly noted by Yavne et al. in their review, while the misgivings may remain regarding the strength of the evidence linking FM to physical and psychological trauma, it is worth keeping in mind that by its very nature this association remains elusive due to the impossibility of conducting randomized controlled trials, the gold standard of medical research. Nevertheless, the substantial cumulative retrospective data gathered throughout the years and presented here establish the presence of a significant association between prior physical or psychological trauma and the subsequent development of chronic widespread pain and FM [3].

## Fibromyalgia in the Workplace

An increasing number of patients attribute their illness to faulty workplace ergonomics or demands, often involving sustained poor posture, repetitive movements, and stress induced by environment. Workplace-related regional pain syndromes are common, and such clinical entities as acute cervical strain or mechanical lower back pain may evolve into generalized diffuse pain and tenderness characteristic of FM [36, 56, 57]. Past studies suggest that the majority of FM cases develop as a result of a peripheral insult and associated long-standing nociceptive input, which finally results in central sensitization and pain. Indeed, it is well demonstrated in research that localized or regional pain in most patients with FM precedes widespread pain, thus supporting the notion that FM can develop from localized pain [58].

Gallinaro et al. reported that among 34 workers diagnosed with repetitive strain injuries (RSIs), 58.8% fulfilled the American College of Rheumatology criteria for FM, while only 10.4% of the controls meeting the same criteria [57]. In a study performed among professional athletes, subgroup of a population which is young, healthy, and as such not prone to FM, the frequency of FM observed was 2.2% [59], a rate which is surprisingly similar to the rate presented in normal population-based studies, potentially due to different repetitive strain injuries.

Several interesting studies have been conducted regarding FM development in stressful unbalanced workplace environments. Firstly, a study conducted among nurses, who work long stressful shifts, demonstrated an increased prevalence of FM, especially in female nurses, with a strong correlation to concurrent symptoms of PTSD [60]. Secondly, in a study which investigated FM prevalence among Israeli kindergarden teachers, FM symptoms were found to be highly prevalent, with a 25% rate that greatly exceeds the ~2% prevalence in the general Israeli population. FM symptoms were associated with an increased rate of days of leave and poorer work performance [61]. Last but not least, a similar study conducted among Israeli school teachers demonstrated an increased prevalence of FM, with concomitant PTSD symptoms and lower motivation [62].

We conclude that stressful work-related events appear to be positively associated with the occurrence of FM symptoms and may serve as triggers for their development. Healthcare professionals treating individuals engaged in such occupations should be vigilant for the occurrence of symptoms that are clinically associated with FM syndrome and overlapping functional disorders.

## Infections

The association of infection and FM has been increasingly reported and studied as a possible triggering event, with a survey answered by FM patients showing that 43% of patients perceived infections as a precipitating or exacerbating event of FM symptoms [63]. Still, the understanding of infection-triggered FM remains limited.

No relationship has been demonstrated between persistent infection and FM or CWP, nor has any relationship been established between infection-aimed therapies and an improvement in pain. Thus, evidence of an association between the two remains tentative [64].

Various infectious agents have been linked to the development of FM, the most common bacterial agents being Lyme disease and mycoplasma, due to overlapping symptoms of arthralgia and myalgia. Viral agents such as HCV, HBV, and HIV are more common with stronger evidence of correlations [65], although data are still insufficient. Research is ongoing regarding the role of SARS-CoV-2 virus in FM, in the context of the ongoing COVID-19 pandemic.

Lyme disease, caused by *Bartonella Burgdorferi*, is recognized as an important confounder in the diagnosis of FM, particularly in areas where prevalence is high, since it causes similar symptoms of diffuse arthralgia, cognitive difficulties such as impaired concentration and memory, as well as fatigue, and since serological testing for Lyme disease is complex and not always conclusive [10]. In an observational cohort study, 8% patients with Lyme disease were found to have FM over a 3.5-year period, suggesting that Lyme disease may frequently be confused with FM, trigger FM development, or may even coexist with the syndrome in a chronic form. The scarce response to antibiotics may serve as an exemplary for other infections, as it implies that once a trigger has initiated the chain of events culminating in FM, it will run its course without the necessity of ongoing infection [66, 67].

There is a strong association between rheumatic diseases and clinical manifestations of HCV infection, with FM frequently appearing as a clinical comorbidity in HCV carriers, in up to 57% of patients. FM comorbidity is a negative prognostic factor, with influence on functional impairment and disability, resulting in a decline in quality of life. The underlying pathophysiology is not clear, with assumptions that range from an immunomodulation basis, implying alterations in cytokines that produce hyperalgesia, to other neutrally mediated symptoms as a result of CNS aberrations, all without real evidence to causal relationship [10, 68, 69]. In addition, other studies inquire the connection between HBV and FM, with evidence for an increased risk of FM symptomatology and diagnosis within carriers of chronic hepatitis B virus, again with diverse explanations, ranging from a psychological link, due to diagnosis-related anxiety, to the purely organic hypothesis focusing on an inflammatory response to HBV [70].

HIV infection is also associated with rheumatic symptoms such as arthralgias and myalgias. In a research performed in order to study the association of HIV with FM, 80% of patients had musculoskeletal symptoms while 10% fulfilled criteria for FM, which remained high after adjustment for depression. Patients with higher risk to develop FM were with prolonged disease duration and depressed mood. Symptoms may derive from the chronic viral infection or secondary to medical therapy. Notably, identification of FM is important for appropriate treatment and improvement of quality of life [71]. It is also widely believed that EBV may serve as a trigger for FM, yet there is minimal supporting evidence for this claim. A research conducted in 50 patients of FM whose symptoms had begun suddenly, as an apparent “virus” infection, appeared to refute this claim, with EBV serology

levels similar to those of the general population and no evidence that reactivation of latent EBV infection was associated with the patients' illness [72].

The COVID-19 outbreak has resulted in uncertainty for patients with autoimmune rheumatic diseases. In preliminary studies, it has been shown that rheumatic patients, including FM, are not more prone to contracting COVID-19, but the long-term effects of this novel pathogen are yet to be fully understood. In addition to the direct sequels of this viral infection, possible impact may be related to stressors such as fear, depression, illness, job loss, and social isolation [71]. It is increasingly acknowledged that stressors worsen FM symptoms with a higher risk of developing PTSD and may generate FM in previously predisposed individuals [73, 74]. One research conducted to study psychosocial and pain-related effects among patients with chronic pain during the COVID-19 pandemic has showed that FM was independently associated with greater pain severity during this time [75]. Risk stratification, sleep disturbance, anxiety, and depression, which are common comorbidities of FM, were associated with greater pain severity and interference. This information may aid to estimate the impact of the COVID-19 pandemic social isolation and emotional stress on chronic pain syndromes and guide development of innovative approaches to support this vulnerable population during this ongoing period.

To conclude, there seems to be a significant relationship between FM and infections: FM may appear or worsen after infections, probably because the antigens act as the trigger in the presence of a possible genetic predisposition or environmental influence. There is some evidence that FM is partially caused by infections; however, no relationship has been demonstrated between persistent infection and FM, nor any relationship between infection-targeted therapies and improvements in FM symptomology [63].

## Vaccinations

Several intriguing lines of evidence suggest that vaccinations may play a role in triggering FM, but the specific effects of antigens and adjuvants or environmental and personal context are still elusive.

The stance of association between vaccinations with FM began with the rubella vaccine. After the rubella vaccination, various conditions were observed including onset of chronic arthropathy and arthritis, arthralgia, and myalgia with a few studies supporting the subsequent development of FM, though the claim was finally contradicted by an RCT which failed to demonstrate a statistically significant increase in FM prevalence [63, 76].

Subsequently attention became directed toward the phenomenon of the Gulf War syndrome, which appeared to be associated with vaccination against various biological agents, with symptomology similar to FM and CWP. This unique clinical entity was first described after the military conflict in the Persian Gulf that took place in the early 1990s, where soldiers received a combination of pre-deployment vaccinations and during deployment for biological agents due to concern regarding

use of unconventional weapons of mass destruction. The Gulf War syndrome was characterized by chronic fatigue, musculoskeletal symptoms, general malaise, irritability, and cognitive disturbances. The syndrome developed with a prevalence of 10–15% and frequently overlapped with PTSD, with both syndromes appearing at a higher rate than observed in servicemen participating in other military conflicts. Thus, the authors conclude that while multiple vaccinations in themselves did not appear to be harmful, the combination between administration of such vaccinations and the concurrent stress associated with deployment in the combat zone and other possible environmental factors may cause an increased risk of developing FM-like syndrome [10, 63, 77].

Of note, a trial performed by Ablin et al., evaluating the efficacy and safety of influenza vaccination in FM patients, demonstrated that influenza vaccination was both safe and effective in FM patients compared to healthy controls [78].

To conclude, the role of vaccination in the pathogenesis of FM is still uncertain. It appears that the mere exposure to one or another specific vaccine is not a trigger for developing FM. Based on the experience of the related Gulf War syndrome, it is believed that the combination between various vaccines and adjuvant and environmental factors may compound the effects of vaccination on the immune system and on the eventual development of chronic FM symptomology [79].

## Conclusions

Fibromyalgia is an intriguing clinical syndrome with an elusive path and winding trajectory. Although extensive research has been dedicated to this important entity throughout the years, to this day there is no evidence for single etiologic factor or mechanism. The pathophysiology of FM is unclear and considered to derive partly from aberrant pain perception, presumably involving neurohormonal and endocrine dysregulation. FM, like other chronic pain syndromes, provokes patients and caregivers to grasp the concept that the medical model of specific cause and effect may not apply in this case.

This chapter has covered comprehensive research which has demonstrated a number of substantial triggers to the development of FM. Physical trauma is a major contributor with a spectrum of mechanical trauma on the one hand with examples of MVA and whiplash injuries and physical or sexual abuse on the other hand. Emotional trauma is by itself an independent trigger for FM development and in many cases may be intertwined with physical trauma as in chronic medical illness, sexual abuse, or childhood trauma and neglect, PTSD, or stressogenic workplace environments. Infections and vaccinations also play a role in the development of FM both as precipitating and as exacerbating factors. The course and prognosis of FM patients is directly related to psychosocial factors, including past and current psychological distress and work status or disability issues.

Currently, despite wide-scale research, FM etiology remains elusive, and an effective remedy is yet unknown. This reality emphasizes the importance of

understanding FM's presumed etiology and pathophysiology, in the aspiration of better predicting FM development and anticipating the disease trajectory, for the benefit of improving quality of life and possibly tailoring patient-specific pharmacological and nonpharmacological treatment.

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# Chapter 4
# Pharmacological Treatment of Fibromyalgia


**Emma Guymer and Geoffrey Littlejohn**

## Pathophysiology Relevant to Pharmacological Therapy in Fibromyalgia

Although the pathophysiology of fibromyalgia will be more fully covered elsewhere in this publication, it is worthwhile briefly reviewing aspects relevant to medications discussed in this chapter. There are multiple pathophysiological mechanisms with varying contributions in individual fibromyalgia patients. This leads to differing responses to drugs between patients and suggests that the symptoms need to be targeted through specific approaches and individualized plans [1].

### *Top-Down Processes*

Emotional distress is commonly present in fibromyalgia. Many physically and psychologically stressful situations are triggers associated with fibromyalgia [2], and the presence of early stressful adverse life events can predict if pain-free people will develop chronic pain [3]. Highly complex central physiologic responses to physical and psychological stress are interwoven and linked to central pain pathways [2]. The sympathetic nervous system (SNS) and the hypothalamic–pituitary–adrenal (HPA) axis comprise the main neurotransmitter and neuroendocrine response systems to stress [4]. Both systems are activated in fibromyalgia and influence descending pain modulation [2], with emotional distress also inducing neuroinflammation

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[5]. These factors combine together and result in downstream influence by higher cognitive and emotional centers to fibromyalgia pathophysiology.

## *Brain Networks*

Networks involved in modulating the brain's influence on the spinal cord are disturbed in fibromyalgia. Connectivity between the default-mode network and pain-inhibitory centers is decreased while connectivity is increased with the insula [6, 7]. Glutamate is an important neurotransmitter in pain pathways and is found in higher levels in the posterior insula and CSF in fibromyalgia compared to controls and results in increased neural sensitivity [8, 9]. Central glutamine levels change in concert with levels of clinical and experimental pain during fibromyalgia treatment response [8, 10, 11]. Central neuroinflammation with activation of glial cells results in cytokine release. Elevation of cytokine IL-8, but not IL-1β, in the CSF of fibromyalgia patients, compared to healthy controls, implies that in this location it is derived from glial cells within the central nervous system [12, 13]. IL-8 is co-localized with the translocator protein (TSPO) in glial cells, which is the rate-limiting step in serotonin synthesis and hence modulates serotonergic synaptic transmission and descending pain modulation. Genetic polymorphisms of TSPO associate with symptom severity and cerebral pain processing in fibromyalgia and interact with the serotonin transporter gene [13].

## *Enhanced Sensory Activity*

Enhanced reactivity in a number of sensory systems, particularly the pain-related nervous system, is an important mechanism in fibromyalgia [14, 15]. The interaction between the peripheral mechanoreceptors and the deep spinal cord neurons relays sensory information to regions of the brain that relate to the perception of pain [16]. This interaction is key to understanding fibromyalgia pathophysiology and is dependent on modulation by numerous neural networks involving neurotransmitters, hormones, neuropeptides, cytokines, and chemokines. In pathological circumstances, low-level non-noxious stimuli that activate mechanoreceptors in structures, such as muscles, tendons, ligaments, and entheses, will be perceived as painful.

## *Spinal Cord Modulation*

Increased sensitivity of spinal cord neurons occurs in fibromyalgia [14, 16]. There is abnormal functioning of descending inhibitory pain pathways that originate in higher brain centers and synapse with the second-order neurons in the dorsal horn,

modulating ascending pain transmission. These descending inhibitory pathways, often referred to as conditioned pain modulation (CPM), depend on serotonergic, noradrenergic, and opioid neurotransmission systems, with lower levels of serotonin and noradrenaline consistently being found in the CSF of fibromyalgia patients [17] and less effective endogenous opioid function [18]. Dysfunction in these neurotransmitter systems allows the more permissive disposition of sensitized neurons involved in reception of nociceptive input, involving C- and A-delta fibers, as well as those more deeply placed neurons that are able to receive mechanoreceptor input [3, 19].

Increased sensitivity of spinal cord neurons is also linked to increased activation by glutamate of the N-methyl-D-aspartate receptor (NMDAR) [16, 20, 21]. There is increased glutamate found in pain-related brain regions and CSF in fibromyalgia patients allowing the sensitization of NMDARs to contribute to central pain mechanisms [22].

### *Peripheral Nerve and Muscle Factors*

In response to a stimulus, there is an antidromal reflex along activated c-fibers resulting in a peripheral neuroinflammatory response. The innate and adaptive immune systems are involved with mast cells and dendritic cells along with T-lymphocytes activated. There is release of neuropeptides such as glutamate, substance P, calcitonin gene-related peptide, and nerve growth factor, as well as inflammatory cytokines [19]. The peripheral c-nociceptors show enhanced spontaneous activity and sensitization to mechanical stimuli [23], and there is evidence of small nerve fiber pathology in around 50% of fibromyalgia patients [24]. Abnormalities in muscle physiology are also observed in fibromyalgia [25], with augmented muscle membrane propagation velocity reactions independent of force load or amount of muscle activity, suggesting central deregulation [26]. These peripheral changes likely contribute to clinical features including swelling and dysesthesia.

### *Sympathetic Nervous System*

The autonomic nervous system is found to function abnormally in many fibromyalgia patients [27] with general increased activity and frequent patient reports of symptoms including postural symptoms, sweating, and palpitations. In animal models, the induction of chronic widespread musculoskeletal pain is associated with autonomic dysregulation including reduced heart rate variability, reduced baroreflex, and increased blood pressure variability [28, 29]. Higher cardiovascular sympathetic drive has been associated with increased magnitude of fibromyalgia pain [30].

With such a highly complex interplay of pathophysiological mechanisms occurring in fibromyalgia leading to a broad range of clinical features, central

sensitization is the most logical general pharmacological target. Different components of sensitization pathways can be influenced through varied strategies, and further scope exists to explore additional pharmacological approaches.

## Overview of Pharmacology

To date, the management of fibromyalgia has been based on a multidisciplinary approach, with education, psychological strategies, and physical exercise being the primary strategies used for symptom control and pharmacotherapy being added to this combined approach when further control is needed. Pharmacotherapeutic agents are more effective when used in combination with non-drug strategies. Most agents used in the treatment of fibromyalgia result in only a modest clinical benefit when used in isolation. Pharmacotherapeutic strategies aim to modulate increased central sensitivity over the longer term by targeting pathophysiological alterations in the central pain processing mechanisms, and the choice of agent can be individualized depending on troublesome features (e.g., pain, poor sleep, anxiety). Newer approaches directed toward more peripheral changes augment the current armamentarium and allow a broader concept of where pharmacologic strategies may be effective in influencing fibromyalgia symptomatology.

## Modulation of Stress and Sleep

The modulation of psychological stress and poor sleep is important to consider alongside the predominant pain aspects of the symptomatology. These factors are tremendously significant in any management approach to fibromyalgia, and to some extent, further interventions targeting pain are unlikely to be overly effective if high levels of psychological stress are continuing to drive the pathophysiological changes responsible for clinical features. As with all fibromyalgia management, non-pharmacological strategies are important first-line interventions and techniques to manage stress and sleep patterns can result in significant improvements in all aspects of clinical fibromyalgia. Medications such as anxiolytics and sedatives will influence stress and sleep problems directly in the short term; however, they have inherent problems such as poor tolerance and dependence issues and do little to modify the underlying fibromyalgia pathophysiology.

Sodium oxybate, the sodium salt of gamma hydroxybutyrate, is used in the management of narcolepsy and has been investigated for use in patients with fibromyalgia. In a small placebo-controlled study, sodium oxybate use resulted in improvement in physiological sleep abnormalities as well as pain and fatigue [31]. Two randomized double-blind placebo-controlled trial of 188 and 548 patients over 8 and 14 weeks, respectively, found improvements in sleep quality, fatigue, and other self-report fibromyalgia symptoms [32, 33]. Headache, nausea, dizziness, vomiting,

diarrhea, anxiety, and sinusitis were the most commonly reported adverse events with an incidence at least twice that of placebo. Tolerance and clinical effect was maintained out to 1 year [34]. The high risk of sodium oxybate abuse and documented criminal use of gamma hydroxybutyrate, however, has resulted in it being considered inappropriate to be included in fibromyalgia management strategy.

## Analgesics

In general, the use of analgesics for fibromyalgia pain is not accompanied by robust evidence of efficacy. Most do not target the pathophysiological mechanisms of fibromyalgia and provide inadequate and temporary influence on symptoms. Some of these agents, however, are helpful in managing pain generated from peripheral pathology including degenerative joint disease and, as such, can find a role in individualized treatment plans.

### *Simple Analgesia*

Simple analgesia is often the first medication patients with fibromyalgia will trial. Analgesics like acetaminophen (paracetamol) or non-steroidal anti-inflammatory drugs (NSAIDs) have little published data to significantly advocate for their use in fibromyalgia management. Paracetamol use has not been studied in fibromyalgia patients, other than in combination with tramadol, where the combination resulted in a modest (18%) improvement in pain compared with placebo [35]. Studies of NSAIDs in fibromyalgia have been small and largely inadequate; consequently, their use for fibromyalgia symptoms is not supported by quality evidence [36]. Despite the lack of available supporting evidence, these medications are easily accessible and frequently used by people with fibromyalgia, either to supplement other regular therapies or in situations of breakthrough pain, and a survey of 1042 FMS patients found that 66.1% deemed NSAIDs more effective than acetaminophen [37].

### *Opioids*

Fibromyalgia patients have reduced opioid-mediated descending nociceptive modulation with reduced numbers of available central μ-opioid receptors and higher levels of endogenous opioids in the cerebrospinal fluid (CSF) [18, 38]. Despite their widespread use, quality data describing benefit from pure opioid analgesia in fibromyalgia are lacking. There is little evidence for any efficacy with a small study of morphine in fibromyalgia patients finding no improvement in pain [39] and a

Cochrane review of the use of oxycodone finding "there is no randomised trial evidence to support or refute the suggestion that oxycodone, alone or in combination with naloxone, reduces pain in fibromyalgia" [40]. Given the absence of supportive data and the very real risk of adverse effects and opioid hyperalgesia, as well as the potential for addiction and abuse, pure opioid analgesics are not recommended for the management of fibromyalgia pain [41, 42].

## *Atypical Opioids*

Atypical opioids including tramadol and tapentadol have serotonin (5-HT)–norepinephrine(NE) reuptake inhibition(SNRI) activity as well as μ-opioid binding, resulting in modulation of descending inhibitory pain pathways. They are more helpful in managing fibromyalgia symptoms, with more available data supporting their efficacy. In addition to the combination trial with paracetamol, other studies have also found some benefit with tramadol use in fibromyalgia [43–45]. Unfortunately, there is a lack of published information regarding long-term efficacy or safety. Tapentadol results in mostly NE reuptake inhibition (NRI) with very little 5-HT effect, as well as weak μ-opioid agonism. There is minimal data regarding its use in fibromyalgia specifically, although tapentadol is generally well tolerated with sustained efficacy found out to 2 years in a broad range of chronic pain conditions [46]. A randomized double-blind controlled trial of 34 patients with fibromyalgia found that sustained-release tramadol use was associated with increased conditioned pain modulation (an experimental measure of descending pain inhibition), and in those patients with a normal corneal fiber state (a measure of peripheral small fiber neuropathy), there was a significant analgesic effect [47]. Tapentadol, due to its NRI property, allowed comparable analgesia achievement at lower opioid doses compared to oxycodone in low back pain patients [48]. Although tramadol and tapentadol are able to provide benefit at lower comparable opioid doses than pure opioids, the issues of long-term opioid use still remain. In addition, there can be SNRI adverse effects including sweating and palpitations [49], and concerns have been raised regarding suicide risk with tramadol [42].

Cebranopadol is a novel centrally acting analgesic that combines dual agonist action at opioid and nociceptin/orphanin FQ peptide (NOP) receptors. There are observations that NOP receptors are upregulated in dorsal root ganglia and downregulated in the thalamus and hippocampus in different chronic pain models [50–52]. The preclinical testing of cebranopadol displays antinociceptive and antihyperalgesic action in acute and chronic pain models in animals [53]. Phase 2 clinical trials have shown improvements in pain, sleep, and functionality in patients with chronic low back pain [54] and in chronic cancer pain [55] with acceptable tolerability and improved respiratory safety with less abuse potential compared to traditional opioids [56, 57]. A possible role of NOP receptors in fibromyalgia pathophysiology and treatment is raised with data describing the administration of NOP receptor ligands resulting in reduced pain and fatigue behaviors in a mouse model

of reserpine-induced fibromyalgia, with the peripheral analgesic effect unaltered by the addition of naloxone [58].

## Serotonin/Noradrenaline Modulators

Medications that elevate levels of serotonin and noradrenaline in the descending pain modulatory pathways of the CNS, such as low-dose tricyclic antidepressants (TCAs) and serotonin-noradrenaline reuptake inhibitors (SNRIs), can provide significant benefit in fibromyalgia patients independent of effects on mood [59]. Amitriptyline, duloxetine, and milnacipran are the best-studied agents in these categories, and all have substantial evidence for the significant improvement of pain, and other symptoms of fibromyalgia, although some early studies were brief [60].

### *Tricyclic Antidepressants*

Amitriptyline is a commonly prescribed TCA for fibromyalgia, and short-term studies have shown clinical improvements in 15–20% of patients taking amitriptyline above that of placebo [61–64]. Improvement in pain, fatigue, sleep, and quality of life is noted [65]. Side effects from amitriptyline are common and include dry mouth, constipation, daytime drowsiness, and mental clouding. Patients may benefit from taking this medication in the evening to promote sleep and minimize daytime side effects. Smaller doses of amitriptyline are typically used in fibromyalgia than in depression [64]. Between 5 mg and 25 mg as an early evening dose is usually prescribed, with doses above 50 mg seldom being used for this indication unless the antidepressant properties are being utilized.

Cyclobenzaprine is a 5-HT2 receptor blocker with a similar chemical structure to amitriptyline. It causes muscle relaxation but is not known to have antidepressant effects and has similar side effects to amitriptyline [66]. Meta-analysis findings indicate effect in one in five fibromyalgia patients, with moderate sleep disturbance benefit but only minimal improvement in pain [67].

### *Serotonin and Noradrenaline Reuptake Inhibitors*

The serotonin and noradrenaline reuptake inhibitors (SNRIs) duloxetine and milnacipran are widely used in the management of fibromyalgia. They have been approved for use in fibromyalgia in several countries and are available for use in other indications such as depression in others [66]. Duloxetine, which has more serotonergic effect, has been shown to have general benefit for pain and mood in fibromyalgia, while those investigating the use of milnacipran, which is more

adrenergic in action, have mostly found benefit in fibromyalgia pain and fatigue [65]. In a meta-analysis of randomized trials of duloxetine, the number needed to treat for significant pain reduction was eight [68], with similar response rates seen for milnacipran [69]. A large meta-analysis found SNRIs in general have evidence for improvement in pain of 30% or more when used in fibromyalgia, modest benefit in patient global impression of change, insubstantial benefit in fatigue, depression, and cognitive disturbance, and no significant benefit with duloxetine or milnacipran use for sleep disturbance [70]. Many patients using duloxetine or milnacipran find tolerance difficult at higher doses, with common side effects including headache, palpitations, nausea, and flushing [71]. Given these agents have antidepressant effect at doses comparable to fibromyalgia use, they may be considered appropriate where there are clinical features of both disorders.

### *Selective Serotonin Reuptake Inhibitors*

Modulation of serotonin alone is of less benefit than dual modulation of noradrenaline and serotonin together in the treatment of fibromyalgia. Selective serotonin reuptake inhibitor (SSRI) medications, however, are frequently prescribed for the treatment of fibromyalgia symptoms. Several studies have evaluated the use of SSRIs in fibromyalgia with inconsistent results [72–75]. A systematic review of the literature found although overall study quality was low, there was some benefit above placebo for improvement in depression in fibromyalgia patients. The authors reported, however, that there were no unbiased high-quality data to support the use of SSRIs in fibromyalgia pain, sleep disturbance, or fatigue management [76].

## Membrane Stabilizers

Pregabalin and gabapentin are alpha$_2$delta ligands and bind to voltage-dependent calcium channels, reducing calcium influx into sensitized spinal cord neurons and reducing the release of neuroactive molecules, including glutamate, substance P, and noradrenaline, into the synapse [77]. Pregabalin can reduce elevated levels of insular glutamate, leading to an associated decreased level of perceived pain [8, 78]. Originally developed for use as anticonvulsants, membrane stabilizers are a significant part of the chronic pain medication armamentarium, and pregabalin has been approved for use in fibromyalgia in Canada and the USA. An in-depth literature review of the use of pregabalin in fibromyalgia found overall clinically relevant improvements in pain, sleep quality, and patient status [79]. Gabapentin has less data to support its use in fibromyalgia. A Cochrane review concluded that at the time, there was insufficient evidence to recommend gabapentin for routine use in fibromyalgia treatment [80]. In a meta-analysis of randomized controlled trials in

fibromyalgia patients, the use of pregabalin or gabapentin resulted in reduced pain, improved sleep, and better quality of life [81]. Many patients are unable to tolerate the highest recommended doses of pregabalin or gabapentin unfortunately, and this can limit their use. The most frequently experienced side effects with these medications are dizziness, somnolence, fatigue, sedation, and ataxia. Peripheral edema and weight gain can also be problematic [82]. Mirogabalin is another agent in this class and is approved for use in Japan for peripheral neuropathy; however, it failed to meet primary endpoints in fibromyalgia phase 3 trials [83], and its development has not been progressed in the USA or Europe.

## NMDA Receptor Inhibitors

The N-methyl-D-aspartate receptor (NMDAR) is involved in spinal cord and brain sensory pathway neural transmission via interaction with the neurotransmitter glutamate. There is elevated glutamate in the central nervous system and cerebrospinal fluid of fibromyalgia patients [8, 10], and its binding to NMDARs results in their activation and increased sensitivity of brain and spinal cord sensory processing pathways, particularly those relating to pain [22].

Intravenous low-dose ketamine, a noncompetitive NMDAR antagonist, has been evaluated in several small trials in fibromyalgia, with approximately half of patients experiencing a reduction in pain intensity of more than 50% [22]. Duration of follow-up was brief however, and there is no long-term data available. Current use of intravenous ketamine for fibromyalgia may involve higher doses over longer timeframes; however, dose escalation is often limited by side effects including agitation and nausea [22]. Memantine, another noncompetitive NMDAR, was evaluated in a randomized trial of 63 fibromyalgia patients and was found to be more successful than placebo at reducing pain intensity by 50%, with a number needed to treat of six [84]. A recent investigation using magnetic resonance spectroscopy explored metabolite changes in the brain of 10 fibromyalgia patients using memantine for 3 months. Elevated metabolite concentrations were found in regions linked to pain processing including the right anterior and posterior insula, both hippocampi and the posterior cingulate cortex, and at 3 months, there were significant improvements in cognitive function, depression, and severity of illness, but no significant improvement in pain threshold or perceived pain [85].

NYX-2925 is a novel NMDAR modulator which enhances synaptic plasticity, and rather than pure receptor agonism or antagonism, it possibly normalizes NMDAR function, enhancing communication between neural cells [86]. It has been studied in animal models of neuropathic pain [87]. In a phase 1 study of healthy volunteers, NYX-2925 was well tolerated and safe without evidence of dissociative side effects or ECG changes at any dose [86].

Further studies of NMDAR inhibitors in fibromyalgia are required before recommendations can be made.

## Cannabinoids

Cannabinoids are the main active chemical components of the cannabis plant (*Cannabis sativa* L.) and act mainly via the cannabinoid type 1 (CB1) receptors mostly in the CNS, and cannabinoid type 2 (CB2) receptors found mostly on immune cells, both part of the endocannabinoid system [88]. The most well studied are $\Delta^9$-tetrahydrocannabinol (THC), a partial CB1 receptor agonist, which produces a variety of effects including altered cognition and motor function, analgesia, and psychotropic effects, and cannabidiol (CBD), a CB2 receptor antagonist, which is nonintoxicating but affects mood and cognition and also has some agonism of 5HT and vanilloid type 1 receptors [89]. There are varying amounts of each of these in differing herbal cannabis specimens, and so efforts to standardize specific doses have led to the investigation of pharmaceutical-grade cannabis or synthetic cannabinoids. The interplay between cannabinoids and the endocannabinoid system in chronic pain is complex [90]. A double-blind placebo-controlled cross-over trial investigated a single inhalation of four pharmaceutical cannabis varieties with different known THC/CBD content in fibromyalgia patients [89]. After 3 h, none of the treatments had an effect greater than placebo on spontaneous pain scores. Pressure pain threshold increased significantly with varieties of cannabis with high THC content, while high CBD content showed no analgesic activity. There seemed to be synergistic pharmacokinetic but antagonistic pharmacodynamic interactions between THC and CBD with inhaled CBD increasing THC plasma concentrations but reducing THC-induced analgesia [89].

Information regarding the effect and safety of cannabinoid use in fibromyalgia patients is limited by a lack of high-quality trials, with studies displaying variable methodology and often low numbers. In a 6-month observational study of 367 fibromyalgia patients prescribed medical cannabis, reported pain intensity was significantly improved in the majority, with most commonly reported side effects being mild and including dizziness (7.9%), dry mouth (6.7%), hyperactivity (5.5%), and nausea and vomiting (5.4%) [91]. THC use for 7 months was found in retrospective interviews to reduce pain and improve quality of life in 172 fibromyalgia patients; however, there was 25% withdrawal from therapy for reasons including self-assessed lack of efficacy. Adverse effects in 10% included tiredness, sedation, and dizziness [92]. An investigation of the safety of herbal cannabis for chronic pain found that the use of a standard preparation (12.5% tetrahydrocannabinol) over 12 months was associated with an increase in mild-moderate side effects, but no higher rate of more serious adverse events when compared to chronic pain patients not using cannabis [93].

Nabilone, a synthetic analogue of THC, has been investigated in two brief small studies of fibromyalgia patients finding some benefit in sleep, pain, anxiety, and quality of life [94, 95].

A systematic review of available medium to low-quality studies examined the evidence for the use of cannabinoids in chronic non-cancer pain. It found a pooled

analysis Number Needed To Benefit of 24 for 30% improvement in pain, Numbers Needed To Harm for any adverse event of six, and high levels of dropout for adverse effects [96].

Certain strategies aimed at improving tolerability are being considered. These include avoiding the unwanted central effects of cannabinoids by restricting CB1/CB2 receptor agonists to the periphery outside the blood–brain barrier [97] or the possibility that the positive allosteric modulation of the CB1 receptor may allow for analgesia with reduced potential for tolerance and dependence [98].

The use of cannabis preparations is widespread among the fibromyalgia community. There is significant public sentiment and political appetite to include these agents in formal chronic pain management strategies despite lack of robust evidence and concern regarding abuse potential [99]. In Canada, medical cannabis is prescribed for chronic pain, and one study in rheumatology patients found that 40% of patients with prescribed medical cannabis reported concurrent recreational use [100]. An Internet questionnaire sent to 2705 people from fibromyalgia groups in Israel resulted in 383 respondents [101]. 84% of these reported consuming cannabis with 44% licensed for medical cannabis, although over half of those using cannabis with a medical license bought further cannabis on the black market beyond the medical allowance. 74% of respondents reported driving "as usual" with cannabis use.

Clinicians are likely, therefore, to be managing patients who are using cannabinoids for their fibromyalgia symptoms. On a practical level, the use of oral preparations with known THC:CBD ratios and potency is preferred. Cannabinoid use may also result in reduction of opioid consumption and dependence [92, 102].

## Melatonin

Melatonin has been investigated for use in fibromyalgia after analgesic effect, thought to be mediated by opioid and by gamma-aminobutyric acid ([GABA]ergic) systems [103], was noted in studies of chronic temporomandibular disorder and pelvic pain sufferers [104, 105]. A prospective randomized controlled trial of 63 fibromyalgia patients divided into three groups, taking amitriptyline and placebo, melatonin and placebo, or both amitriptyline and melatonin, found improved FIQ scores and some evidence of improving the descending inhibitory pain modulation system in those taking 10 mg of melatonin/day for 6 weeks [106]. Administration of 9, 12, or 15 mg/day doses of melatonin in a 10-day longitudinal placebo-controlled study of 36 patients appeared to decrease the severity of some fibromyalgia-related symptoms, such as low mood, anxiety levels, pain, and impaired quality of life [107]. Further small, brief studies have investigated the use of various doses of melatonin in the management of fibromyalgia symptoms [108, 109]. Beneficial effects were found in self-reported symptoms; however, larger studies with rigorous methodology are needed to clarify any significant benefit of melatonin use in fibromyalgia patients.

## Low-Dose Naltrexone

Naltrexone is a reversible competitive μ- and κ-opioid receptor antagonist used in opioid and alcohol use disorders in doses between 50 and 150 mg. When used in low doses between 1 and 5 mg, it follows alternate pharmacodynamic pathways and acts as a glial cell modulator with inhibition of microglial activation in the central nervous system and neuroinflammation reduction [110]. It blocks Toll-like receptor 4, reducing downstream pro-inflammatory cytokine release and inhibiting T and B cell proliferation and inflammatory response. Use in low doses also results in transient and intermittent opioid receptor blockade resulting in upregulation of opioid signaling, increased endogenous opioid production, and analgesic effects [110, 111]. There is evidence to support its safety and tolerability when used in fibromyalgia patients, and a few small studies report efficacy in reducing self-reported pain and quality of life compared to placebo although no data from randomized controlled are published. A pilot study of naltrexone 4.5 mg daily in 10 patients and a randomized placebo-controlled cross-over trial in 31 subjects both found improvements in fibromyalgia self-report symptoms and pain with naltrexone use [112, 113]. A further prospective open-label community-based study of 25 fibromyalgia patients taking 1.5–4.5 mg naltrexone daily reported improvements in the Revised Fibromyalgia Impact Questionnaire (FIQR) scores [114]. A small cross-over trial of eight fibromyalgia patients revealed that naltrexone use over 8 weeks led to a reduction in plasma concentrations of inflammatory cytokines and pain [115]. Due to opioid receptor antagonism, care must be taken if prescribing naltrexone in patients using opioids as it can result in significant adverse effects in this situation [116].

## Intravenous Immunoglobulin

In the subset of fibromyalgia patients with evidence of small fiber neuropathy (SFN) [24, 117], there has been interest in trialing immunoglobulin therapy. In a small trial of fibromyalgia patients with electrodiagnostic evidence of small fiber neuropathy, intravenous immunoglobulin (IVIG) administration was associated with significant improvement in pain, tenderness, and proximal muscle strength [118]. In a retrospective pilot study of seven patients with fibromyalgia and SFN, 6 months of IVIG treatment resulted in reports of less fibromyalgia symptoms and improvement of skin biopsy nerve fiber density [119]. An uncontrolled prospective, open-label trial of IVIG in 130 chronic pain patients (48 with fibromyalgia) found 47.7% of subjects reported >25% pain improvement. It was unknown if these participants had SFN changes [120]. Further investigation is needed to support the use of this treatment in fibromyalgia patients.

## Comparisons

Direct comparisons between agents are few in the literature. An open-label study examined the effect of duloxetine versus pregabalin in fibromyalgia in modest doses, with an advantage found for duloxetine in reported pain [121]. A Bayesian network meta-analysis of randomized controlled trials comparing efficacy and tolerability of duloxetine, pregabalin, and milnacipran at recommended doses agreed that they were all more efficacious than placebo but that there was no significant difference between them [122]. In daily practice, however, it is often the patient's clinical features guiding initial agent choice and intolerances or lack of efficacy prompting change.

## Clinical Strategies

The efficacy of most medications in fibromyalgia is traditionally summarized by the 30/50 rule: about 30% of patients achieve 50% improvement in pain and about 50% achieve at least 30% improvement. Patient satisfaction is generally low with pharmacological therapies for fibromyalgia [123]. Use of typical agents and dose escalation is often limited by side effects, especially nausea, dizziness, drowsiness, or cognitive dulling. Patients may need to trial multiple drugs before finding one that is helpful and tolerable. Beginning with an agent that targets underlying fibromyalgia pathophysiology and tailored to the clinical symptom profile is important. Characteristics such as fatigue levels, sleep disturbance, mood, and neuropathic-type features are important to consider, together with pain, when choosing an initial medication (Table 4.1). An adequate therapeutic trial with gradual dose incrementation is recommended, with expected benefits at any one dose usually evident in 1–2

**Table 4.1** A pragmatic approach to targeting symptoms with common fibromyalgia medications

| Medication class | Symptom target |
|---|---|
| *Tricyclic antidepressants* | |
| Amitriptyline | Sleep, pain |
| *Serotonin-noradrenaline reuptake inhibitors* | |
| Duloxetine | Pain, sleep, mood |
| Milnacipran | Pain, fatigue |
| *Alpha$_2$delta ligands* | |
| Pregabalin | Pain, sleep, other neuropathic features |
| *Glial cell modulators* | |
| Low-dose naltrexone | Pain |
| *Atypical opioids* | |
| Tramadol and tapentadol | Mixed pain states, e.g., osteoarthritis and fibromyalgia |

weeks. Adding a second medication may be appropriate if there is inadequate response, and combination therapy is useful in some patients, but there is limited guiding evidence [124]. In practice, combining agents in some patients allows therapeutic effect at lower doses of each agent which may be more tolerable and sustainable. Pregabalin, in most cases, may be safely combined with SNRIs, TCAs, and most analgesics. Pregabalin–duloxetine combination resulted in improved scores for moderate global pain relief, self-reported illness impact, and health-related quality of life compared to monotherapy or placebo [125]. A retrospective cohort study using a healthcare claims database found better medication adherence, suggesting clinical benefit in fibromyalgia patients combining duloxetine, milnacipran, or venlafaxine with pregabalin compared to monotherapy [126]. There are potential serotonergic adverse effects when combining serotonin modulators such as duloxetine, tramadol, or TCAs, so these are best avoided, although the practice of adding a low-dose TCA to SNRIs is not uncommon and usually well tolerated.

## Conclusion

There are many different medications used in the management of fibromyalgia. Those with most data for efficacy are target-specific pathophysiological pathways in fibromyalgia. Despite this, often patients are being treated with agents for which there is little or no published research to support their use in fibromyalgia and prescription is based on extrapolation from other clinical situations. Many patients are also self-medicating. This speaks to the lack of agents with high efficacy in this illness, and the frustration of both patients and their physicians. The currently available pharmacotherapeutic approaches for fibromyalgia management have a mostly modest influence on symptoms when used alone. Medicines need to be combined with psychological and exercise therapies for maximum benefit, and this multidisciplinary approach to management endures as the most important basic principle in the management of fibromyalgia.

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# Chapter 5
# Nonpharmacologial Treatment for Fibromyalgia


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Fibromyalgia (FM) is a complex entity of chronic pain, sleep disorders, fatigue, functional symptoms, cognitive dysfunction, often associated with anxiety and depression. Moreover, even the pain itself, the core symptom of FM, is a construct of physical and psychological components, and thus, the ultimate functional consequences of FM pain, the resulting disability, may in many cases exceed the direct magnitude of pain.

In response to the multilayer nature of FM, a multimodal treatment is needed in order to address the various aspects of the syndrome, combining pharmacological, psychological, and complementary and alternative medicines (CAM), which are playing a central role in treating FM and similar central sensitivity syndromes and appears to be among the most attractive options for the patients, with higher acceptability and lower side effects [1]. In terms of cost-effectiveness, multiple studies have demonstrated that the use of CAM leads to significant economic benefits when compared to pharmacological treatment alone [2].

In this chapter, we will review the current evidence for nonpharmacological strategies for management of fibromyalgia.

## Education

Education is the first mandatory step to ensure cooperation of the patient and treatment adherence and include diagnosis confirmation, explanation about the nature of the disorder (concept of central pain), prognosis (not a degenerative/life-threatening disease), and the rationale for treatment approach (role of stress and mood disorder, role of sleep disorders, role of exercise). Educating and reassuring results in less

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diagnostic testing and imaging, fewer specialty referrals, fewer primary care visits, and fewer drug prescriptions.

## Exercise

Exercise is the cornerstone of any treatment program even if it is a real challenge for fibromyalgia patients, with difficulties to start and maintain because of worsening pain and fatigue at the beginning. Education is granted for incremental cardiovascular fitness program with gradual increases in exercise to an optimal training of 30 min at least three times per week. Low-impact aerobics activities such as fast walking, biking, swimming, or water aerobics are the most recommended. In this regard, some studies show superiority of pool-based exercise in terms of pain relief in adults with fibromyalgia compared to land-based exercise [3].

Exercise program must be individualized upon patient preferences and presence of any other cardiovascular, pulmonary, or musculoskeletal comorbidities.

Aerobic exercise has been shown to result in improved health-related quality of life (HRQoL), improved physical function, decreased pain, fatigue, and stiffness, and gains in submaximal cardiorespiratory function. Effects on pain and physical function are effective in the long term [4].

During the last few years, there is accumulation of data on the physiologic and therapeutic effects of exercise: it acts on the autonomic system, increasing vagal tone, and has effects on various neurotransmitters, endocannabinoid, and opioid system, all of them leading to a bottom line of anti-nociception [5].

## Hydrotherapy

Hydrotherapy is a physical treatment that uses the therapeutic properties of water. While hydrotherapy uses normal tap water, balneotherapy uses thermal mineral water from natural springs, natural gases, and peloids (mud), and thalassotherapy uses seawater and seaside climate. Hydrotherapy leads to a moderate improvement in pain and HRQoL, and better effects were obtained with balneotherapy. The mechanisms of action of these therapies are not completely understood and are probably a result of a combination of mechanical, thermal, and chemical effects. Nonspecific effects include mechanisms of simple bathing in hot tap water, for all kinds of hydrotherapy, and the special therapeutic atmosphere of spa scenery for balneotherapy and thalassotherapy. Specific hydromineral and crenotherapeutic mechanisms, which depend on the chemical and physical properties of the water used, also play a role. Pain relief may be due to the temperature and hydrostatic pressure of water on the skin and muscle relaxation [6].

## Mind-Body Approaches

Mind-body approaches are practices that generate the state of mental and physical relaxation and some of them incorporate movements that could be considered physical exercise. These practices are increasingly being used as complementary approaches to health and healing.

Meditative movement therapies include tai chi, qigong, and yoga.

The principles of these therapies include focus of the mind in meditative practice (clearing the mind to the point of quiet emptiness), some form of slow, relaxed, and flowing body movement (including dynamic movement and quiescent static postures), and focus on breathing bringing additional oxygenation and energy to the body, leading to a deep state of relaxation.

Tai chi is a martial art extremely popular in China, practiced for health and wellness purposes. A growing body of research supports tai chi as an important adjunct to standard medical treatment for fibromyalgia. On meta-analysis, supervised tai chi instruction and practice sessions 2–3 times per week for 60–90 min during 12–28 weeks led to benefits (compared with control groups or before/after comparisons) in all core symptom domains, including pain, sleep, physical function, and mental function [7].

Practice of qigong for 30–45 min daily led to improvement in all domains relevant to FM (pain, sleep, physical, and mental function) that manifest after 6–8 weeks of practice, and benefits are sustained up to 6 months [8].

Yoga practice showed significant effects on pain, fatigue, depression, and HRQoL, but with short-term effects only.

Neuroimaging study performed on fibromyalgia patients, before and after a 12-week tai chi program, showed an increased connectivity between the cognitive control network in the DLPFC and a key region in the descending pain modulation system after completing the program, indicating that tai chi practice amplifies self-regulation and adaptation to chronic pain. These results were significantly associated with improved clinical outcomes [9].

Movement therapy may also influence pain processing through modulation of the autonomic system. Studies showed significant effects of a tai chi program on various parameters of the sympathetic/parasympathetic system, including significant decreases of the sympatho-vagal balance and sympathetic tone and increased parasympathetic tone. These changes were associated with decrease in pain and fatigue and increase in strength and flexibility [10].

## Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) enables patients to better understand, recognize, and modify counterproductive psychological and behavioral patterns, using thought exercises or real experiences to facilitate symptom reduction, improve

functioning, and lead to attenuation of psychological factors such as anxiety, depression, and pain catastrophizing. It has also been found to be cost-effective, with short- and long-term benefit in all functional somatic syndromes, including fibromyalgia.

A meta-analysis of more than 30 studies showed that CBT was superior to controls (waiting list, attention control, treatment as usual, other active non-pharmacological therapies) in pain relief of 50% or greater, improving health-related quality of life by 20% or greater, and reducing negative mood and disability at the end of treatment and at long-term follow-up [11].

Several neuroimaging studies led to better understanding of how cognitive therapy may modulate pain and pain perception. Functional MRI studies showed increased activation of prefrontal cortex, orbitofrontal cortex, somatosensory cortices, and limbic system following cognitive strategies, indicating that cognitive strategies can alter functioning of brain regions in an extensive network including non-nociceptive regions. In fact, CBT can reduce the affective experience of pain, leading to improvements in outcomes such as mental health, pain self-management, perceived control over pain, self-rated symptoms, self-efficacy for pain management, as well as reduction of anticipatory anxiety, catastrophism, pain intensity, and unpleasantness ratings [12].

## Acupuncture

This physical therapy of traditional Chinese medicine has been used to treat chronic pain for over 2 millennia in China and is also used by patients for alleviating the symptoms associated with fibromyalgia. Evidence base for this treatment includes few randomized trials with high levels of heterogeneity in terms of treatment protocols, control conditions, and populations studied, so that findings should be interpreted with caution. Overall, these studies suggest that acupuncture treatment (4–13 weeks, once or twice a week) may be associated with a significant decrease in pain and improvement of fibromyalgia symptoms compared with a variety of controls. Significant improvement in depression, functional capacity, and quality of life compared with placebo treatment was also reported [13]. One study observed a significant increase in serum serotonin level and decrease in substance P values after eight sessions of acupuncture treatment, indicating that acupuncture may affect pain modulation [14].

## Nutrition

Specific diet for fibromyalgia is a frequently asked question by patients.

Numerous studies have shown that oxidative stress, diets deficient in amino acids, and deficiency in certain minerals (selenium, magnesium, zinc) and vitamins

(vitamin B6, vitamin B12, vitamin D, folic acid) may influence muscle pain, and that supplementation with those micronutrients and antioxidants (vitamin C, vitamin E, polyphenols) may improve these symptoms. Glutamate and aspartame are non-essential amino acids that act as excitatory neurotransmitters on the NDMA receptor and play an active role in chronic pain and central sensitization. Glutamate is found as bound forms in full protein sources like meat, and as free forms in food additives (monosodium glutamate), hydrolyzed proteins, and protein concentrates. Aspartame is found in diet soda and products with artificial sweetener.

Diet including a good balance in micronutrients, vitamins, antioxidants, and avoiding potentially neuro-excitatory nutriments may improve inflammation, dysmetabolism, and obesity, and may ultimately improve fibromyalgia symptoms [15].

## Weight Loss

A strong correlation exists between obesity and fibromyalgia. Obesity and FM share similar clinical features such as higher pain sensitivity and poorer sleep quality since both cause alterations in endocrine activity and opioid system that may influence the level of pain perception. Increased body mass index (BMI) is associated with higher IL 6 levels which play an important role in inflammatory pathways and pain processing. Higher BMI is also a strong and independent risk factor for future development of FM. Weight control is a critical factor in the management of FMS symptomatology.

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# Chapter 6
# Physical Activity and Exercise Training for Adults with Fibromyalgia


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## Introduction

Fibromyalgia is an illness for which there are no particularly effective forms of treatment. The disease has been described as disruptive of an individual's sense of normality, affecting all aspects of life [1, 2]. Individuals often report unpredictable and diffuse pain, and exhaustion as their main symptoms; the chronic pain makes living with fibromyalgia and negotiating their bodies challenging. Given the complexity of the disease and the unique presentation of symptoms for each individual, health professionals need to approach management of fibromyalgia in a personalized manner.

The importance of physical activity and exercise in maintaining and enhancing physical function and other health benefits in adults are well documented [3–6]. Adults who are more involved in physical activities (i.e., walking, recreational

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sports, or household chores) and/or exercise (i.e., structured and planned activity) have lower rates of mortality and lower incidence of chronic diseases (e.g., high blood pressure, stroke, type 2 diabetes) [3–6]. Adults engaged in physical activity are also more likely to achieve weight maintenance, and have a healthier body mass and composition [6].

In the past three decades, there has been a steady increase in the number of studies investigating the benefits of physical activity and exercise for adults with fibromyalgia, and the evidence supporting exercise training for this population is mounting [7–21]. Unfortunately, the overall certainty of the evidence is often hindered by the small number of participants within research studies and design flaws. In addition, translation into practice and uptake by individuals with fibromyalgia may be less than ideal [22]. Factors such as personal preferences, values, beliefs, and past experiences of both adults with fibromyalgia and healthcare professionals influence decisions about physical activity and exercise [22, 23]. An updated foundation for the best practice guidelines considering current evidence for physical activity and exercise and the expectations, environment, ethics, and experiences of both the client and healthcare professional will aid in achieving personalized physical activity and exercise treatment plans for individuals with fibromyalgia.

This chapter summarizes current evidence for physical activity and exercise in adults with fibromyalgia. First, quantitative evidence on the benefits and effects of exercise training and physical activity is reviewed. This is followed by a review of the qualitative evidence on the physical activity and exercise preferences and experiences of both the individuals with fibromyalgia and healthcare professionals. The chapter ends with a discussion of how to integrate these findings through the lens of the E-model [24] as a framework for best practice decision making.

## Exercise Training

Exercise training is defined as planned body movements performed for the purpose of having positive benefits on physical fitness [25]. It has been promoted as an essential component in the management of fibromyalgia for general health benefits as well as symptom management and reduction of disability [26]. The frequency, intensity, time, and type (FITT) principles are a structured approach to exercise prescription described by the American College of Sports Medicine and helps participants know how long and how hard they should exercise [27]. Below, the evidence for the four most common forms of exercise training and benefits to adults with fibromyalgia are summarized.

### *Aerobic Exercise Training*

***What is aerobic exercise?*** It is a form of exercise also known as cardiorespiratory or endurance exercise, which includes planned movements that cause breathing and heart rates to increase [28, 29]. This type of exercise involves moving large muscles

in a rhythmic manner for minutes or hours [29]. Examples of moderate intensity activities include brisk walking, raking the yard, or playing volleyball, while jogging or running and strenuous fitness classes and are classified as vigorous intensity activities [29].

***What are the health benefits of aerobic exercise?*** These benefits are well established for the general population and include improving circulation, strengthening the heart, lowering blood pressure, and enhancing control of blood sugar and body weight [6]. Aerobic exercise can lower risks of death, heart disease and stroke, diabetes, depression, dementia, falls, and cancers of the bladder, breast, colon, endometrium, esophagus, kidney, lung, and stomach [29].

***Evidence for individuals with fibromyalgia*** Research shows that when compared to non-exercisers, people with fibromyalgia doing aerobic exercise increased their health-related quality of life, and their physical functioning, and decreased pain intensity, fatigue, and stiffness symptoms [7, 13, 30]. The evidence shows that while maximal cardiorespiratory fitness may not change, submaximal cardiorespiratory function can be improved through aerobic exercise [7]. These improvements are experienced across aerobic exercise programs typically conducted three times per week, ranging from 6 to 24 weeks in duration. Activities studied among individuals with fibromyalgia to date primarily include walking, with some studies of stationary cycling, low-impact aerobics to music, aquasize, and games [7, 13, 30]. Table 6.1 presents recommendations for resistance exercise for individuals with fibromyalgia.

## *Resistance Exercise Training*

***What is resistance exercise?*** Resistance exercise, or muscle-strengthening exercise, including weight lifting, requires the body's muscles to hold or work against an applied force or weight [29]. Resistance exercises can involve lifting heavy objects, such as weights, or may involve exercise machines, elastic bands, or body weight for resistance [10, 29]. Resistance exercises increase skeletal muscle strength, power, endurance, and mass [29]. Resistance exercise training is characterized by the intensity, how much weight or force is used relative to how much the person can lift, the frequency, how often a person does resistance training exercise,

**Table 6.1** FITT principles for aerobic exercise for individuals with fibromyalgia

| | |
|---|---|
| Frequency | Begin with 1–2 days·week$^{-1}$ and gradually progress to 2–3 days·week$^{-1}$. |
| Intensity | Begin with light (30–39% $VO_2R$ or HRR). Gradually progress to moderate intensity (40–59% $VO_2R$ or HRR). |
| Time | Begin with 10 min·day$^{-1}$ and progress to a total of 30–60 min·day$^{-1}$ as soon as tolerated. |
| Type | Low-impact (e.g., water exercise, walking, dance and other aerobic movement to music, swimming, cycling). |

*$VO_2R$* oxygen uptake reserve, *HRR* heart rate reserve

and the sets, groups of repetitions performed without resting, and repetitions, how many times a person repeats the resistance activity in a set [29]. The effects of resistance training are limited to the working muscles of the exercise, meaning it is important to work all the major muscle groups in the body over successive exercises [29]. This would include muscle exercises to work the legs, hips, back, abdomen, chest, shoulders, and arms [29].

***What are the health benefits of resistance exercise?*** Resistance exercise can reduce risks of heart disease and stroke, and improve blood sugar control [31]. This type of exercise can be particularly beneficial for adults, to combat losses in muscle mass and strength with age, which can lead to reductions in independence [31].

***Evidence for individuals with fibromyalgia*** A Cochrane systematic review [10] and two recent trials [12, 15] have evaluated the benefits of resistance exercise for adults with fibromyalgia. Adults with fibromyalgia improve the rating of their well-being with participation in resistance exercise [10]. Improved physical function and reduced experiences of pain and tenderness among adults with fibromyalgia were also identified with resistance exercise training [10]. Muscle strength can be improved through resistance exercise training for adults with fibromyalgia [10, 15]. Table 6.2 presents recommendations for resistance exercise for individuals with fibromyalgia.

## *Flexibility Exercise Training*

***What is flexibility exercise?*** This is a type of exercise that focuses on improving or maintaining the range of motion in muscles and joint structures by holding or stretching the body in specific positions [28]. With flexibility exercise training, a muscle or muscle group is stretched beyond what would customarily be used in normal activity. Static stretching, holding at the point of tightness or slight discomfort, is the most commonly used stretching mode [32], and this can be actively or passively applied. Active static stretching involves holding the stretched position using the strength of the agonist muscle. In passive static stretching, a position is

**Table 6.2** FITT recommendations for resistance exercise for individuals with fibromyalgia

| | |
|---|---|
| Frequency | 2–3 days·week$^{-1}$ with a minimum of 48 h between sessions |
| Intensity | 40–80% 1-RM. Gradually increase to 60–80% concentric 1-RM for strength. For muscle endurance, use ≤50% 1-RM |
| Time | Strength: Gradually progress from 4–5 to 8–12 repetitions, increasing from 1 to 2–4 sets per muscle group with at least 2–3 min between sets. Endurance: 15–25 repetitions, increasing from 1 to 2 sets with a shorter rest interval |
| Type | Elastic bands, dumbbells, cuff/ankle weights, weight machines, or body weight exercises; for resistance in water: changing water resistance, floatation devices |

*1-RM* one repetition maximum, *$VO_2R$* oxygen uptake reserve, *HRR* heart rate reserve

assumed while holding a limb or other part of the body in a certain position, and this can be achieved with or without the assistance of another person or a device [33]. Flexibility exercise is often incorporated into programs for adults with fibromyalgia. It is often a part of a larger program that may include aerobic and/or resistance training and in many instances is included in the warm-up or cool-down of a program.

***What are the health benefits of flexibility exercise?*** Our ability to perform activities of daily living is influenced by the amount of joint range of motion we have available [34]; thus, flexibility exercise can improve physical function [22], postural stability, and balance [35].

***Evidence for individuals with fibromyalgia*** In a recent systematic review including 12 randomized control trials, the benefits of flexibility exercise training were compared to controls and other types of exercise such as land-based aerobic exercise, resistance training, or other interventions such as tai chi, pilates, or medications [36]. Within this review, findings from the comparison of flexibility and land-based aerobic exercise were prioritized. There was evidence of no effect of flexibility exercises on health-related quality of life, pain intensity, fatigue, stiffness, and physical function. Although authors found flexibility exercise to have a positive effect on stiffness, this was based on only one small study. The flexibility interventions of the studies included in the review by Kim et al. [36] did not meet all recommended FITT principles for flexibility exercise training for healthy individuals as outlined above [28]. Consequently, the benefits of flexibility exercise training may be underestimated. Table 6.3 presents the recommendations for flexibility exercise for individuals with fibromyalgia.

## *Mixed Exercise Training*

***What is mixed exercise training?*** Mixed interventions include multiple forms for exercises such as the ones discussed above (e.g., aerobic, resistance, and flexibility) as well as non-exercise components such as education. In clinical practice, recommendations for mixed exercise programs may be most common as seen by the larger number of mixed intervention studies.

**Table 6.3** FITT recommendations for flexibility exercise for individuals with fibromyalgia

| | |
|---|---|
| Frequency | Begin with 1–3 days·week$^{-1}$ |
| Intensity | Stretch within limits of pain to the point of tightness or slight discomfort |
| Time | Initially hold the stretch for 10–30 s. Progress to holding each stretch for up to 60 s |
| Type | Static stretches (passive and/or active), for all major muscle tendon groups. Dynamic stretches may also be used |

***What are the health benefits of mixed exercise training?*** As mixed exercise training includes a combination of aerobic, resistance, and/or flexibility exercise, there is potential to train the cardiorespiratory, vascular, and neuromusculoskeletal systems. Thus, mixed exercise training methods may offer unique advantages beyond those which include only one type of exercise.

***Evidence for individuals with fibromyalgia?*** A recent systematic review of mixed interventions included 29 randomized control trials [8]; mixed intervention was defined as regular sessions of two or more types of exercise including aerobic (walking or cycling), strengthening (lifting weights or pulling against resistance bands), or flexibility (stretching) [8]. When compared to control, individuals in the mixed exercise groups had improvements in health-related quality of life, stiffness, and physical function and decreases in pain intensity and fatigue.

Recommendations—Depending on the combination of exercises, the recommendations for each of the components (i.e., aerobic, resistance, or flexibility) would be consistent with those presented in Tables 6.1, 6.2, and 6.3.

## Physical Activity

Previously, individuals with fibromyalgia were told to rest [37], but the evidence suggests individuals should keep as active as their pain (or other symptoms) allows them. Physical activity, when done within appropriate frequency, duration, and intensity, is preferable to resting seated or reclining activities. Any physical activity is most successful when tailored, progressed slowly, and accounts for individual's physical, psychosocial, and other resources.

***What is physical activity?*** Physical activity is defined by any bodily movement produced by muscles [25]. The World Health Organization recommends physical activity including leisure time physical activity (e.g., walking the dog, dancing, gardening, hikings), transportation (e.g., walking or cycling), occupational (i.e., work), household chores, games, sports, or planned exercise, in the context of daily, family, and community activities [38].

***What are the Health Benefits of Physical Activity?*** There is strong evidence that demonstrates individuals who are more active gain many benefits including lower rates of all-cause mortality, coronary heart disease, high blood pressure, stroke, type 2 diabetes, metabolic syndrome, colon and breast cancer, and depression, are more likely to achieve weight maintenance, have healthier body mass, and increase their cardiorespiratory and muscular fitness [38]. Several international bodies have put forward physical activity guidelines or recommendations for healthy adults [29, 39].

***Evidence for individuals with fibromyalgia*** Encouraging any form of physical activity is important; health benefits can be achieved even when individuals are not

achieving the current exercise recommendations [40]. However, fear of symptom exacerbation is a known obstacle for physical activity participation that both perpetuates pain and leads to disability [41, 42].

While available literature identifying health benefits of physical activity for individuals with fibromyalgia is sparse, increasing physical activity may improve (e.g., reduce pain, fatigue) symptoms of fibromyalgia and overall health.

Recommendation—Increasing physical activity throughout the day can be achieved through activities of daily life such as housekeeping and yardwork, active modes of transportation (e.g., cycling or walking), and leisure activities such as games [43]. Small changes in daily activities can result in overall increases in physical activity, even in the absence of planned exercise sessions [43]. Increasing the steps a person takes throughout the day is one way of increasing daily physical activity [44], which has become easily manageable and achievable with recent wearable technology [45].

## Challenges, Barriers, and Facilitators

Qualitative evidence indicates that individuals with fibromyalgia experience a myriad of life changes after diagnosis. They deal with many and diverse symptoms, quality of life fluctuations, stigmatization, and often lack of credibility and understanding [46]. They describe living a "new unexpected new life" [47]. Despite the circumstances, these individuals are "not giving up" and work toward making lifestyle modifications to continue being physically active [48]. In this section, general challenges, barriers, and facilitators from the perspectives of individuals with fibromyalgia and health professionals are outlined. This is followed by "strategies" to help adopt physical activity and exercise as put forward by individuals with fibromyalgia.

The literature presents a detailed picture of *the challenges* individuals with fibromyalgia are facing. A major challenge is the minimization or invisibility of the disease in their social and medical interactions; this is often done by people who still believe fibromyalgia is a fake, made up, "in the head," or not a "real" disease [46]. Individuals reported:

- Being disbelieved or having low credibility not only from healthcare professionals but also social circles such as friends and neighbors [49]; they reported some healthcare professionals "have mixed beliefs about fibromyalgia and some do not believe in it" while others reported being labeled and known as "the complainer patient" or "a demanding patient" [50, 51].

Another big challenge is autonomy and independence and the ability to carry out with their normal activities, including physical activity and exercise. Individuals from qualitative studies reported:

- Experiencing random, unpredictable, uncontrollable symptoms like pain, fatigue, poor sleep and depression [46, 51], and feeling at the mercy of these symptoms [51, 52] which affect the broader circumstances of their lives (e.g., work, family commitments, financial stability, intimacy).

*Barriers* to physical activity and exercise were broad and varied, encompassing emotional, social, cognitive, and practical factors. Some of the barriers made individuals fall in a "chronic vicious cycle of inactivity" which they found hard to break [53]. Individuals with fibromyalgia expressed:

- Fearing activity induced exacerbation, "paying for it," or experiencing flare-ups following exercise [47, 53]
- Having limited daily energy or experiencing overexertion [54]
- Lacking motivation or support
- Having to fulfill social expectations (e.g., having to show a "healthy façade") [55]
- Experiencing cognitive difficulties, such as lack of concentration and bad memory [56]
- Limiting their participation in exercise or physical activity due to the characteristics of the available exercise program (e.g., too strenuous) [46, 47] or not being able to do it at their own pace [52–54]

Identified *facilitators* (or motivators) for physical activity typically focused on factors such as:

- Sustaining social integration and finding social support networks (e.g., avoiding isolation).

The evidence identified being part of a group facilitates individuals' sense of commitment, accountability, and purpose [47], and small group settings impact the ability of the individuals to better connect with each other and share their experiences [51]. Important motivation also came from the support of neighbors, acquaintances, and friends, as well as relatives, husbands, partners, and children [52].

- Keeping the body in shape while avoiding weight gain, stiffness, or tenderness,
- Learning how to relax, better rest, taking time for themselves, experiencing physical capacity and facilitating activities of daily living, redefining their sense of balance and well-being [46, 52, 53, 55, 57, 58].

Physical activity was more likely to happen when individuals had access to safe places to exercise, when there were favorable weather conditions (e.g., not too cold, not to hot or windy) and when they found ways to include movement in their everyday routine such as walking, doing household chores, and being active with children.

## *Healthcare Professionals*

Healthcare professionals play an important role providing information and support for healthy lifestyle and management of fibromyalgia [52]. The lack of known effective therapies to treat fibromyalgia makes it challenging for healthcare providers to help patients with this diagnosis. In addition, the literature suggests health professionals take different stances with recognizing fibromyalgia as a diagnosis

[50]; some reported that given the paucity of effective treatments for these individuals, treatment and management of the condition are difficult tasks [47].

Individuals with fibromyalgia felt distrust, judgment, and lack of understanding of their condition [51], and were often left to manage the condition on their own [47, 51]. They were less likely to trust the professionals and less invested in following advice or instructions about management. Individuals felt frustrated to hear providers who "fail to show compassion or empathy, or who prescribed unrealistic diet or exercise regimens" [53]. The sensitivity of discussing physical activity or exercise contributes to the common finding that health professionals were unlikely to discuss it consistently, with many individuals reporting that conversations about physical activity and exercise were contradictory, inconsistent, or absent.

The absence of clear, consistent messages about physical activity or exercise is a huge barrier, adding disappointment to individuals with fibromyalgia who interpreted this inconsistent messaging to mean physical activity and exercise are not important [59].

### *Strategies for Physical Activity and Exercise*

Individuals identified a variety of factors that would help to increase their quality of life and physical activity and exercise. They reported:

- Learning to live and cope with their "new" bodies and their "new normal" [54, 58]; understanding how symptoms intersect with everyday life in order to get the life back on track again [60].
- Avoiding unnecessary stress, utilizing good days, pacing the activities throughout the day, planning activities in advance, distracting themselves from the pain, and ignoring pain sensations. Specifically, distracting from pain seems to be an especially helpful strategy [46].
- Engaging in exercise classes geared to individuals with fibromyalgia, "something light" [59], increasing social connections with peers who understand them [47].
- Participating in exercise programs (traditional as well as alternative) to reduce pain, stiffness, and fatigue [58].
- Avoiding daily activities (e.g., housework or shopping) which involved "standing up for too long" or "worsened pain and stiffness" [59].
- Maintaining social connections as an important form of external motivation for initiating an exercise routine as well as reducing isolation [46, 59].

## E-Model as a Framework for Best Practice Decision-Making

To facilitate best practice decision making around physical activity and exercise recommendations for individuals with fibromyalgia, this last section aims to integrate the evidence presented above through the lens of the E-model framework. The E-Model [24] highlights that evidence, environment, expectations, ethics,

and experiences all shape prescription practices of clinicians. Ethical guidelines for health care and the individual's expectations or treatment goals are important considerations in the clinical decision-making process. The clinician must also determine and weigh the various physical, social, cultural, political, economic, and environmental factors. These factors impact intervention choices and attainability of goals. When considering interventions, the clinician draws on past experiences, recognizing patterns and integrating reflective practice learning, as well as identifying and weighing the best available evidence regarding the intervention. By using the E-model, gaps and discrepancies in the literature can be identified and guidance for future research and knowledge translation can be derived.

***Evidence*** Steadily growing evidence on the effectiveness and safety of resistance, aerobic, flexibility, and mixed exercise interventions provides guidance on FITT principles. However, the overall certainty of the evidence, although improving, is still often hindered by the small number of participants within research studies and study design flaws. The evidence for physical activity is less clear and requires a more rigorous approach. Evidence derived from qualitative studies has also grown at a slower pace in the past few years and is needed to enhance understanding of barriers, facilitators, and experiences from individual and healthcare professional perspectives.

***Environment*** While studies have been conducted in a variety of settings, for example, clinical, home, or indoor vs. outdoor, these settings have not been systematically compared. Water-based and land-based programs have been compared without showing substantive differences [61]. Participants indicated "favorable weather conditions (not too cold, not too hot)" are best suited for physical activity participation. Literature evaluating changes in pain levels of patients with fibromyalgia according to weather conditions is conflicting [62, 63]. Given the current evidence in the area to guide practice, clinicians and individuals need to discuss directions for best practice.

***Expectations and Experiences*** Individuals' accounts reveal compromised physical, mental, and social health, at times overwhelming and affecting their identity [60]. Fibromyalgia evokes uneasiness for healthcare professionals as current diagnostic criteria are not well supported by objective markers, and because of difficulties managing it in clinical practice [64]. Not surprisingly, some individuals with fibromyalgia have experienced distrust and lack of understanding in their relationships with healthcare providers. But information presented in this chapter suggests clinicians can reasonably expect most individuals with fibromyalgia want to maintain some degree of physical activity or fitness [48]. Addressing concerns and insecurities related to supporting individuals with fibromyalgia in maintaining or achieving a physically active lifestyle is an important task for clinicians.

***Ethics*** The negative feelings reported by individuals with fibromyalgia experienced in their interactions with healthcare professionals suggest that greater attention to the therapeutic relationship is needed. Prescription of exercise or recommendation for physical activity takes place within an ethical framework that underlies all clinical practice. The evidence emphasizes the essential role of healthcare providers in counseling individuals with fibromyalgia to achieve healthier lifestyles. Thorne et al. [65] stated, "the most critical dimensions of health care communications for these patients are respect and engagement." Thus, at the clinical level, where prescription "best practices" are implemented, assessment and treatment must be provided in a manner that is genuinely respectful.

In summary, exercise and physical activity are important components of effective management of fibromyalgia. Exercise prescriptions based on best practice guidelines include appropriate intensities, durations, frequencies, and modalities personalized to the patient's abilities and comfort. Exercise options include aerobic, resistance, flexibility and mixed exercise training, and physical activity. Physical activity and exercise preferences, experiences, and beliefs of the individual with fibromyalgia should be considered. Healthcare professionals should consider their biases and beliefs about fibromyalgia and their experiences, beliefs, and preferences regarding physical activity and exercise in prescriptions for individuals with fibromyalgia.

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# Chapter 7
# Neuromodulation and Biofeedback in the Treatment of Fibromyalgia


**Tal Gonen and Howard Amital**

## Introduction

The treatment of fibromyalgia syndrome (FMS) poses many challenges for clinicians. Current therapeutics for this condition are generally directed at symptom alleviation rather than treatment of the initial insult, the nature of which is still under debate. As such, these treatments are often ineffective, and they also carry certain risks and many effects. Another difficulty that is often faced is the variety of symptoms that these patients present with, ranging from depression to fatigue and pain. Most FMS pharmaceutical treatments are known to relieve just a minority of the core symptoms of the FMS [1]. As a result of these challenges and since FMS is currently considered a lifelong illness, non-pharmacological treatments, and especially such that have been used in the treatment of other pain syndromes and psychiatric conditions, have been studied for this indication [2]. The methods discussed in this chapter are all generally thought to be safe and well-tolerated among patients, and of course devoid of toxicity and side effects, making them appealing options for patients and clinicians [3]. Certain neuromodulatory treatments that will be discussed are also thought to exert long-term effects on patients, and thus perhaps offer a solution to patients with low compliance to pharmacological therapy.

Several treatment modalities have been studied in FMS and are thought to confer neuromodulatory effects. These include transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), electroconvulsive therapy (ECT), biofeedback, hyperbaric oxygen therapy (HBOT), and transcutaneous electric neurostimulation (TENS) alongside electric acupuncture (EA). These therapies

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vary in respect of their suggested mechanism of action: while TENS, HBOT, EA, and biofeedback exert their effect on the nervous system via peripheral nervous system stimulation which alters central nervous system (CNS) processing, ECT, TMS, and tDCS are thought to directly affect the CNS and in the case of TMS and tDCS the effect is directed toward specific regions within it.

## Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation

The pathophysiology of FMS is still unknown, but nowadays it is hypothesized that it is a disorder evolving from reduced pain thresholds. The abnormalities in pain perception are thought to involve central sensitization and diffuse noxious inhibitory control (DNIC) dysfunction. Based on this hypothesis, the utilization of neuromodulation may intervene and affect target areas within the CNS. Such target areas include the primary motor cortex (M1) that has an antinociceptive effect when stimulated and the dorsolateral prefrontal cortex (DLPFC) that is thought to exert an antidepressant effect upon stimulation.

At the moment, the European League Against Rheumatism (EULAR) guidelines do not recommend treatment of FMS by neuromodulatory approaches [4]. The evidence-based guidelines on the therapeutic use of repetitive TMS that were updated in 2020 concluded that there is a probable efficacy of high-frequency left M1 stimulation in the context of FMS treatment for the purpose of improving quality of life. The guidelines also suggest that high-frequency left dorsolateral prefrontal cortex stimulation probably has an analgesic effect in FMS [5]. TMS has been suggested as an effective treatment option for neuropathic pain (in a protocol of contralateral high-frequency M1 stimulation) by the same guidelines [5], and tDCS was found to be potentially useful in the treatment of depression and psychosis by a systematic review [6].

TMS is a noninvasive brain stimulation modality in which an electromagnetic field is utilized to stimulate various regions within the brain, modulating neural activity in them. In repetitive TMS, target areas are stimulated for several minutes, with the aim of inducing long-lasting effects. tDCS is thought to exert its effect on the CNS by affecting cortical excitability, in a process that applies weak direct currents (of 1–2 mA) through scalp electrodes [7] (unlike the stronger currents used in ECT, which generate convulsions). A 2012 review found that tDCS and repetitive TMS discontinuation in FMS patients due to adverse events was relatively rare. The authors also reported that side effects caused by both repetitive TMS and tDCS include headache and nausea, while side effects of repetitive TMS alone included scalp pain, and temporary hearing impairment (that can be prevented by ear plugs), as well as two less common side effects—syncope and transient cognitive changes. Other effects of tDCS include a tingling sensation and dizziness [8]. Although tDCS is thought to be associated with less risks than repetitive TMS (which is known to

cause seizures, although this is uncommon [9]), repetitive TMS is thought to exert a powerful localized effect. It should be noted that repetitive TMS is considered a more expensive treatment modality than tDCS, and that tDCS can be done individually at home [8].

A meta-analysis of 16 studies on both TMS and tDCS by Hou and colleagues [10] found that repetitive TMS (regardless of stimulation site) was effective in reducing pain, depression, fatigue, sleeping problems, and improved general health and function in FMS patients. The review found that tDCS was effective in those same domains (apart from depression and fatigue) and was also effective in reducing the number of tender points. Therefore, the authors concluded that both modalities are reasonable add-on therapies for FMS. A 2012 systematic review on tCDS and repetitive TMS for the treatment of FMS found that both methods, when used to stimulate left M1, had shown long-lasting pain reduction, as well as improved scores in the Fibromyalgia Impact Questionnaire (FIQ) in four out of five studies that assessed for it. Less compelling conclusions arise from another systematic review, which included some of the same studies as the latter, as well as others, and found that repetitive TMS had a significant effect on quality of life measures assessed by the FIQ, but was not superior to sham in alleviating depression or pain. The analysis based its results on data obtained at around 30 days after last repetitive TMS stimulation, to assess for long-lasting effects [11]. A more recent 2017 review included seven trials and concluded that there was moderate evidence that repetitive TMS was not superior to sham in reducing pain in FMS patients [12].

As for tDCS, a meta-analysis by Brighina et al. (2019) [13] found that M1 stimulation was effective in reducing FMS pain, and had a positive effect on quality of life measures. Another systematic review, from 2017, found that stimulation of M1 significantly reduced pain and improved fibromyalgia-related function as assessed by the FIQ, compared with sham tDCS stimulation [14]. A 2020 meta-analysis assessed for the analgesic effect of tDCS [15] and concluded it was a safe therapeutic option (with either no adverse events or only mild ones), which had had a small-moderate effect compared with sham in decreasing pain in FMS patients. The authors, however, mention that due to statistical heterogenicity and bias, more research needs to be conducted to reach more precise conclusions.

## Transcutaneous Electrical Nerve Stimulation and Electric Acupuncture

Transcutaneous electrical nerve stimulation (TENS) is a noninvasive intervention in which electric stimulation, as pulsed electric currents, is passed across the patients' skin. It is thought to stimulate peripheral nerves and alleviate pain and had been studied as a therapeutic option in FMS. Devices used for TENS therapy are usually portable, and users can adjust certain qualities of the electric pulses they generate. TENS is considered to be safe, with adverse effects that are rare, although there are

certain contraindications (cardiac pacemakers and ventricular assist devices) and precautions (including pregnancy, epilepsy, and malignancy) [16].

TENS has been assessed as a therapeutic modality for many pain syndromes. A Cochrane review [17] that included eight studies found that there was insufficient evidence to suggest TENS as a treatment for FMS due to lack of data, low quality, and overall number of studies, as well as the studies being under-powered. A systematic review and meta-analysis [18] evaluated TENS and electric acupuncture (EA, a method in which traditional Chinese acupuncture is combined with electric current stimulation) as FMS treatments. It concluded that electric stimulation (i.e., both TENS and EA) was effective for pain relief in FMS, but that the evidence supporting this claim was of low quality. The authors also concluded that when evaluated by itself, EA was effective in reducing pain (whether combined with other therapies or not)—and the evidence supporting this claim was of moderate quality. According to the authors, no effect of electric stimulation on quality of life or fatigue was found by their meta-analysis. A 2019 study evaluated the therapeutic efficacy of TENS through quantitative electroencephalography (qEEG), comparing TENS with acupuncture. Each patient underwent qEEG recording, followed by 20 min of therapy with either TENS or acupuncture, followed by a second qEEG recording. Both TENS and acupuncture resulted in a decrease in pain scores and to qEEG changes that led the authors to conclude that both interventions could be beneficial for FMS patients [19]. It should be noted that certain studies included in these reviews used TENS in combination with physical activity, and it had been suggested that pain modulation observed by these studies could occur in a less direct manner, as TENS improves patients' ability to participate in physical activity, which alleviates pain [20]. Acupuncture was suggested as a weak recommendation for the treatment of FMS by EULAR guidelines [4], where it was also mentioned that EA was associated with a decrease in fatigue and pain, and only had mild and transient adverse effects.

## Electroconvulsive Therapy

The very high efficacy of ECT treatment for depression had been known for decades, and therefore, this type of neuromodulation method had also been suggested as a possible therapeutic option for FMS [2]. Despite being a widely used and effective modality in the treatment of psychiatric disorders such as depression, ECT was scarcely studied as a therapeutic option for FMS. A few case reports have been published in the past [21, 22], with mixed results, and two studies assessed the effect of ECT on FMS patients in small-sized cohorts. To the best of our knowledge, no reviews on ECT as a therapeutic modality for FMS have been published so far. One study from 2006 by Usui and colleagues [23] showed that ECT improved pain and reduced the number of tender points significantly. It should be noted that the study group consisted of 15 patients and 14 of them received antidepressants as FMS treatment throughout the study period. In their 2004 study, Huuhka and colleagues

[24] enrolled 13 patients with concomitant FMS and depression in an ECT study that found there was significant improvement on certain FIQ items, but no significant improvement in pain in those patients.

## Hyperbaric Oxygen Therapy

HBOT was shown to be beneficial in the treatment of certain chronic pain syndromes. Evidence suggesting HBOT can be useful for treating FMS symptoms includes its inflammatory-modulating qualities as well as neuromodulatory ones. It has been suggested that oxidative stress along with mitochondrial dysfunction plays a role in the pathophysiology of FMS and that HBOT might exert its effects through mitochondrial mechanisms [25].

During HBOT patients breathe 100% oxygen while situated in a chamber in which the pressure is higher than the normal 1 atmosphere absolute (ATA), thus increasing oxygen concentration in the blood and throughout the body. In 2004, Yildiz and colleagues [26] included in their study 50 FMS patients whose disease was refractory to medical and physical therapy. Twenty-six patients received HBOT in 15 sessions (5 sessions per week), 90 min each, at 2.4 ATA. A control group of 24 FMS patients followed a similar protocol but was treated in a chamber in which the pressure was 1 ATA. Pain threshold, number of tender points, and VAS score all showed statistically significant improvement after the 1st and 15th treatment in the HBOT group. A more recent prospective study by Efrati and colleagues [27] was conducted using a crossover protocol. The treatment protocol included 40 daily sessions (5 days per week), 90 min each, while breathing 100% oxygen at 2 ATA. Evaluation included assessment via questionnaires, pain threshold examination, tender point assessment, and brain activity assessment by SPECT imaging. Results showed that HBOT in both groups led to significant improvements, while the no-treatment period that the crossover group had undergone did not lead to similar changes. SPECT imaging showed that patients who responded to therapy had altered activity in certain brain areas. The authors mention that FMS had been previously associated with hyperactivity in the somatosensory cortex and reduced activity in the frontal, cingulate, medial temporal, and cerebellar cortices, and responders to HBOT had decreased activity of hyperactive regions and increased activity of underactive regions. Pain threshold scores were increased following HBOT, and the number of tender points was reduced. FIQ, SCL-90, and SF-36 scores were all significantly improved after HBOT in both groups.

In another HBOT study, following a similar protocol to those previously described [28], a group of patients suffering from both FMS and interstitial cystitis had no improvement in quality of life, symptoms, and urodynamic parameters (apart from hydrodistention tolerance and an improvement in cystoscopic pattern). An observational longitudinal study published in 2019 utilized surface electromyography (sEMG) to assess the neuromuscular changes exerted by HBOT in FMS and showed that HBOT increased neuromuscular efficiency—improving the ability

of central motor commands to produce efforts using fewer fibers [29]. A prospective observational study on HBOT that included 20 HBOT sessions with 100% oxygen and 2.5 ATA showed a significant improvement in pain, anxiety, fatigue, and FMS severity scores, although depression symptoms and quality of sleep did not significantly improve [30]. A prospective randomized clinical trial had found that post-traumatic stress disorder (PTSD) symptoms, quality of life, and fibromyalgia questionnaires all improved significantly after HBOT in patients with FMS who have a history of childhood sexual abuse [31]. A study by Guggino and colleagues [32] assessed for the effect of HBOT on quality of life and pain in FMS patients, while also studying its effect on several biochemical and immunological parameters, by collecting peripheral blood samples. The study showed that FMS patients treated with HBOT had significant improvement in pain, an increase in serotonin serum levels (however not in a manner that correlated with improvement in mood or fatigue), and a reduction in all measured cytokines.

## Biofeedback

Biofeedback is psycho-physiological intervention in which patients use devices that monitor certain autonomic bodily functions (e.g., EMG, EEG) and report those parameters back to the patients, allowing them to attempt to control or alter these functions, by receiving feedback when they reach target values. Biofeedback, being an appealing non-pharmacological intervention, had been studied in FMS for over 20 years now [33]. Current EULAR guidelines do not suggest biofeedback as treatment for FMS [4]. A 2013 meta-analysis found that EMG biofeedback led to significant short-term decrease in pain comparing with the control intervention (which varied and included sham biofeedback, attention-placebo treatment, and others), but failed to improve other symptoms such as fatigue, sleep, depression, or health-related quality of life [34]. A randomized controlled trial published in 2017 included 36 FMS patients and showed that EMG biofeedback did not improve the health status (as assessed by the FIQ) of FMS patients, but did improve the pressure-pain threshold [35].

Neurofeedback is a biofeedback method in which patients attempt to modulate neuronal activation. A meta-analysis published in 2014 [36] found neurofeedback to be effective in improving certain somatic and psychological complaints of FMS patients, but claimed that some of the included studies were of a very low methodological quality. In a randomized, double-blind controlled trial, Goldway et al. [37] evaluated the effect of an fMRI-based neurofeedback method and compared it with sham neurofeedback. The authors found an immediate improvement in objective quality of sleep (assessed by home sleep monitoring) in the active neurofeedback group, while a subjective improvement in sleep and pain was observed during long-term follow-up. In another study, neurofeedback was compared with pharmacotherapy with escitalopram [38]. Assessment through questionnaires showed that both interventions improved FMS symptoms, but the effect of neurofeedback was

greater. However, another study that assessed the efficacy of a novel variant of electroencephalograph biofeedback, based on a low-energy neurofeedback system, which utilizes minute pulses of electromagnetic stimulation to change brainwave activity, did not seem to be superior to sham neurofeedback based on measurements of cognitive dysfunction, fatigue, pain, and sleep, and overall activity level [39].

Heart rate variability biofeedback (HRVB) is a biofeedback method in which patients attempt to change the variability and rhythm of their heart rate. A 2019 literature review on HRVB as an intervention to alleviate FMS symptoms included six different studies [40]. Most of them found a reduction in pain with HRVB. Depression scores also decreased following HRVB [39].

In conclusion, the neuromodulation therapeutic options mentioned in this review all showed a certain promise in alleviating at least one of the core symptoms of FMS. At the same time, most of the data that are reported in this chapter rely on relatively small sample sized studies, with limited long-term follow-up. Further investigation for long-term effects of these therapies and their efficacy should be conducted, but in the meantime, we believe that these therapeutic modalities may offer an element to the solution to certain FMS patients—such as those with low compliance to therapy.

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# Chapter 8
# Fibromyalgia: Classification, Criteria, and Diagnosis—What Is Fibromyalgia?

**Roie Tzadok**

## Controversies in FMS Classification

The classification of fibromyalgia remains controversial [1], starting with arguments over whether the condition should even be referred to as a disease or not [2]. On the one hand, if a disease is defined by WHO recognition, then fibromyalgia can be considered as one. It was also listed as a disease by the 11th revision of the International classification of diseases (ICD-11) [3].

On the other hand, lacking a defined etiology and/or a consensual pathophysiology, some may say it cannot be ultimately defined as disease [4]. Therefore, the term "syndrome" is commonly used, as it will be used in this chapter. The term may be suitable as it describes a collection of symptoms that form a pathological pattern.

Another aspect of the controversy regards the medical discipline that should treat fibromyalgia: Is it a rheumatic disorder (as was indeed first defined by the 1990 American College of Rheumatology criteria) [5], a pain disorder (as evidence of dysfunctional pain—modulation in fibromyalgia patients does exist [6]), or simply a neurologic disorder (as there is evidence of some patients suffering from small fiber neuropathy) [7]?

On top of all—some physicians, especially psychiatrists, consider fibromyalgia to be an atypical presentation of other affective disorders, such as depression [8], thus associating it with a mental health disorder. The question becomes even more complicated because not all fibromyalgia patients have a mood disorder, or a defined

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neuropathy—which further supports the notion of it being a wide clinical spectrum, not necessarily fitting into an established classification system.

A wider perspective of classification can be found in the term "functional somatic syndrome," which is used to describe a complex of physical symptoms over a defined period of time in the absence of another suitable etiology [9]. The 2017 fibromyalgia German guidelines classified it as a "functional somatic syndrome," in a manner similar to irritable bowel syndrome (IBS) [4]. Interestingly, functional somatic syndromes sometimes overlap, as do fibromyalgia, IBS, and tension headache. This led Yunus to unify all these disorders under the title of "central sensitivity syndromes," indicating neuroendocrine aberrations interacting with patient-specific psychosocial factors to cause an overlap of somatic complaints [10]. This definition, taking into consideration both physiological and psychosocial parameters, reflects the complexity of fibromyalgia definition and the multidisciplinary approach necessary in understanding its heterogeneity.

## Social Aspects of Defining Fibromyalgia

Common manifestations of fibromyalgia, as well as its prevalence, change between societies and cultures [11, 12]. This may pose a difficulty in formulating a definition of the syndrome and objectively measuring it. It is not surprising, therefore, that conflicting views of it have emerged over time: The first one sees it as a disease, with a distinct pathogenesis of neurobiological dysregulation. As neuroscience progresses, this approach tends to gain popularity [13]. However, an alternative approach sees the roots of fibromyalgia in cultural and individual differences [12, 14, 15]: According to this approach, what is defined today as fibromyalgia by clinical guidelines is only an arbitrary dominion based on symptoms which have been defined back in the nineteenth century as "neurasthenia" or "weakness of the nerves." While in the nineteenth century neurasthenia was associated with the psychologic term "hysteria," the same concept has reappeared in previous decades as "fibromyalgia." Supporters of this theory believe that in reality—neurasthenia and fibromyalgia are simply the same spectrum of "functional" symptoms [12, 16].

Thus, while the first neurobiological approach is more neuroscience-oriented in nature, the latter is more nominalist. It sees neurobiological alterations that may be found in fibromyalgia patients not as a cause of the disease, but rather as one of its consequences, which may also be seen in many other pain conditions. In other words—these alterations are only the neurobiological mechanism by which the fibromyalgia phenotype is expressed. In that case, chronic widespread pain may not be the essence of fibromyalgia, as all the classification criteria might suggest. It could be that the clinician's perspective of widespread pain as the central part of fibromyalgia is all wrong. This may also explain previous findings, showing that only a minority of clinically diagnosed fibromyalgia patients actually fulfill its diagnostic criteria [17, 18].

The possibility that fibromyalgia is indeed not a separate clinical entity, but rather a clinical continuum, was demonstrated by Wolfe et al. in 2013 [19]: In their work patients' symptom intensity was assessed using the polysymptomatic distress

("fibromyalgianess") scale of the ACR 2010 criteria [20, 21]. It was shown that fibromyalgia symptoms were present in patients who did not meet fibromyalgia criteria. This continuous perspective may be more suitable when understanding how psychosocial factors dictate the way we perceive fibromyalgia.

If indeed our ability to objectively define fibromyalgia as an objective and distinct phenomenon with an established pathogenesis is so problematic, one may ask what fibromyalgia actually is, or what defines it: it has been clear for decades that fibromyalgia, as well as other functional somatic disorders, is associated with great distress. There is no wonder, therefore, that these disorders sometimes overlap. Distress is both physical and mental, as mental and cognitive manifestations of fibromyalgia cannot be ignored. As every human being responds differently to stress, in fibromyalgia this response is increased.

An individual's response to distress is influenced by the stressing stimulus itself, and also by his personality, social background, and prior medical conditions. All of these factors are part of a person's social construct. However, diagnostic criteria for fibromyalgia are based on the assumption that one's response to distress is excessive, or that there is a "legitimate" extent of such response. The meaning of using these diagnostic tools is that the clinician's social construct is used to assess another person's symptoms, an attempt that is inherently subjective and inaccurate.

In that case, looking at every distress disorder, fibromyalgia included, as a spectrum may be more accurate, because it lacks the diagnostic aspect and allows us to approach the symptoms in a descriptive fashion.

Lacking a binding definition or an objective testing method, for many years fibromyalgia acquired a somewhat dubious reputation as a "psychological" illness, often referred to as "not real" or "self-induced." As mentioned, it was often related with mental disorders.

Views have somewhat changed over the years. Patients' self-reported symptoms cannot be ignored, but the way the individual experiences them, and the way the clinician interprets them, cannot be separated from their biopsychosocial backgrounds. In a similar manner, social perspectives also affect the way fibromyalgia is perceived: patients would benefit from developing construct diagnostic tools for fibromyalgia, which could be perceived as validating the "realness" of their condition and would mitigate previously held negative perspectives of the condition. Thus, from the perspective of patients, the formulation and validation of clear and practical diagnostic criteria would be a desirable goal and could pave the road toward better research and treatment of their condition. All these trends are eventually aspects of the "social construction" of fibromyalgia into a well-defined disorder.

## Criteria Development

The use of the term "neurasthenia" was abandoned by the 1920s, because it was considered a psychiatric rather than an organic disorder [16]. However, the same concept has reappeared in previous decades as "fibrositis," as a somewhat vague term describing pain, or "soreness" [22], shifting in location [23, 24]. The term

"widespread pain," or even the acknowledgment of the pain being generalized, was not even described until Smythe and Moldofsky first set the specific criteria for fibrositis in 1977, describing it as "widespread aching" [25].

This term was renamed as "fibromyalgia" in the 1970s–1980s [26], and in 1981, Yunus et al. set a first quantitative definition of fibromyalgia, describing it as involving three or more sites of the body [27]. It was not until 1990 that the American College of Rheumatology (ACR) established classification criteria for fibromyalgia [5]. These criteria were based on having tenderness in at least 11 of 18 points, and "widespread pain"—a general assessment of pain involving different body areas. Interestingly, the widespread pain criterion was added to the tender points criterion only to facilitate screening of patients. The ACR criteria were further revised in 2010 [21]. The new criteria were based mostly on symptoms, not on tender points. Symptoms were both somatic (muscle pain, weakness, irritable bowel syndrome, headache) and cognitive (depression, fatigue, difficulty concentrating). These criteria attempted to incorporate the clinical spectrum of fibromyalgia symptoms, beyond pain and tenderness, into the diagnostic framework. A self-reported version of the 2010 criteria for research use was published in 2011 [20], and was further modified in 2016 [28].

The ACR criteria included a component of the polysyndromatic distress (PSD) scale, comprised of the widespread pain index (WPI) score and the symptom severity scale (SSS) score, assessing self-reported painful regions and symptoms, respectively. A sum of 12 or more was considered diagnostic for fibromyalgia, with a higher score indicating a higher level of "fibromyalgianess" [29]. However, this continuum of PSD showed that essentially every patient with pain has some degree of fibromyalgia symptoms. This has led to a situation in which the dichotomist perception of "having" or "not having" fibromyalgia is no longer suitable for the nature of the phenomenon. In an attempt to solve this problem and better distinguish fibromyalgia from other pain disorders, the 2016 criteria added a generalized pain criterion, defined as pain in at least four of five body regions (left upper, right upper, left lower, right lower, and an axial region), in addition to calculating the PSD score [28]. In 2019, the ICD-11 defined fibromyalgia as a widespread pain disorder [30].

The repeated changes in fibromyalgia clinical definition over the years reflect the shift from physical signs (i.e., tender points) as a diagnostic tool to a more descriptive, symptom-related, and patient self-reported approach, reflecting a growing understanding that all fibromyalgia is not the same. With change in disease definition comes also greater awareness of the complexity of human behavior and social frames.

## Validity and Reliability of Fibromyalgia Diagnosis

In 2016, Walitt et al. published the NHIS study [17], showing that 75% of patients with a clinical diagnosis of fibromyalgia did not satisfy ACR criteria. This finding may indicate the discrepancy between clinical and research-oriented diagnosis in

fibromyalgia, thus leading to the question if a gold standard for fibromyalgia definition even exists.

Even if the ACR criteria are viewed as a gold standard for diagnosis, they are associated with reliability and validity issues [28]: while the 2010 criteria are dependent on the physician's technique and interpretation of eliciting pain in tender points, the self-report in the PSD component may not be reliable for the individual patient, whose symptoms do not quite match the PSD scale [31].

In addition, fibromyalgia patients address physicians long before they are diagnosed as such. This reflects some of the diagnostic problems in fibromyalgia. As a result, many patients may be found to manifest "fibromyalgic" symptoms before fully satisfying diagnostic criteria. This finding has led to attempts to broaden the definition to "subclinical" or "pre-fibromyalgia" [32–34].

The other side of the spectrum is patients whose symptoms improve, making them no longer "eligible" to the title of having fibromyalgia after a while. This issue is not solely hypothetical, as some studies have shown that one-third of patients diagnosed with fibromyalgia do not meet criteria on follow-up examinations [20]. One may therefore ask—where does fibromyalgia begin or end? Especially when it is sometimes clinically indistinguishable from other central sensitivity syndromes [35] or chronic fatigue syndrome [36, 37].

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# Chapter 9
# Psychiatric Comorbidity and Fibromyalgia


**Megha G. Fatabhoy and Afton L. Hassett**

## Introduction

The co-occurrence of psychiatric conditions in chronic pain states is common and perhaps even more pronounced in fibromyalgia (FM). This could be due to the idea that FM represents the right tail of the bell-shaped curve depicting pain sensitivity [1] and thus provides the context for where the greatest pain, stress, and distress is experienced. It is also possible that depression, anxiety, and other psychiatric diagnoses are present at higher rates in fibromyalgia because there are common genetic and environmental factors that predispose to both chronic pain and comorbid psychiatric conditions.

This chicken or the egg problem has challenged researchers, healthcare professionals, and patients alike for decades. Does living with disabling pain lead to worry, helplessness, and hopelessness or might there be a significant underlying biological predisposition and set of environmental circumstances (e.g., trauma, persistent stress, social isolation) that result in both pain and psychiatric disorders. The unsatisfying answer is that both possibilities are likely true. Regardless of the cause, the reality is that as many as half of patients with FM evaluated in clinical settings will

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present with substantial psychiatric comorbidity. To ignore the powerful impact of such mental health conditions on pain outcomes is to ensure that the patient's care will be suboptimal and frustrating for all involved.

Yet, there is another side to the coin; many patients with FM do not have psychiatric comorbidity and these individuals tend to have better outcomes. Some of these patients even thrive in spite of the pain they experience often on a daily basis. It is from these individuals that we might learn the most about how to move chronic pain patients toward leading more active and productive lives. Current behavioral therapies focus on education, improving coping and providing the skills needed to function more successfully, as well as how to add meaning and joy to a life that was not what the patient expected or deserved.

Here, we provide an overview about the most commonly encountered psychiatric comorbidities, depression and anxiety, and then a discussion about several other psychiatric conditions such as bipolar disorder, posttraumatic stress disorder (PTSD), substance use disorders, and somatization disorders that may be present. We will also touch on the difficult topic of suicidality in FM. Throughout, we will then delve into neurobiological and behavioral factors thought to underlie psychiatric comorbidity in FM. After that, the notion of resilience and affective balance (promoting a healthier balance of both negative and positive emotions) will be described. Lastly, we will explore the clinical implications for psychiatric comorbidities with some specific suggestions for how to organize treatment planning and resources that can help support care.

## Comorbidity Between Fibromyalgia and Mood Disorders

Perhaps the best place to start when evaluating patients with FM for psychiatric comorbidity is mood disorders. Mood disorders, including major depressive disorders (MDD) and bipolar disorders, have high prevalence rates among patients with FM when compared to the general population [2]. Specifically, depressive symptoms have a lifetime prevalence rate of 90% in FM patients, while MDD appears in 86% of patients [3, 4]. Several studies have also suggested that patients diagnosed with FM also frequently experience manic symptoms with rates of bipolar I and bipolar II disorders appearing in approximately 21.7% of FM patients [5–7]. Given such high prevalence rates among both disorders, depressive and bipolar disorders are important to consider regarding psychiatric comorbidity among patients with FM compared to the general population.

***Major Depressive Disorder and Fibromyalgia*** Patients with FM often experience depressed mood, sleep disturbance, fatigue, poor concentration, and other symptoms that are frequently also found in MDD [8]. Given the overlap of symptomology, many researchers have sought to determine how exactly the two disorders are connected [2, 9, 10].

Biological similarities exist between depression and FM. Both disorders are frequently treated with antidepressants including selective serotonin and selective norepinephrine reuptake inhibitors (SSRIs and SNRIs; [10]). Such concomitant use of antidepressants for both disorders might be interpreted as evidence that shared biological mechanisms underlie both FM and MDD. Indeed, several studies have suggested disturbances in neurotransmitter systems including serotonin, norepinephrine, and dopamine have similar pathways that are associated with an increased risk of developing FM and/or MDD [11–14]. Dysregulation in these neurotransmitters impacts both mood and other psychiatric symptoms, as well as pain transmission [15]. In addition to neurotransmitter similarities, several neuroimaging studies suggest that MDD and pain evoke similar neural activations within the brain [2, 16]. For example, Giesecke and colleagues [16] found that both clinical pain and MDD activate regions of the brain such as the amygdala and contralateral anterior insula, which are both associated with affect and mood.

Other evidence suggests that both FM and MDD are associated with dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis [9, 11, 17, 18]. The HPA axis is often activated by acute stressors such as psychosocial stress or physical traumas. Many studies have established that early and late life stressors are often associated with depressive episodes and FM [9, 11, 17]. Typically, the HPA axis is activated in response to stressors in a protective manner; however, if chronically activated, the HPA axis can become dysregulated. Prolonged stimulation of the HPA axis can lead to symptoms such as fatigue, negative affect, and increased pain—all symptoms that can be found in both depression and fibromyalgia [9, 11, 17].

Altogether, the physiological similarities between FM and MDD lead to the question of whether FM is a manifestation of MDD or if MDD follows FM. The developmental trajectory of FM and MDD has caused some dispute within the literature [19, 20]. While some evidence has indicated that depression can precede the development of FM [21, 22], there is also substantial evidence that suggests that depression can also develop following FM [23, 24].

For example, Marangell and Clauw [25] conducted a secondary analysis of data from patients with both FM and MDD treated with duloxetine, a selective norepinephrine reuptake inhibitor (SNRI) antidepressant. SNRIs are approved by the US Food and Drug Administration (FDA) for the treatment of both depression and FM [1]. Their analysis revealed that improvements in mood accounted for a 31% reduction in pain. However, at the same time, reductions in pain were found to account for a 40% improvement in mood symptoms. Such results support a more recent prevailing notion that the interactions between FM and MDD might be a bidirectional rather than having a unidirectional relationship.

Overall, regardless of whether FM causes MDD or MDD causes FM, numerous studies have suggested that certain behavioral factors can prolong the trajectory of both conditions [26, 27]. Indeed, living with chronic pain conditions such as FM can lead to fear-based avoidance of activities that are assumed to increase disability. Over time, should individuals continue to avoid physical activity, deconditioning may follow, and such loss of physical functioning may contribute to exacerbated pain, feelings of loss, and further deterioration of mood [26, 27].

***Bipolar Disorder and Fibromyalgia*** Similar to MDD, significant pathophysiological overlap has been found between bipolar disorder and FM. FM and bipolar disorder share similar symptom profiles including sleep disturbance, fatigue, cognitive impairment, and an altered stress response [28–31]. Neuroimaging research suggests that both disorders are associated with impaired neuroplasticity in the brain including altered neurotrophic factor signaling [32]. A growing body of literature also suggests that such overlap might be explained by shared overlapping neurocircuits related to emotional control, cognitive regulation, and pain processing found in both FM and bipolar disorder [32]. Additionally, similar to MDD, functional deficits within the HPA axis related to the stress response in the body have been found in both disorders [33].

While the literature on the association between MDD and FM is abundant, in comparison, the research related to other comorbid mood disorders such as bipolar disorder and FM is lacking. A systematic review conducted by Kudlow and Rosenblat [4] identified nine studies that examined the association between bipolar disorder and FM and found that the pooled prevalence rate of bipolar disorder in FM is 21%. The study authors, however, concluded that this rate should be interpreted with caution given the heterogeneity in study methodology which led to distinct prevalence rates across studies (0–70%).

Earlier studies often used outdated diagnostic criteria from the Diagnostic and Statistics Manual (DSM), DSM-III and DSM-III-R, to diagnose bipolar disorder [8, 34]. Since bipolar II disorder, characterized by milder hypomanic instead of severe manic disorders, was not added into the DSM until the introduction of the fourth edition (DSM-IV; [31]), it is possible that many of the earlier studies missed identifying patients with lifetime mania symptoms. Indeed, many of the later studies that used the DSM-IV criteria to identify lifetime prevalence of manic episodes found the rates of bipolar disorder might be higher than originally thought in FM patients, with some studies reporting up to 70% of their samples screening positive for manic symptoms [5, 7].

Such results have important clinical implications since many patients with bipolar disorder and FM are often misdiagnosed as having MDD because the clinical course of depressive symptoms often is more prolonged than the clinical course of manic symptoms [35]. However, misdiagnosis of bipolar disorder in FM can have severe ramifications. For one, individuals with bipolar disorder often have more severe FM clinical courses than individuals with MDD and FM [36, 37]. Individuals with bipolar disorder and FM are more likely to develop greater functional impairment, disability, and unemployment when compared to individuals with MDD and FM [38, 39]. Also, a greater number of lifetime manic symptoms have been associated with greater pain intensity and worse quality of life [40].

Another possible and most important repercussion of misdiagnosis of bipolar disorder as MDD is, as stated in the comorbid depression and FM section of this chapter, FM is typically treated with SNRI and SSRI antidepressants [1]. However, in patients with bipolar disorder, antidepressants can promote further mood destabilization, further complicating the course of bipolar disorder [36, 37]. Treating

patients who have FM and underlying bipolar disorder or manic symptoms with antidepressants without a concomitant mood stabilizing agent might increase the risk of mania, psychotic episodes, suicidal behavior, and/or rapid cycling [38, 39]. Taken altogether, thorough assessment and pharmacological and behavioral management of patients with FM who might have suspected bipolar disorder or manic symptoms is warranted since misdiagnosis within this population is frequent among providers.

## Comorbidity Between Fibromyalgia and Anxiety Disorders

Anxiety disorders are also common in FM. Multiple studies have reported that anxiety, trauma-related, and obsessive-compulsive disorders generally affect 27–60% of patients with FM [41–43]. Comparing patients with and without FM, Arnold and Hudson [3] found that patients with FM are more likely to have obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), social anxiety disorder, and panic disorder. Interestingly, however, the authors found that generalized anxiety disorder (GAD) was lower among patients with FM compared to patients without FM. Yet, many other studies have refuted this finding [44, 45].

It should be mentioned that in older versions of the DSM (i.e., DSM-I to DSM-IV-TR), PTSD was encompassed within the anxiety disorders section [46]. However, in the current DSM-V, PTSD has its own category. Nonetheless, regardless of their distinctions, PTSD and anxiety disorders share many pathophysiological and phenomenological similarities including avoidance behavior, hypervigilance, cognitive difficulties, sleep disturbance, and fatigue [46, 47]. Thus, PTSD appears to still present with symptoms of anxiety with the added component of a traumatic stressful event that triggers a stress response.

Regarding anxiety generally, somewhat fewer data are available on the relationship between anxiety and FM [12]. Some researchers have theorized that anxiety might predispose individuals to develop chronic pain conditions such as FM. Specifically, when in a state of acute pain, the body's stress system—the HPA axis—becomes activated leading to a "fight or flight" response. As expected, this stress response can lead to a heightened sense of apprehension and anxiety accompanied by increased physiological reactivity [48].

Anxiety in chronic pain is typically associated with the cognitive constructs pain catastrophizing and kinesiophobia (i.e., fear of movement)—the latter resulting in avoidance behaviors that aim to circumvent possible injury [49]. Over time, it is believed that should these maladaptive thoughts and avoidance behaviors continue to persist, individuals will remain in a chronic alarm state in which there will likely be an increase in social isolation, inactivity, deconditioning, and eventual disability. Long-term anxiety in FM patients has been associated with increased pain intensity and pain interfering behaviors [50]. Consequently, prolonged activation of the HPA axis can lead to the compensatory response of hypoactivation of this system [48].

Overall, dysregulation of the HPA axis has been thought to mediate the transition from acute to chronic pain conditions such as FM [51, 52].

Stressful events often precede the onset of FM symptoms [53]. Of the main stressful or even traumatic experiences reported by patient with FM, emotional traumas are often highest in prevalence, followed by physical traumas, physical abuse, and finally sexual trauma [45, 54]. The most frequent form of emotional trauma reported by FM patients includes the unexpected death of family member or close friend. Regarding physical traumas, the most commonly reported physical traumas reported include car accidents, physical injuries, and surgery [54]. Rates of PTSD have been shown to range from 15% to 56% [55], but having a trauma history has been reported in up to 75.2% of patients with FM [54].

In a meta-analysis conducted by Miro and colleagues [50], results revealed that trauma history was connected with FM through the mediator anxiety, suggesting that early trauma experiences might precipitate a stress response that could generate greater anxiety. Given the research that links anxiety to HPA axis dysfunction, it could thus be theorized that should dysfunction of the HPA axis be prolonged, the possibility of the emergence of a nociplastic pain such as FM might be more likely to occur.

Miro and colleagues' study also highlights the notion that traumatic events often precede the onset of FM symptoms. Indeed, their meta-analysis additionally revealed that 66.5% of patients report that their traumatic experiences led to FM symptom development. Such data support the notion that traumatic events causing a chronic stress response can lead to physical manifestations such as FM. However, their results also revealed that many patients (29.5%) reported their first symptoms of PTSD occurring after the onset of their FM. Their results are supported by other studies which report similar prevalence rates [40, 55, 56].

Overall, Miro's meta-analysis has important clinical implications. Similar to MDD and FM, it appears possible that certain anxiety disorders such as PTSD might also have a bidirectional relationship with FM. That is, PTSD can be a risk factor for the development of FM but not always. Individuals with FM might also have a greater susceptibility to perceive major life events as traumatic. Indeed, some research has revealed that individuals with FM might perceive stress differently than healthy controls. For example, Stisi and Venditti [57] found that patients with FM were more likely to rate mild stressors as more severe compared to controls. Thus, stress sensitivity could be due to the heightened sensitivity of the central nervous system and could help explain why a subset of patients with FM go on to later develop PTSD.

## Other Psychiatric Disorders and Conditions to Consider in Fibromyalgia

There are numerous psychiatric disorders other than those related to depressive and anxiety symptoms that could appear in an individual with FM. For brevity, we will focus on those that are more likely to require some consideration in clinical settings

including substance use disorders, somatic symptoms disorders, and suicidality. Substance use disorders are important to consider since some chronic pain patients may use drugs and alcohol to self-medicate to cope with pain, while others may have been ill-advisedly placed on opioids and such use needs to be carefully evaluated. Somatic symptoms disorders are important to discuss in regard to FM since there has been a long-standing and highly inaccurate bias that FM itself is purely a psychiatric disorder. Lastly, we will touch on the increased risk for suicide that has been observed in FM—while it is hard to ask, it is important to know.

***Substance Use Disorders and Fibromyalgia*** It has long been observed that individuals with chronic pain are at risk for substance use disorders often in the context of trying to manage pain and cope with life disruption [58]. Moreover, there is an ever-growing concern about the potential risk for substance abuse in FM in light of the opioid epidemic. Data in regard to the propensity of individuals with FM to abuse substances are mixed. Some studies suggest that substance abuse rates in FM are elevated, while other studies suggest that the commonly observed sensitivity to medications and other stimuli may also apply to alcohol and recreational drugs.

In a study conducted by Arnold and colleagues [4], it was reported that the lifetime history of having any substance use disorder was high where 25.6% of FM patients met those criteria. A history of alcohol abuse or dependence was reported in 21.8%, while drug abuse or dependence was found in 15.4% [4]. In a more recent study of opioid use in FM, Fitzcharles et al. [59] reported that 11% of their sample of FM patients met criteria for having a substance use disorder and those patients were more likely to be taking opioids and engaging in drug seeking behavior. In a study of patients with a number of rheumatic diseases and conditions, Wolfe et al. found that a lifetime history of drug or alcohol problems was endorsed by significantly more FM patients compared to other diagnoses. However, only 6.1% of FM patients endorsed substance use problems, and the authors cautioned that in the context of the large sample considered, rates reported were generally low and differences between conditions were often not clinically significant [60].

Other studies finding the rates of substance abuse in FM to be quite low include a US community-based study conducted by Raphael, Janal [61] of 129 women with FM and 2419 women without FM. Using structured interviews, they found uniformly low rates of current alcohol and drug dependence in both groups. In patients with FM, current alcohol dependence was detected in none of the patients, while current drug dependence was observed in only 1.6%. In another study using structured interviews to evaluate psychiatric comorbidity in FM, Hassett and colleagues reported that none met the criteria for any current or past substance use/abuse disorder [62].

Based upon the available literature, estimates of alcohol use in FM are below the general US rates but may be consistent with other forms of chronic pain (which again are below the general US rates). Abuse of alcohol in FM, in many reports, is lower than the US population rate and rates for other chronic pain conditions; however, at least one report placed alcohol abuse in FM as being twice as high as the comparator groups. Current use of illicit drugs in FM is extremely low relative to

the US and other chronic pain groups. Moreover, in a recent study we reported that moderate alcohol use might even be beneficial [63].

***Somatization and Somatic Disorders*** Somatization disorders were thought to be the result of the expression of psychological distress as bodily symptoms. While psychological stress can indeed have physical consequences impacting the cardiovascular, immune, autonomic, and central nervous systems, such distress rarely explains the symptoms of people with chronic pain. Moreover, there has been a rich history of dismissing pain disorders like FM as solely psychiatric disorders, more akin to hysteria as conceptualized by Freud in the late 1800s, as opposed to the more enlightened view of FM as a medical disorder with common psychiatric comorbidity. Thus, it is not surprising that there are previous data suggesting that somatization disorder and hypochondriasis are common in FM although these diagnoses miss the mark.

In 2013, the Disease and Statistical Manual-5 (DSM-5) established a new term to describe conditions like FM, irritable bowel syndrome, and interstitial cystitis—somatic symptom disorder (SSD). This new term superseded the previous somatic symptom category, somatoform disorders. To meet criteria for SSD, patients need to have one or more somatic symptoms that are distressing or result in significant disruption of daily life. They also had to have at least one of the following: (1) disproportionate and persistent thoughts about the seriousness of one's symptoms; (2) persistently high level of anxiety about health or symptoms; or (3) excessive time and energy devoted to these symptoms or health concerns (APA DSM-5, 2013).

Wolfe and colleagues noted that the new SSD criteria along with other changes in the DSM "unleashed a firestorm of criticism," which included the concern that the new SSD criteria would result in mental illness diagnoses for numerous otherwise normal individuals with physical illnesses [64]. They concluded in their exploration of the use of the new SSD diagnostic criteria in FM that the reliability and validity of the criteria were likely to be low. They posed that the new diagnostic criteria place a much greater emphasis on the patient's maladaptive reaction to the symptoms than the symptoms themselves, and this is very difficult to judge. Thus, making a diagnosis of SSD for individuals with FM is generally not advised.

***Suicidality in Fibromyalgia*** Having chronic pain is a risk factor for suicide. Individuals with chronic pain, especially those with FM, are frequently depressed and/or anxious—also risk factors for suicide. Further, such depression and anxiety have been found to be higher among women with FM who have previously attempted suicide compared to those who had not [65]. This psychiatric comorbidity is compounded by the fact that people with FM often experience financial hardship, relationship strain, and loss of social support and tend to feel misunderstood by society.

While suicidal ideation is common in many chronic illness populations, a recent review of the literature exploring suicidality in FM found that they were at a significantly greater higher risk of having suicidal ideation, making suicide attempts, and dying by suicide [66]. For example, in a study of all-cause mortality in FM, Wolfe and colleagues reported that individuals with FM were at least three times as likely

(OR = 3.31) of dying from suicide compared to individuals in the general population. For women with FM, death from suicide occurred at a younger age (46.5 ± 11.4) compared to death from other causes (60.2 ± 13.0). Similarly, in a 15-year prospective cohort study of Danish patients with FM, Dreyer, Kendall [67] found that although women with FM were not at increased risk for all-cause mortality, they were at increased risk of death from suicide, with a standardized mortality rate (SMR) of 10.5 (95 % CI; 5.5–20.7).

These studies illustrate that women with FM may have a uniquely high risk of death by suicide; thus, it is imperative to conduct proper screening and follow-up. Osteen, Frey, and Ko [68] proposed that physicians be regularly evaluated on suicide assessment and intervention training given the high rates of suicidal ideation present among patients in primary care and emergency department settings. Specifically, they suggest that periodical skill checks with booster trainings should be regularly mandated. Skill checks might include testing of basic knowledge of warning signs, risk and protective factors, as well as locale-specific referral resources for patients. Additionally, training in standardized screening tools such as the Columbia Suicide Severity Rating Scale [69], the Patient Health Questionnaire Item 9 [70], and the Patient Safety Screener [71] along with brief intervention skills in safety planning is also recommended [68].

## Resilience and Positive Emotions in Fibromyalgia

Despite the voluminous data that highlight the importance of assessing and treating psychiatric comorbidities, no study to date has shown that all individuals with FM have current or a history of psychiatric disorder. There is always a subset of participants studied who display normal if not good psychological health and functioning. As a matter of fact, some remarkably talented, accomplished, and inspirational people have been diagnosed with or likely had FM, including the artist Frida Kahlo, the actor Morgan Freeman, singer-songwriter Lady Gaga, comedian and actor Janeane Garofalo, and President John F. Kennedy [72], to name just a few. One factor that likely underlies their success is resilience.

Resilience is commonly defined as the ability to bounce back after an initial setback and decline in functional status [73]. Resilience is also considered the ability to maintain one's functional status through a period of adversity such as living with a chronic pain disorder [74] or even thriving despite adversity [75]. The idea that "resilience mechanisms" contribute to better adaptation to living with a chronic pain such as FM currently enjoys substantial empirical support [76, 77]. Examples of *resilience mechanisms or states* include but are not limited to positive thoughts (e.g., optimism, self-efficacy), positive interpersonal relationships, active and adaptive coping, feelings of gratitude and purpose, and having high levels of positive affect (i.e., happiness and other positive emotions). A noble treatment goal for all individuals regardless of diagnosis is to ameliorate excessive negative affective states, while enhancing more positive affective states.

Each individual has a unique combination of thoughts and feelings that can fluctuate over time. Cognitive-behavioral therapy theory posits that negative thoughts tend to lead to the experience of negative affective states, while positive thoughts result in the expression of more positive affective states. Negative affect is characterized by emotions such as anger, sadness, irritability, and fear. In chronic pain, negative affective states are associated with greater pain severity [78], increased disability [79], and worse outcomes after treatment [80]. In contrast, positive affective states such as joy, vitality, engagement, and contentment are beneficial and associated with better pain outcomes [76, 81, 82]. Negative thoughts and affective states can result in maladaptive behavior, while positive thoughts and emotional states result in more adaptive behavior.

Affect balance style, a measure of the relative levels of positive and negative trait affect within an individual, has been predictive of clinical pain, functional impairment, and psychiatric comorbidity in adults with fibromyalgia [83, 84]. Growing evidence suggests that affect balance style may be a more informative way to understand the relationships between affect, pain, and physical and psychological functioning than considering positive and negative affect independently [83–86].

Affect balance styles are defined by four distinct patterns [83]. Individuals with high positive affect and low negative affect are classified as having a "healthy" affect balance style. Individuals with low positive affect and high negative affect are classified as having a "depressive" style. A "low" style is characterized by both low positive and low negative affect patterns, while individuals with a "reactive" affect balance style have a tendency toward heightened affective responses (high positive affect and high negative affect). Though relatively stable over time, affective traits such as affect balance styles are modifiable by experience, learning, and exposure [87, 88]. The dynamic nature of affect is a compelling target for pain intervention.

While it is tempting to default into the habit of identifying all that is wrong with our patients, some good could come out of helping patients identify and utilize their strengths. There are a number of evidence-based activities that could be suggested to patients that build positive emotions, improve their affective balance, and increase resilience. Keeping a gratitude journal, taking a few minutes each day to savor the good things in life, and scheduling and taking part in pleasant activities several times a week are great places to start. The power of pleasant activity scheduling, and the related behavioral activation, has effect sizes for improving depression that can far surpass those associated with traditional medical interventions [89].

## Psychological Treatments for Psychiatric Comorbidity in Fibromyalgia

The most common drug therapies offered for fibromyalgia include SSRI and SNRI antidepressants and sometimes anticonvulsant medications such as pregabalin [1]. While drug therapies have their merit in the treatment of FM, it is often recommended that pharmacological intervention be combined with psychological

intervention to more effectively treat the symptoms of FM [5, 53]. A number of behavioral interventions have been used for the treatment of FM including biofeedback training [90], emotional awareness and expression therapy (EAET; [91, 92]), mindfulness-based stress reduction (MBSR; [93]), guided imagery/hypnosis [94], psychodynamic therapies [95], and cognitive-behavioral therapies (CBT) such as operant behavioral therapy, traditional CBT, and acceptance and commitment therapy (ACT; [96]).

Hauser and Jones [97] comprehensively reviewed the aforementioned therapies for fibromyalgia patients. Combining information from multiple meta-analyses and individual randomized control trials (RCTs), their study concluded that of the available evidence, it is difficult to come to a definitive conclusion as to which behavioral therapy might be most useful for the treatment of FM given the paucity of high-quality RCTs. While all of the interventions above demonstrated certain improvements in FM, most of the studies for guided imagery/hypnosis, biofeedback, and MBSR reported low-quality evidence [64]. However, of the high-quality evidence studies, it appears that traditional CBT, operant therapy, and ACT seem to reduce FM symptoms and disability most effectively. Specifically, cognitive-behavioral therapies were found to provide >50% pain relief, reduce negative mood, disability, and fatigue in the short term. In the long term, CBTs were found to maintain these effects [64].

Traditional CBT protocols for FM are generally diverse with a number of tools including relaxation, mindfulness, graded behavioral activation, pleasant activity scheduling, sleep hygiene improvement, cognitive restructuring, and problem-solving training. Such technical heterogeneity allows traditional CBT to tackle symptoms of FM and its comorbidities such as sleep disturbance, anxiety, and depression [53, 98]. Another CBT, operant behavioral therapy, focuses on the modification of behaviors that maintain pain behaviors by reinforcing certain behaviors that lead to healthy living and ignoring other behaviors that enable and increase disability [99]. Finally, ACT focuses on increasing mindfulness and acceptance of FM symptoms. Thus, the goals of ACT for FM might include increasing patients' ability to act in accordance with their values and enhance awareness and acceptance of pain and distress [100].

In addition to CBTs, Hauser and Jones [67] concluded that emotional awareness and expression therapy (EAET) held some promise in treating FM. EAET is based upon the premise that failure to adapt to unresolved emotional conflicts that are often the result of traumatic and stressful experiences leads to both somatic and psychological symptoms [91, 92, 101]. Thus, EAET integrates trauma and emotion-focused therapies. The therapy is designed to help patients attribute their pain to emotionally salient experiences and help patients to become better aware of, experience, and adaptively express their emotions in a way that provides healing and improved functioning. Lumley and Schubiner [56] conducted an RCT comparing EAET, traditional CBT, and education for FM patients. Compared to education and traditional CBT, EAET showed a clinically relevant benefit at reducing pain >50% for patients. However, between CBT and EAET, while there were reductions in depression, disability, and fatigue, there were no statistically significant differences in the therapies on these outcomes.

Overall, while reviewing the evidence on psychological interventions for the treatment of FM, it is important to keep in mind that it is difficult to determine the superiority of one type of treatment over another. For one, as stated earlier, the quality of evidence has been shown to be low in many studies [97]. Second, even though Hauser and Jones [64] were able to find that the highest quality evidence belonged to CBTs, and CBTs were shown to have good clinical outcomes for individuals with FM, many of these studies frequently used comparison groups such as wait lists and treatment as usual groups [102]. However, there needs to be more comparison studies that actually compare gold standard treatments to one another to better determine the upper hand of one treatment over another. Additionally, while many of these therapies compared treatment outcomes, many studies ignored the measurement of process variables. That is, just as it is important to measure outcome variables, it is equally important to examine the "ingredients" that make each of the therapies effective [103].

## Clinical Implications, Screening Considerations, and Overall Words of Wisdom

Due to the paucity of etiological knowledge about FM, there is no universal agreed-upon therapy for the condition [71]. However, given its association with comorbid psychiatric conditions, most experts agree that the current best practice involves a combination of pharmacological and psychological therapies for the treatment of FM. Furthermore, lifestyle-oriented interventions are also efficacious in helping subdue symptoms of FM. For example, moderate to vigorous physical activity has been shown to improve physical functioning and overall well-being in FM patients [104].

Regarding pharmacological interventions, given the high comorbidity of FM with psychiatric disorders, drug therapies should target such comorbid conditions including mood, anxiety, and trauma-related disorders [104]. As stated in an earlier section on the comorbidity between bipolar disorder and FM, many individuals with FM are misdiagnosed with MDD when in fact they also have experienced manic episodes during their lifetime [24–27]. Given that the most common pharmacological treatment for FM is antidepressants, such drug therapies might inadvertently lead to treatment-emergent manic switches and destabilization in patients with FM and bipolar disorder [34, 105]. Overall, screening of psychiatric comorbidities should be an essential aspect of clinical assessment and care since (1) misdiagnosis can potentially lead to perilous and life-threatening consequences, and (2) it is well known that psychiatric comorbidities often lead to worsening of FM symptoms [104].

The current gold standard for assessing psychiatric comorbidity is the structured clinical interview [5]. However, even this tool has been found to have low clinical sensitivity and specificity and thus is prone to misdiagnosis [35]. Other more

specific screening tools might prove more useful, and given the higher comorbidity rates of mood disorders, anxiety, and trauma-related disorders, it might be more useful to use screening tools that are more specific and sensitive for each of these disorders.

For the assessment of bipolar disorder, one possible screening tool is the Mood Disorder Questionnaire (MDQ), which has been thoroughly studied and has achieved high reliability and validity among inpatients and outpatients and among different populations around the world [106, 107]. For MDD, the Beck Depression Inventory (BDI-I and -II) and Center For Epidemiological Studies Depression Scale (CES-D) have been found to be highly reliable and valid for patients with fibromyalgia [108]. For the assessment of anxiety, the Kessler-10 and Generalized Anxiety Disorder Scale (GAD-7) have been highly validated for patients with FM [108]. Finally, for PTSD, the Posttraumatic Diagnostic Scale and Harvard Trauma Questionnaire are validated tools for the assessment of trauma symptoms [109].

Overall, FM can be a debilitating condition that frequently coexists with psychiatric disorders. Studies addressing psychiatric comorbidity rates have traditionally been conducted in tertiary care clinics and thus might not reflect potentially lower rates observed in community settings. Nonetheless, commonly occurring depressive and anxiety symptoms are likely to be present in at least a subset of patients and can profoundly impact care; thus, attention is warranted. Suggestions for the screening and treatment of psychiatric comorbidity in FM include (1) proper screening of psychiatric conditions and disorders using well-validated measures for specific conditions, (2) proper precaution in prescribing antidepressants especially among patients prone to manic episodes and/or having a lifetime history of bipolar disorders, and (3) should any uncertainty exist regarding whether or not patients might have bipolar disorder or other conditions where antidepressants could be contraindicated, clinicians should have a low threshold for referral to a psychiatrist or psychologist. These professional partners can be powerful allies in providing the most comprehensive and successful care for these often highly complex patients.

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# Chapter 10
# Genetics of Fibromyalgia


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While the etiology and pathogenesis of fibromyalgia (FM) remain frustratingly elusive, as in other complex and multifactorial conditions, the generally accepted concept describes an interaction between a genetically determined predisposition and the aggravating effect of multiple triggers impacting on the individual from early childhood to adulthood. This conceptual framework makes it possible to incorporate evidence regarding specific triggers, such as physical trauma, stress, infection, etc., as discussed in detail in other chapters of this book, while attempting to explain why such extensive variability exists in the way different individuals respond to such triggers, and why one person may develop severe debilitating FM in response to a relatively mild insult, while another individual undergoing a similar exposure will emerge unscathed. But beyond this aspect of traditional genetic research, which focuses on genes as risk factors, another fascinating aspect which is highly relevant for the understanding of FM is concerned with the *epigenetic* modifications taking place in response to various triggers, thus moving beyond the field of predisposition and into the field of pathogenesis, or in other words posing a mechanism which may partially explain how a specific trigger may move an individual from health into the condition of heightened CNS pain processing, which is the hallmark of FM.

In this chapter, we shall attempt to cover the various aspects related to the genetics of FM and try to point toward future directions.

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## Familial Aggregation in FM

FM and chronic pain conditions tend to run in families. This clinical observation is quite self-evident to clinicians who treat such patients and take a comprehensive family history [1]. While many patients may report a first-degree relative such as a parent, who has been diagnosed with FM, many others describe other relatives, often older ones, who were given titles such as "rheumatism" or other non-specific diagnostic labels, which served to describe individuals suffering from chronic widespread musculoskeletal pain. Other more specific clinical pain conditions, such as temporo-mandibular joint disorder (TMJD), may also be encountered in the family [2]. In fact, the identification of family members suffering from FM or chronic pain may serve as an important diagnostic clue when contemplating the diagnosis of FM. The familial aggregation of FM was documented in the seminal work done by Arnold et al. who found that both FM and reduced pain thresholds strongly aggregated in families and that FM co-aggregated with major mood disorders [3]. In this study, the odds ratio (OR) of FM in the family member of a proband with FM was 8.5 relative to the OR of FM in a relative of a proband with rheumatoid arthritis (RA). Notably, as a significant percent of RA patients may have comorbid FM [4], comparing the OR to controls without RA may have led to even higher differences. Twin studies are a time-honored tool for evaluating a genetic contribution to complex disorders [5] and have also been implemented in the research of chronic pain conditions. In one large such study, Kato et al. looked at 15,950 pairs of twins from the Swedish twin registry and documented the presence of chronic widespread pain [6]. Proband concordance rates indicated a modest genetic influence, and the authors concluded that genetic and shared environmental factors explained about half of the variance, with a concordance rate of 30% among monozygotic female twins and 16% for dizygotic female twins. In view of such striking familial aggregation, the existence of a genetic basis for FM appears extremely likely. This holds true notwithstanding the possible contribution of various nongenetic (i.e., environmental) factors which might contribute to the phenomenon of familial aggregation.

While the abovementioned studies have convincingly documented a significant familial component in FM, they obviously do not indicate that FM is the result of a single genetic trait. As in many other complex disorders which involve the central nervous system (CNS), it is much more likely to assume that FM, like chronic pain in general, is a multifactorial and spectrum-like trait. Since we now know that multiple neurotransmitters as well as additional factors are involved in the transmission and processing of pain, it is natural to assume that a large number of genetic traits may likewise be involved in determining the tendency of an individual to ultimately develop FM. A host of factors which are not intuitively directly related to pain may in fact bear upon this process. Thus, genetic markers which are related to the autonomic nervous system can also be related to pain processing, but even more tangentially related genetic disorders related to hypermobility (e.g., Ehlers–Danlos syndromes), which are associated with autonomic dysfunction, can also pose a genetically determined risk for FM development. Lastly, one must keep in mind the

fact that FM is not a congenital disorder but rather develops over years in each affected individual. Some patients will deserve a diagnosis of FM in their teens while others will not reach this state until well after menopause. Thus, one must assume that the genetic predisposition toward developing FM is subsequently exposed to and influenced by a host of external triggers, to which the individual is exposed throughout life, eventually culminating in the development of FM.

Understanding the nature of this process, through which a genetically prone individual moves from being asymptomatic to being a fully manifest clinical patient, is a major challenge of modern genetics. Moving from classical genetic research into the fields of epigenetics and gene-expression patterns are fields which are beginning to shed light on these aspects and will be discussed subsequently in this chapter.

## Candidate Gene Studies

Studying candidate genes in complex polygenetic syndromes can be complicated, labor-intensive, and frustrating. It is tempting to look for polymorphisms in genes coding for mediators of pain processing, but a very large number of possible targets exist. Nonetheless, the candidate gene approach has achieved some significant breakthroughs in understanding the genetics of FM.

## Cathechol-O-Methyl Transferase (COMT) Polymorphisms and Their Relationship to FM

COMT, an enzyme which plays a major role in the metabolism of catecholamines, has been one of the first targets for genetic analysis in FM, in view of the presumed role of the autonomic nervous system in the processing of pain. Early studies by Zubieta et al. drew attention to this gene, showing that COMT polymorphisms predicted pain thresholds in healthy individuals, as could be demonstrated both through quantitative sensory testing (QST) and by functional neuroimaging [7].

An increased risk of chronic pain has been associated with the Val158Met (rs4680) polymorphism of the COMT gene, encoding an enzyme with lower activity [8]. A number of additional studies have been conducted relating to COMT in chronic pain, including the investigation of haplotypes which modify both expression and activity [9, 10]. Tammimaki et al. have conducted a systemic review and meta-analysis regarding the role of COMT polymorphisms in chronic pain conditions, including migraine headache, FM (or chronic widespread pain), and chronic musculoskeletal pain.

Their results indicated that FM is the only type of chronic pain that could be associated with the COMT single-nucleotide polymorphism rs4680 (Val158Met), which results in the low-activity variant of COMT [11].

Besides the polymorphisms of the COMT gene, additional sympathetic nervous system-related genetic markers have been investigated in the search for FM-related genetic markers. Arg16Gly (rs1042713) and Gln27Glu (rs1042714), which encode polymorphisms of the β2-adrenergic receptor gene (ADRB2), have been shown to be associated with an increased risk of FM [12]. Similarly, β2-adrenergic receptor haplotypes, which affect the function of this receptor, have also been investigated in the context of chronic pain [13]. Moving beyond genetic markers of the sympathetic nervous system, additional candidate genes have focused on other neurotransmitter-related markers.

## Serotonin-Related Genetic Markers

The paradigm of central sensitization as a leading cause of increased pain in FM originally was supported by studies demonstrating an increase in CSF levels of pain-excitatory transmitters such as substance P, as well as a decrease in levels of pain-inhibitory transmitters such as serotonin and noradrenaline [14].

This paradigm attracted attention to genetic markers related to these neurotransmitters. Indeed, serotonin-related genetic variants were among the first targets studied. These included the 5-hydroxytryptamine receptor 2A, which is encoded by the HTR2A gene as well as the 5HT transporter (5HTT, or sodium-dependent serotonin transporter, encoded by SLC6A4 gene) [15].

An insertion/deletion polymorphism in the SLC6A4 gene has been shown to be associated with an increased risk for the development of FM and chronic pain, while an increased frequency of the S/S genotype of the 5HT transporter gene has been discovered among FM patients [16, 17].

## Genetic Markers Associated with Dopamine Receptors

Dopamine is another multi-tasking neurotransmitter with multiple and crucial roles throughout the central nervous system [18]. Among its many roles, dopamine also plays a role in the processing of pain [19, 20] and has been hypothesized to play a role in FM [21, 22]. In view of this background, dopamine-related genetic markers have been among candidate genes studied in FM. The dopamine D4 receptor exon III repeat polymorphism has been shown to be significantly decreased in FM patients [23]. This finding was also associated with a particular personality type and was suggested by the authors as a possible pathogenetic contributor.

The largest candidate gene study to date has been published by Smith et al. [24], who compared 496 FM patients to 348 controls. Using a dedicated gene array chip, these researchers analyzed over 350 genes based on candidate analysis. Three genes were found to have significant differences between FM patient's and controls: *GABRB3*, *TAAR1*, and *GBP1* while a replication study found four genes—*TAAR1,*

**Table 10.1** Examples of FM-related SNPs and genes

| SNP | Gene |
|---|---|
| rs4680 [25] | *COMT* |
| Intronic CNV [26] | NRXN3 |
| 5-HTTLPR [3] | SLC6A4 |
| rs1048101 [27] | HTR2A |
| rs11127292 [26] | MYT1L |

*RGS4, CNR1*, and *GRIA4*. Notably, *CNR1* gene codes for the CB-1 cannabinoid receptor, which may play an important role in pain transmission. Thus, this broad candidate gene approach was able to identify a previously unexpected potential marker of FM.

Table 10.1 lists some of the specific SNPs which have been found in genes related to FM.

## Studying FM through Genome-Wide Association Studies

Genome-wide association studies (GWAS) studies would appear to provide another level in the search for genetic markers in FM, not being dependent on candidate genes. Using a family-based design, Arnold et al. were able to identify linkage at specific regions on chromosome 17p11.2–q11.2, coinciding with two possible FM genes. These included *SLC6A4* (serotonin transporter gene) and *TRPV2* (transient receptor and the vanilloid channel 2 gene). Notably, *SLC6A4* polymorphisms had previously been found to be associated with another chronic pain condition—temporo-mandibular joint disorder (TMJD) [28], while TRP channels are considered to be key transducers in nociception [29]. Another extensive study using GWAS and evaluating copy number variations (CNV) focused on 313 FM patients with few comorbidities who were compared with 220 healthy controls [26]. In this study, using a replication analysis, the researchers identified an intronic deletion in *NRXN3,* which is a gene considered to play an important role in development of the nervous system, which was in association with FM in female patients. rs11127292, another nervous system-related SNP, was also identified, implying a linkage between genetic background and nervous system development in FM.

## Genome-Wide Expression Profiling

Kim et al. have shifted from the traditional efforts to identify genetic predisposition to FM toward the approach of looking at gene expression—as a way to both identify an objective biomarker for FM and explore the possible roles of specific alterations in gene expression in the pathogenetic process [30]. Using this approach, they analyzed mRNA from 70 FM patients and 70 controls. The results indicated that

FM patients showed differential expression of 421 genes including genes relevant for pain processing (e.g., glutamine/glutamate) and axonal development. They further demonstrated upregulation of inflammatory pathways and downregulation of pathways related to hypersensitivity and allergy. Finally, this study was able to achieve a diagnostic sensitivity of 95% and a specificity of 96% for the diagnosis of FM.

## MicroRNA Signature

MicroRNAs, which are short, noncoding RNA molecules, play diverse roles in regulation of gene expression in many different biological processes, including response to stress, growth, and differentiation [31].

MicroRNAs play an important role in development of the CNS and in response to stress [32]. Several studies have focused on comparing microRNA profiles in FM patients and healthy controls [33, 34]. Liquid biopsies obtained from serum or saliva have been in order to identify six different microRNA signatures among FM patients [35]. MicroRNAs have thus become key factors in comparing FM patients to controls, with many recent studies attempting to identify such potential biomarkers in FM, creating both a CSF microRNA profile for FM [33] and a circulation microRNA profile [34]. Specific microRNA markers were also found to be associated with specific aspect of FM such as pain threshold and sleep [36]. microRNA expression thus appears to be a promising field for further subgrouping and diagnosis of FM.

## Epigenetics of Fibromyalgia

The traditional view concerning the pathogenesis of FM has envisioned a genetic matrix an individual inherits at the time of conception, determining a certain level of predisposition, which subsequently can be modulated and affected by the impact of various triggers to which the individual is exposed throughout life. In this way of thinking the end result (the development of clinical FM) is the result of an interaction between genetic and environmental factors. In fact, as has become increasingly evident over time, environmental factors can lead to changes in genetic material and in its expression. This field of epigenetic research thus blurs the distinction between genetic and environmental and actually offers a new way of understanding how environmental triggers change the way our genes work. This is particularly important in understanding the way in which remote life events, such as childhood adversity, can ultimately have a pathogenetic role in FM.

Three main epigenetic processes have been described in this context, which include DNA methylation, histone modifications, and miRNA expression.

## DNA Methylation Studies in FM

In the process of DNA methylation, a methyl group is added to cytosine residues of DNA, forming 5-methyl-cytosine through the activity of specific enzymes [37]. The application of genome-wide DNA methylation analysis to the study of FM has demonstrated 69 differentially methylated sites, including genes such as BDNF and other genes which may be relevant for neural development and function [38]. A subsequent study identified 1610 differentially methylated genes among FM patients compared with controls, many of which could be linked to functions such as calcium signaling, ligand–receptor interactions, etc. [39].

Histone modifications, which change chromatin structure, can alter various biological processes, including DNA repair as well as gene translation and transcription [40]. Acetylation and deacetylation are among the histone modifications studied in chronic pain and inflammation [41]. No specific alterations in patterns of histone modification have so far been described in FM.

## Gene Expression Studies

Studying differential gene expression among patients and healthy controls is another emerging method for identifying pathogenetic changes in FM. In one large such study, Jones et al. were able to identify 482 differentially expressed genes in FM patients among which were upregulated genes of cytokines such as IL-10, IL-25, and IL-36A [30]. Using a somewhat different approach, Iacob at al. have studied RNA gene expression from FM patients, comparing them to healthy controls, patients with depression, and patients with chronic fatigue syndrome (CFS), with or without comorbid FM. The results showed that the expression of candidate genes could be grouped into clusters, with CSF and depression associated with the same clusters but in opposite directions, when controlling for comorbid FM [42]. Thus, analysis of gene expression may serve as a tool for patient subgrouping and as a potential biomarker.

## Conclusion

As the field of medical genetics moves forward into ever-increasing technological progress, complex conditions such as FM are prime candidates for reaching hitherto unexpected insight and clarification. In view of the elusive nature of FM, including the ongoing skepticism regarding its very existence, such insight is particularly important in order to replace vagueness with precision, in order to improve the subclassification and diagnostic endeavor, and ultimately of course in order to reach rational and patient-specific treatment. Despite all progress made, these last

promises have so far not been fulfilled and the management of FM remains empiric and non-specific. The future, however, points toward the necessity of cooperation between geneticists, clinicians, and experts from other fields, such as neuroscientists, in order to achieve true breakthrough in the field of FM.

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# Chapter 11
# The Clinical Spectrum of Fibromyalgia and Its Treatment: An Overview

**Jacob N. Ablin and Shai Shtrozberg**

## Overview of the Approach to Treatment

FMS is a clinical constellation that consists of a vast spectrum of symptoms, often presenting in various degrees of severity. While specifically characterized and defined by the presence of chronic widespread musculoskeletal pain, it is simultaneously accompanied by a broad array of additional somatic symptoms as well as by multiple comorbidities. Among these, sleep disturbances and fatigue, as well as cognitive and psychiatric disturbances, play a central role [1–3]. Tenderness in multiple soft tissue anatomical locations, although no longer constituting the diagnostic prerequisite, can typically be demonstrated on physical examination. Unfortunately, the diagnosis of FMS remains one which is completely predicated on subjective symptoms, lacking so far reliable biomarkers, thus challenging physicians and the patients alike [4].

Despite increased interest and understanding of the mechanisms behind FMS, hitherto no gold standard of treatment has evolved. Treating FMS remains a complicated and frustrating journey. Notably, over recent years the therapeutic stratagem has tended to shift away from pharmacotherapy, due to the relatively disappointing real-life results encountered with the existing agents. While evidence shows that some patients can significantly improve with specific pharmacological treatments, many patients suffer a chronic, albeit undulating, trajectory, which in some cases may appear refractory to any effect from approved treatments [5].

On the other hand, some patients will improve to a surprising extent; in fact, as demonstrated by Walitt et al. [6], up to three-quarters of individuals previously diagnosed with FMS can be expected *not* to fulfill diagnostic criteria when examined at

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another point in time. To what extent this finding is the result of misdiagnosis or true improvement (or both) remains debatable. Nonetheless, FMS patients can improve, and patients in primary care appear to have a better prognosis than those referred to specialized centers [7]. Unfortunately, it appears to be very difficult to "copy–paste" therapeutic triumphs from one patient to the next, since each case calls for a very personal and tailor-made approach; thus, FMS is the ideal area for the introduction of personalized medicine.

After the introduction of the first three FDA-approved medications for FMS (pregabalin, duloxetine, and milnacipran), clinical data have shown that only a relatively small proportion of patients attain significant and ongoing benefit from these agents [8]. While one may have anticipated the further approval of "me-too" agents such as additional SNRIs and anticonvulsant agents, as often seen after the introduction of first-in-class medications in other conditions (e.g., SSRIs for depression, anti-TNFα for inflammatory rheumatic disease), no such process has been observed in the field of FMS. This has focused increasing emphasis on the role of nonpharmacological modalities, including neuromodulatory techniques, a change which is gradually being incorporated into practice guidelines [9].

## Evaluation and Patient Education

The clinical hallmark of FMS remains the presence of chronic, widespread pain. While FMS is often considered to be notoriously difficult to diagnose, and in fact many patients continue to go undiagnosed and undergo unnecessary investigations for extended periods of time, it is not difficult to contemplate the correct diagnosis in any patient who presents with aching pain throughout the musculoskeletal system lasting for months and years. The recognition that pain must be widespread in order to qualify for a diagnosis of FMS has been reaffirmed in recent diagnostic criteria [10].

Nonetheless, it is important to understand that FMS goes way beyond pain *per se* and encompasses an extremely broad array of additional symptoms, including chronic fatigue, disturbed sleep, and cognitive difficulties [1, 11].

Alongside these symptoms, many patients present with other comorbidities, including systemic inflammatory or metabolic disorder, as well as with localized, presumably nociceptive-based, pain syndromes. Therefore, treatment must be individualized and tailored to each patient's specific symptom profile. In most cases, treatment is multidisciplinary and includes both nonpharmacological aspects and drug therapy. It is important to note that some patients, in particular those who do not suffer from a coexisting mood or sleep disorder, may respond to a treatment consisting of nonpharmacological measures alone. While some patients may encounter the physician with an expectation to receive a prescription for medications, many may find the nonpharmacological approach more agreeable and less anxiety-provoking, particularly after being provided with adequate education.

The importance of creating a multidisciplinary treatment regime, including patient education, exercise, psychological treatment (mainly CBT), counseling, and other interventions, has currently been extensively documented in systematic reviews and meta-analyses [1, 12–15].

Many FMS patients have gone through extensive medical diagnostic evaluation and tests before a final diagnosis was made. It is widely agreed that patient education and engagement during decision-making have a beneficial effect on the patient's well-being [16, 17]. Comprehensive patient education leads to reduced anxiety and pain levels, with higher rates of improvement [17]. It is therefore crucial to address several key points when teaching the patient about the disease: the mechanism and pathogenesis of the syndrome (and of centralized pain in general), the importance of addressing coexisting mood and stress disorders, the efficacy of exercise and weight reduction (in overweight patients), the role of sleep disorders and sleep hygiene, the prognosis, and the legitimacy of the diagnoses. Obviously, this information must be conveyed with patience and empathy and in comprehensible terms.

## Pharmacological Treatment

Only three drugs, pregabalin (a gabapentinoid that acts by blocking calcium channels), duloxetine, and milnacipran (both serotonin-noradrenaline reuptake inhibitors), have been approved for use in the treatment of FMS by the US FDA. However, other types of antidepressants are used for the treatment of various chronic pain syndromes, including FMS, with varying levels of evidence regarding their efficacy.

Research regarding FMS pathophysiology has focused on the role of a decrease in the efficacy of inhibitory control, i.e., a reduced capacity of the central nervous system to achieve pain inhibition (mainly at a spinal level) in response to the sensation of painful stimuli. This so-called reduced conditioned pain modulation (CPM), previously termed diffuse noxious inhibitory control (DNIC), is associated with a decrease in the CNS levels of pain-inhibitory neurotransmitters such as serotonin and noradrenaline [18].

This observation called attention to the possibility of improving pain inhibition using agents capable of increasing CNS levels of these neurotransmitters, i.e., SNRIs as well as tricyclic agents [19].

Considering these findings, tricyclic antidepressants were proposed for FMS patients, independently of their traditional use for mood disorders. Because of their efficacy, availability, and affordability, even now patients who are willing to try pharmacological treatment will often start out with a trial of a low-dose (bedtime) tricyclic agent such as amitriptyline.

For patients with severe fatigue or depression, an SNRI agent may be considered as initial treatment, while for patients who suffer from severe sleep disturbances, an anticonvulsant from the alpha-2-ligand group (either pregabalin or gabapentin) may initially be preferred.

The use of SNRIs and/or anticonvulsants may also be added when patients fail to respond to initial therapy with tricyclic agents. Each drug is administered for at least 3 months, provided there are no side effects, slowly increasing its dose, before switching to other agents. Efficacy over placebo of the three medications has been tested and demonstrated; however, few direct comparisons between the three have been reported [20, 21].

## Initial Treatment (Tricyclic Antidepressants)

For first-line treatment with tricyclic antidepressants such as amitriptyline, initially a low dose (5–10 mg) should be administered before bedtime. The final dose should be set according to the patients' reported side effects and efficacy and kept as low as possible, with a dose of 20–30 mg generally adequate for most patients. For patients who respond to amitriptyline, its use can be continued for at least 12 months—for some indefinitely, while some patients can be weaned off. Tachyphylaxis may also occur. The comparative efficacy vs. side effect profile of amitriptyline has been documented in several reviews and meta-analyses [21, 22]. Clinically important improvement was found in 25–24% of patients (compared with 0–20% treated with placebo), with a tendency for efficacy to decrease over time [20]. While side effects of low-dose amitriptyline are relatively mild (e.g., constipation and dry mouth), safety must be carefully considered, particularly in elderly patients and those with cardiac comorbidities.

Cyclobenzaprine, a non-antidepressant, muscle relaxant with a structure similar to amitriptyline, is frequently considered an alternative initial treatment for FMS. While the use of very-low-dose cyclobenzaprine has been investigated for this indication, results have been disappointing and thus the agent is usually prescribed at the standard doses starting at 10 mg/day [23].

## SNRI

Serotonin-norepinephrine reuptake inhibitors (SNRIs), also referred to as dual reuptake inhibitors, include milnacipran, duloxetine, and venlafaxine. Both milnacipran and duloxetine are FDA approved for FMS and have demonstrated efficacy over placebo in randomized controlled trials [24–28]. As earlier mentioned, SNRIs are preferred as first-line treatment for FMS for patients who exhibit severe fatigue or depression, or for those unresponsive or intolerant to amitriptyline.

The preferred starting dose of duloxetine for FMS is 20–30 mg, taken at breakfast. The dose can increase up to 120 mg/day. Duloxetine was shown to reduce pain levels [29] and mental fatigue [28]. The most common side effects are nausea,

headache, and dry mouth, which usually occur within the first 3 months of therapy. The preferred starting dose of milnacipran is 12.5 mg, taken at breakfast, and can gradually increase to 100 mg twice daily. Milnacipran improves global well-being and physical function, with increased pain relief [24–26]. Most common side effects include headache, constipation, and nausea.

## Anticonvulsants

The alpha-2-ligands (also termed alpha-2/delta [α2δ] channel modulators)—gabapentin and pregabalin—are used for conditions causing chronic pain, including FMS. Their analgesic effect is derived from the ability to block the release of relevant neurotransmitters [30]. As mentioned above, they are preferred over other agents in patients suffering from severe sleep disturbances. Alpha-2-ligands were shown to reduce pain levels and improve quality of life and sleep [31].

Pregabalin is started at a dose of 25–50 mg taken at night, which can be titrated up to 450 mg/day. Randomized trials and systematic reviews have shown efficacy over placebo [31–33]. Pregabalin was shown to reduce pain and improve sleep, fatigue, and quality of life [30]. Common side effects include weight gain, dry mouth, somnolence, and peripheral edema.

Evidence is limited for the use of gabapentin for FMS. It is used as an alternative for pregabalin (mainly because of its lower price). Starting dose is 100 mg at bedtime and can increase gradually toward 2400 mg (taken up to three times a day). Evidence supporting gabapentin's efficacy and safety is scarce [34], and more research is needed warranted.

## Cannabinoids

Cannabinoids in general and cannabis in particular continue to attract a great deal of attention both by patients and by the medical community as a possible remedy for FMS (and other forms of chronic pain). Nonetheless, evidence-based data regarding the safety and efficacy of these compounds remain limited and most guidelines refrain from addressing this matter.

Numerous anecdotal indications, as well as theoretical frameworks, support the use of cannabinoids in FMS, both to alleviate pain and to improve sleep [35]. Moreover, there is currently no consensus regarding the question *which* cannabinoid or cannabinoids are optimal for FMS, i.e., THC, CBD, or any given combination. Further research is needed to demonstrate cannabinoids' efficacy and safety in FMS, as well as in order to understand the mechanisms through which cannabinoids may modulate FMS symptoms.

## Analgesics and Opioids

As the main clinical manifestations of FMS are spontaneous pain, hyperalgesia, and allodynia [36] , patients naturally turn to the use of analgesics. However, research shows their efficacy is poor.

In a recent review [37] on the use of NSAIDs in FMS, their efficacy was low. The use of acetaminophen was proven effective (mainly for short-term use) only in combination with tramadol—a weak opioid with 5-HT and norepinephrine reuptake inhibition activity [38].

The use of strong opioids in FMS is highly discouraged for more reasons than one. Besides the well-known hazards of addiction and overdose, research has pointed toward the possibility that opioids may be specifically deleterious in FMS, through the exacerbation of opioid-induced hyperalgesia [39]. Furthermore, FMS patients on opioids have poorer outcomes than those not taking opioids [40]. These lines of evidence have in fact led researchers toward the opposite path—the use of *opioid antagonists* such as naltrexone for treating FMS. If used at low doses, naltrexone has been shown to have a neuroprotective effect (acting as a glial modulator, inhibiting microglial activation). Furthermore, it elicits the so-called rebound effect of opioids, since a transitory block of the opioid receptor increases opioid endogenous production [41].

## Nonpharmacological Treatments

### *Physical Exercise, Physiotherapy, and Hydrotherapy*

By far the most evidence-based treatment for FMS, low impact aerobic cardiovascular training is recommended for all FMS patients [12, 15, 42], with even modest increases in daily physical activity having a beneficial effect of function [43]. Exercise can have a significant effect on reducing pain levels, improving sleep, and increasing daily function [44]. It is important to educate patients about this aspect and advise them to begin physical activity gradually, with incremental increases according to exercise tolerance. Subsequently, the type and intensity of the regime should be tailored according to preference and other comorbidities. Low impact aerobic activities such as swimming, fast walking, and biking are most successful among interventions [12, 14, 15]. Optimal training should last for a minimum of 30 min, three times a week; however, any physical activity is recommended, as most patients cannot achieve this target and should be encouraged to start with low doses of exercise. For patients who struggle to achieve a sufficient aerobic exercise regime, participation in a physical exercise program is recommended. Patients that have continued difficulties with exercise can be referred to a physical therapist for evaluation and assistance in improving physical functioning.

Water-based therapies (hydrotherapy and spa therapy) can be effective [42, 45] and have shown to improve pain and functional capacity in some patients. Considerable research has recently been aimed at elucidating mechanisms of exercise-induced analgesia, which unravels complex mechanisms [46].

### *Role of Movement-Meditative Therapy*

While many different alternative or complementary treatments are routinely offered to FMS patients, based on relatively meager evidence, relatively positive results have been demonstrated in treatments which can generally be grouped under the headline of movement-meditative treatments. Recent studies have demonstrated the way in which such treatments can alter CNS pain processing in FMS patients, thus adding a theoretical foundation for previously observed clinical benefits.

### *Tai Chi*

Tai chi, a Chinese martial art, practiced both for meditation and for health benefits combines gentle, flowing moving exercises with mind–body practice. It has shown to be beneficial for FMS symptoms, even when compared to aerobic exercise and other educational interventions [47, 48]. In these trials, tai chi improved pain levels and functional mobility. Similar results may be attainable with other movement-meditative treatments such as qigong.

Intriguingly, recent research is beginning to demonstrate that movement-meditative treatments such as tai chi can alter CNS functional connectivity in FMS while eliciting clinical improvement [49].

### *Psychological Treatment*

For patients with symptoms refractory to initial therapy, a multidisciplinary treatment is usually recommended, combining as best possible education, exercise, pharmacological treatment, and psychological treatment. Such treatment should be tailored to individual needs, availability, and preferences [50, 51]. The treatment often includes a referral to specialists for psychological interventions such as cognitive behavioral therapy (CBT). CBT is predicated on the assumption that patients suffering from chronic pain conditions such as FMS often tend to develop or acquire negative cognitive patterns, such as pain catastrophizing, as well as negative behavioral patterns, such as over-exertion during the occasional “better days”; these patterns are relatively easy targets for CBT, which can teach patients to identify them

and to adopt alternative ways of thinking and acting. The benefits of psychological interventions, and specifically CBT in FMS patients, are widely supported [52]. The treatment of CBT in FMS patients has proved to be more cost-effective than the use of pregabalin and duloxetine [53]. Further mind–body measures may be effective in FMS patients, including behavioral treatments, practicing mindfulness, biofeedback, and more [54].

## Neuromodulation

Since the basic pathogenesis of FMS is considered to result from an alteration in the way the CNS processes pain, i.e., the occurrence of neuroplasticity [55], it is tempting to consider that neuroplasticity may also be attainable in the other direction. Thus, various methods are alternatively used in an attempt to achieve such neuromodulation by nonpharmacological means.

Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are noninvasive forms of brain stimulation that have shown therapeutic potential in a wide variety of neurological psychiatric disorders. While further research is necessary, preliminary data show promising results for these modalities in FMS [56].

## Hyperbaric Oxygen

Another promising therapy for FMS and other chronic pain syndromes is the use of hyperbaric oxygen (HBOT) or the use of oxygen in a mixture with ozone (O2O3). In this procedure, the intermittent breathing of 100% oxygen creates an anti-inflammatory effect, through the reduction of production of glial cells and inflammatory mediators [57]. This process results in pain alleviation in various chronic pain conditions. It can also influence neuroplasticity and affects the mitochondrial mechanisms resulting in functional brain changes. In addition, HBOT stimulates nitric oxide (NO) synthesis which helps in alleviating hyperalgesia and NO-dependent release of endogenous opioids [58]. Several studies have currently demonstrated salutary effects of HBOT in FMS, some focusing on particular subgroups of patients, such as patients who developed FMS after childhood trauma or other triggers [59]. The long-term role of HBOT in the treatment of FMS, as well as the precise regimen, remains to be determined.

## Neurofeedback

New frontiers in the treatment for FMS are underway, and neurofeedback is one of these treatments. Neurofeedback is a version of biofeedback, which teaches self-control of brain functions to subjects by measuring brain waves and providing a

feedback signal (either by audio or by video). Positive or negative feedback is produced for desirable or undesirable brain activities, respectively. The power of neurofeedback is currently harnessed to achieve neuromodulation in FMS patients, with the potential of achieving significant improvement in various clinical domains including pain and sleep [60].

## Conclusion

As our understanding of the essence of FMS continues to expand, novel therapeutic options, such as methods of neuromodulation, emerge. At the same time, we gain insight into the scientific basis for the effectivity of ancient methods such as movement-meditative treatments and the way they affect our physiology. Thus, the science and medicine of FMS continue to evolve as a paradigm for tackling medical complexity. Future breakthroughs, in fields such as AI and genetics, will doubtless lead to additional fields of research and treatment. Until then, the multidisciplinary treatment of FMS remains one of the more challenging and intriguing fields on the art of medicine.

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# Chapter 12
# The Functional Syndromes as Fibromyalgia Comorbidities

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## Introduction

Fibromyalgia (FM) is a condition characterized by chronic widespread pain (CWP) associated with sleeping and cognitive disorders, fatigue, and many other symptoms which alter the quality of life [1].

Its diagnosis can be difficult due to the unavailability of specific diagnostic markers, and the symptom of CWP can be also found in other conditions. For years, the American College of Rheumatology (ACR) classification criteria published in 1990 have been used in clinical practice. These criteria required the presence of CWP for at least three consecutive months on both sides and on the superior and inferior part of the body, in addition to the positivity of at least 11 out of 18 specific points on the body resulting tender on palpation [2]. It is clear how the ACR 1990 criteria were focused only on the concept of peripherical pain [3].

The most recent ACR 2010 classification criteria define CWP as a condition associated with other systemic and somatic symptoms such as fatigue, sleeping, and cognitive disorders, and require the use of the widespread pain index (WPI), the evaluation of the number of painful body areas, the assessment of the somatic symptoms, and a somatic symptoms scale to evaluate the severity of these symptoms, in particular with regard to fatigue, sleeping, and cognitive alterations [4, 5].

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Therefore, these ACR 2010 criteria switch from the concept of FM as a "peripheral pain-defined disease" to a "systemic symptom-based disease" [3].

The formulation of new classification criteria is based on the concept that the fibromyalgia syndrome (FMS) is not only a condition characterized by peripheral chronic pain but also a more complex clinical condition. If on the one hand the ACR 1990 classification criteria risked to underestimate its diagnosis, on the other hand the new criteria conversely risk to overestimate it, defining as FM also other conditions included within the functional somatic syndromes (FSS) [6]. However, FMS itself belongs to the wide category of FSS with whom frequently is associated and shares part of the etiopathogenetic hypotheses. Some authors also consider FMS as the "whole-body variant" of FSS [6].

FSS are clinical conditions where the typical symptoms of each syndrome are always accompanied by chronic pain. Amongst them, in addition to FM, there is the irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS), vulvodynia, interstitial cystitis, chronic migraine, temporomandibular disorder, chronic lower back pain, chronic pelvic pain and all those conditions characterized by the presence of not clinically justifiable chronic pain. In fact, in this context pain is not supported by clinical or laboratory abnormalities, peripheral tissue alterations, or alterations of those peripheral nerves involving the body areas where the patient reports pain [7].

However, pain is not the only key symptom they have in common, and other symptoms are fatigue, sleeping disorders, cognitive problems, physical dysfunction, and affective disorders (i.e., anxiety, anger, depression) [8].

Moreover, several disorders belonging to FSS are frequently associated with each other in the same individual, and some authors define these as "chronic overlapping pain conditions" (COPCs)" [8, 9].

FMS, in addition to be frequently associated with other FSS and sharing some of their characteristics, also shares with them several etiopathogenetic hypotheses, including the concept of central sensitization. Some authors, such as Yunus, prefer the definition "central sensitivity syndromes" (CSSs), underlining the pathogenetic role undertaken by "central sensitization" [10] a condition which has been operationally defined as heightened generalized pain sensitivity due to pathological nociceptive processing within the central nervous system (CNS). The concept that CSSs are associated with FMS is based on the fact that they: (a) cluster in the same patient groups more frequently than in an appropriate control group; (b) share many clinical features; (c) are not associated with microscopic or macroscopic tissue damage; (d) respond to a similar group of centrally acting medications; and (e) share similar central and neuroendocrine alterations.

However, although central sensitization appears to have a key role as a pathogenetic mechanism, it does not seem to be the only one involved.

## Pathogenesis

From a pathogenetic point of view, many authors justify the occurrence of FSS through the biopsychosocial model [8], where multiple generic factors, if associated with environmental exposures (such as injuries, infections, physical and

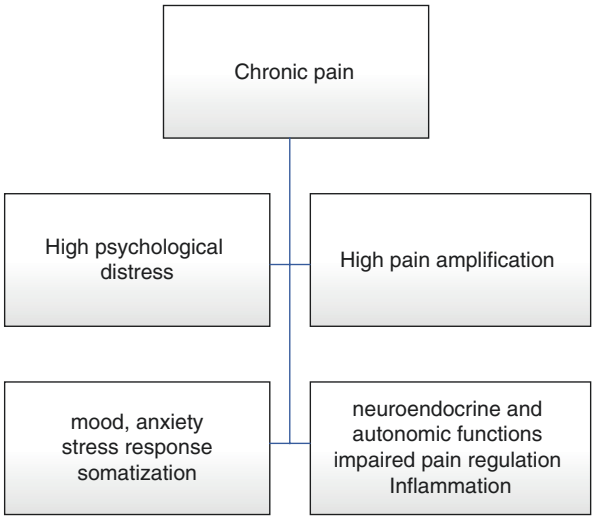


**Fig. 12.1** Chronic pain and risk factors

psychological trauma), increase the susceptibility to FFS through heightened sensitization to pain and/or through impaired psychological vulnerability [7, 8, 11] (Fig. 12.1).

## *Genetic Predisposition*

Pain and cognitive and affective responses associated with it are regulated by physiological processes. Subjects developing a pain hypersensitivity mechanism and having a psychosocial vulnerability to pain itself appear to have a genetic predisposition. This predisposition would be determined by polymorphisms affecting genes involved in the synthesis of proteins responsible for regulating pain and the affective response connected to it. When this genetic predisposition interacts with environmental factors such as physical or emotional stress, leads to the phenotype that is vulnerable to the development of FSS.

Examples of genes involved in pain sensitivity include the adrenergic receptor β2 [12], catechol-O-methyltransferase [13–15], dopamine D4 receptor [16], guanosine-5′-triphosphate cyclohydrolase 1 [17], μ-opioid receptor [18, 19], and serotonin transporter [20]. However, these genes are also involved in those mechanisms regulating the emotional sphere. In fact, certain polymorphisms affecting them are also associated with a greater risk for the development of psychological disorders such as depression [12, 21, 22], anxiety [12, 23], and stress response [24–26].

This suggests that the emotional sphere and the mechanism of pain transmission share some mechanisms and this would explain the association that is often found between psychological/psychiatric disorders and chronic pain syndromes. For example, the single nucleotide polymorphism of codon 158 (Val $^{158}$Met) of the catechol-O-methyltransferase gene is associated with pain amplification [27], risk

of developing TMD [14] and FM [28], as well as to develop certain affective disorders [29]. The common polymorphisms in the serotonin transporter gene promoter are associated with depression, susceptibility to stress [30], anxiety [31], somatization, and risk of TMD [32].

However, it should be stressed that a variation of a single gene is not considered necessary or sufficient to determine a genetic predisposition for the development of one or more FSS, but necessary is the association of polymorphisms affecting multiple genes [8].

## *Psychosocial Factors*

The increased psychosocial vulnerability represents an additional risk factor for the development of FSS. In fact, many patients tend to have anxiety disorders, depression, and increased susceptibility to stress [8]. Patients with Fibromyalgia syndrome have a higher prevalence of psychiatric disorders than the general population, such as anxiety and mood disorders. This increased prevalence has been also found in other syndromes associated with chronic pain [33]. A 2004 study observed, in fibromyalgia patients with anxiety disorder, a strong association with symptoms attributable to post-traumatic stress syndrome and sexual or physical abuse, while fibromyalgia patients with mood disorders (first of all depression), showed affective disorders [33].

Psychosocial factors also seem to be involved in other FSS, such as irritable bowel syndrome [34], chronic low back pain [35], or temporomandibular syndrome [36]. In fact, there is evidence in favor of a link between the experience of abuse in childhood and the development of conditions characterized by chronic pain [37–41].

In this context, the so-called "sensitization hypothesis" was formulated. According to this hypothesis, individuals who experienced traumatic experiences in childhood, subsequently present more intense responses to stress factors [42], partly also due to a dysregulation of the Hypothalamic–pituitary–adrenal (HPA) axis in response to stress [43]. Furthermore, childhood adversity is assumed to be related to "pro-inflammatory tendencies," a condition that continues to sustain itself throughout life, representing a risk factor for the development of chronic painful conditions [44, 45]. Childhood adversity is also associated with the manifestation in adulthood of cognitive disorders of various extent [46, 47]. For instance, abuse by parental figures is associated with a state of hypervigilance which can favor the development of states of cognitive distortions, altering in turn the pain sensitivity threshold [48, 49].

## *Environmental Factors*

Patients who develop FSS generally report an acute event during their lives preceding the onset of a chronic pain syndrome. Physical stress such as surgeries, physical injuries, or road accidents have been described as precipitating factors in patients

with FM [50]. In patients with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), the most frequent acute events preceding the onset of CFS/ME are: infectious episodes (64%) mainly affecting the respiratory tract and more frequently caused by herpes virus and parvovirus B19, accidents (39%) and exposure to environmental toxins (20%) [51].

As previously mentioned, an association between emotional trauma caused by psychological, physical, or sexual abuse and the risk of developing FSS has been also observed. A meta-analysis reported a risk 2.7 higher of developing an FSS in subjects who underwent emotional trauma compared to subjects who did not suffer from it [52].

## *Increased Sensitisation to Pain*

The increased sensitization to pain seems to be a distinguishing feature of FSS [10]. However, it is not clear yet whether it represents a determining factor in the onset of one of the FSS or if it is a maintenance mechanism consolidating the chronic and persistent perception of the painful experience [8]. The results of a study aimed at assessing chronic pain in patients who develop a temporomandibular disorder suggest that the amplification of pain plays a more relevant role in maintenance and chronicization than in the onset of FSS [53]. Central sensitization (CS) manifests with the presence of hypersensitization of the subject to various types of stimuli, both harmful (such as pressure and heat) and non-harmful, such as touch [54]. In other words, the subject presents hyperalgesia (excessive sensitivity to normally painful stimuli, such as pressure), allodynia (pain to usually painless stimuli, such as touch), spatial extension of pain (pain is felt in larger areas than the terminations nerves involved in the stimulus), temporal extension (the painful impulse is transmitted longer), and finally the persistence of unpleasant sensations such as numbness or tingling after the painful stimulus has been removed [10].

This situation is determined by an abnormal and intense “enhancement” of pain caused by the central nervous system (CNS) [54].

Physiologically, the presence of harmful stimuli determines the activation of peripheral nociceptors, expressed both viscerally and somatically [55]. The generated nociceptive signal reaches the dorsal horns of the spinal cord via the A-delta and C fibers, where the second-order neurons are present. The A-delta fibers transmit acute, pungent, and well-localized pain (primary pain), while the slower C fibers transmit a less localizable and deeper pain sensation (secondary pain), and are involved in chronic pain. Second-order neurons are of two types: nociceptive specific (NS), which respond specifically to painful stimuli, and those with wide dynamic range (WDR: Wide Dynamic Range), which respond to stimuli of varying intensity. In fact, the latter integrates impulses from A-delta and C fibers, but also from A-beta fibers which transmit non-nociceptive impulses [54]. In the presence of intense activation of nociceptive fibers, the surrounding non-nociceptive fibers can also be activated, which are usually stimulated by the A-delta fibers. In this way, a painless stimulus, such as touch, is perceived as a painful sensation [10].

Second-order neurons transmit the stimulus to the thalamus, hypothalamus, limbic system, and finally to the somatosensory cortex. These supra-spinal structures are involved in the elaboration of the different dimensions of pain such as sensory, evaluative, and affective dimensions [55–57].

Once activated, the nociceptive C fibers, in correspondence with their terminal afferent portion in the dorsal horns of the medulla, release a series of neurotransmitters/neuromodulators such as substance P (SP), glutamate, and the nerve growth factor (NGF). These substances interact with receptors on post-synaptic second-order neurons, leading to their activation. For example, SP activates the Neurokinin-1 (NK-1) receptor, glutamate activates the *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate (AMPA), and metabotropic glutamine (mGlu) receptors, while NFG activates the tyrosine kinase B receptor.

Some of these substances and receptors seem to be involved in the CS mechanism. Amongst these, SP is believed to play an important role. In the presence of CS, SP, which is involved in the mechanisms of transmission and amplification of pain, recruits also silent receptor structures present on second-order neurons, leading to their hyperexcitability. In addition, SP can spread causing the activation of other adjacent neurons, leading to an anatomical expansion of the painful area [55–57]. Therefore, the excessive release of SP and other neurotransmitters such as NFG and glutamate in the synaptic space determines the hyperexcitability of second-order neurons [57]. This neuronal hyperexcitability is at first functional, with time causing neuroplasticity, and as a final result leading to an excessive amplification of peripheral stimuli. Consequently, a harmless stimulus such as touch is perceived as pain. Amongst the post-synaptic receptors, those mainly involved in these mechanisms seem to be NMDA [57].

Dopamine also appears to play a role in amplifying nociception in CS. It has two opposite functions in the context of neuronal excitability: On the one hand, it has an excitatory effect if binding to D1-like receptor structures, whereas, on the other hand, it has an inhibitory effect if binding to D2-like receptors. To reinforce the hypothesis of a role of dopamine in CS, the results of a double-blind study reports that piraxone (D2-like receptor agonist drug) has shown positive effects in fibromyalgia patients [58].

In addition to the hyperexcitability of the ascending pathways responsible for the transmission and processing of pain, an inhibitory mechanism of the pain inhibitory descending pathways also appears to have a role, which is the physiological task of modulating and attenuating the physiological stimulus [59].

In summary, in the presence of CS, there is a general hyperexcitation of the CNS neurons responsible for the transport of peripheral stimuli. This general hyperexcitation can also explain hypersensitivity to many environmental (i.e., noise, weather, stress) and chemical (i.e., pesticides and drugs) stimuli. With time, due to neuroplasticity phenomena, CS becomes self-sufficient without further stimuli, and it is probably accentuated by the presence of chronic diseases [54]. Hence, initially harmful stimuli may increase neuronal sensitivity to a level where further stimuli, even non-harmful, may be sufficient to support and perpetuate hyperalgesia and

allodynia [60, 61]. The affective dimension of pain, such as unpleasantness and emotional reactions, is mediated by spinal pathways toward the limbic structures, the medial thalamic nuclei, and by the anterior insular cortex, the anterior cingulate cortex, and the somatosensory cortical areas [62].

## Fibromyalgia and Functional Syndromes

The association between fibromyalgia syndrome and other FSS, or in general the mutual association between them, was observed as early as 1981 [63]. Below we analyze the association of fibromyalgia with the main FSS most often associated with this syndrome (Table 12.1).

### *Fibromyalgia and Irritable Bowel Syndrome*

Irritable bowel syndrome (IBS) is a fairly frequent and widely spread condition characterized by abdominal pain associated with alterations of the bowel function which cannot be justified by anatomical, structural, or metabolic alterations. Nonspecific symptoms such as nausea, bloating, flatulence, and fecal urgency are often present [64, 65]. The diagnosis is made when the Rome IV criteria for the diagnosis and treatment of functional gastrointestinal disorders are met. These define IBS as a condition characterized by recurrent abdominal pain (at least one day a week), present for at least 3 months, and related to at least 2 of the 3 following conditions: defecation, alterations in the frequency of the bowel function, alterations in the consistency of feces [66, 67].

The pathogenetic mechanism leading to IBS is not entirely clear, although the hypothesis of a dysregulation of the intestine–brain axis seems to be the most favored [68]. The dysregulation is probably multifactorial, with multiple elements contributing to the development of IBS: impaired intestinal motility, visceral hypersensitivity, alterations of the intestinal mucosa and of immunological functions, changes in the intestinal microbiota, and altered processing of the intestinal sensory input by the CNS [69, 70].

Numerous studies have shown an increased prevalence of IBD in patients with fibromyalgia [71, 72]. According to these results, other studies have observed a higher frequency of fibromyalgia in patients with IBD [73, 74].

Whitehead et al. reported a prevalence of fibromyalgia in patients with IBD of 32.5% (range: 28–65%) and a prevalence of IBS in patients with fibromyalgia syndrome of 48% (range: 32–77%) [75].

In a study conducted in Oslo aimed at studying a group of patients who reported food hypersensitivity, most of them presented with IBD, and extra-gastrointestinal symptoms indicative of fibromyalgia syndrome were found in 71% of these patients [72].

**Table 12.1** Fibromyalgia and functional syndromes

| Functional syndrome | Clinical picture | Prevalence | Symptoms/conditions shared with FM | Risk factors |
|---|---|---|---|---|
| Irritable bowel syndrome (IBS) | Recurrent abdominal pain (at least 1 day/week), for at least 3 months and related to at least 2 of the following conditions: defecation, change in the frequency of stool, alterations in the consistency of stool | From 32 to 77% | Sleep disorders, chronic fatigue, anxiety and/or depression as comorbidities | Stressful or traumatic events |
| Chronic pelvic pain (CPP) | Non-cyclical pain, for at least 6 months, involving the pelvic region, the anterior abdominal wall below the navel, and posteriorly the lumbosacral region, with an extent of the pain such to alter the quality of life | From 12 to 65% of FM patients complain of CPP, 44% of FM patients report vulvodynia, 48% pelvic floor hypertonicity | Comorbidity with anxiety and/or depression | History of abuse |
| Painful bladder syndrome/interstitial cystitis (PBS/IC) | Chronic condition of pelvic pain, pressure, or discomfort perceived in the bladder and with at least one urinary symptom such as urinary urgency or increased urinary frequency | From 11 to 17% of patients with PBS/IC have FM | Urinary urgency (UP) and urinary frequency (UF) scores significantly higher in FM patients than in controls | Urinary infections; inflammatory or autoimmune processes; abnormalities of the bladder mucosa; urinary toxins; local neurological dysfunctions |
| Temporomandibular disorders | Pain or dysfunction of the masticatory muscles, temporomandibular joint (TMJ), and/or related structures | From 10 to 18.4% | Sleep disturbances, cognitive problems, gastrointestinal disorders, and diffuse myalgias | Genetic polymorphism; physical or emotional trauma |
| Chronic tension-type headache (CTTH) | CTTH: Headache on ≥15 days/month for >3 months with episodes lasting from 30 minutes to 7 days and at least 2 of the following 4 characteristics: bilateral location; pressing quality; mild/moderate intensity; not aggravated by routine physical activity | | Low back pain | High intake of alcoholic beverages low level of education |

| | | | | |
|---|---|---|---|---|
| Chronic migraine (CM) | CM: Headache on ≥15 days/month for >3 months with attacks lasting 4–72 hours and at least 2 of 4 characteristics: unilateral location; pulsating quality; moderate/severe pain intensity; aggravation by physical activity | Ranges from 11.7% prevalence of FM (ACR 1990 criteria) in patients with CM from 11% to 22% prevalence of FM (ACR 2010 criteria) much higher (69.9%) in patients with CM than in those with CTTH (25.7%) | Low back pain cutaneous allodynia in patients with CM there was an association with anxiety disorder, depression, and somatic symptoms more frequently than in patients with CTTH, | Smoking, obesity |
| Multiple chemical sensitivity (MCS) | Symptoms involving multiple organ systems caused by low levels of exposure to multiple chemically unrelated substances<br>Symptoms improve when the chemical agents are removed | 16.7% of patients with chronic fatigue syndrome (CSF) met the criteria for all the three conditions. CFS/MCS/FMS | Fatigue, muscle and joint pain, headache, cognitive impairment, gastrointestinal problems high levels of anxiety, and depressive symptoms | Substances causing skin irritation, fatigue, fevers, neurocognitive dysfunction |
| Myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS) | Medically unexplained, new onset, disabling fatigue for at least 6 months, not relieved by rest and not resulting from overexertion and at least 4 symptoms as listed: sore throats; painful lymph nodes; muscle/joint pain; headaches; altered sleep; cognitive problems; post-exertional malaise of more than 24 h. | From 20 to70% of patients with FMS meet the criteria for CFS, 35–70% of those with CFS also have FMS | Pain fatigue sleep disorders irritable bowel syndrome chronic headaches cognitive impairment dizziness | Infections and physical and/or psychological stressors specific gene mutations |

Slim et al. [76] in their work focused the attention on the gastrointestinal symptoms reported by fibromyalgia patients, observing a high incidence rate of IBD among patients with FMS. In a national prospective cohort study, Yang et al. [71] compared 33,729 patients with FMS and 134,915 controls. During the follow-up period from 2000 to 2011, they found an overall incidence of IBS higher in FM patients than in patients without FM (7.47 vs. 4.42 per 1000 person/year), with an index of crude risk of 1.69 (95% CI 1.59–1.79). After adjustment for age, sex, and comorbidities, FM was associated with a 1.54-fold increased risk of IBS.

FM and IBS share numerous aspects: a predominance in women, the association with sleep disorders, chronic fatigue, anxiety, and/or depression as comorbidities [77]. Both disorders alter the quality of life of the affected patients and represent a major health care cost. Their onset is often associated with stressful or traumatic events, and they have similar therapeutic schemes such as psychotherapy, cognitive-behavioral therapy, and the use of antidepressant drugs [77, 78]. Both FM and IBS are categorized within the "central sensitivity disorders" (preferred terminology by some to identify FSS), since in both cases the presence of CS is assumed. In the case of IBS, there is chronic visceral hyperalgesia, while in FM the chronic pain is somatic [76].

Their coexistence in the same individual can be explained by the fact that some visceral and somatic pain fibers affect the same areas at the level of the spinal cord and brain. For instance, the anterior cingulate cortex, which modulates the affective response and induces pain, receives both visceral and somatic inputs, and is believed to be an area involved in the pain processing of both disorders [77–79]. The insula and the somatosensory cortex also play an important role in the processing of pain in both FM and IBS [80]. Furthermore, in both syndromes, the attenuation of the pain inhibition mechanisms by the descending pathways is hypothesized [77]. Finally, both in patients with FM and in patients with IBS, a pronounced hyperalgesia at the lumbosacral level has been observed, which could also explain the increased thermal sensitivity and visceral hypersensitivity that has been observed in patients with IBS or FM plus IBS, compared to healthy controls [81]. Probably, the coexistence of visceral and somatic hyperalgesia at this level is due to an anatomical convergence of both somatic and visceral nociceptive fibers within a common pool of neurons at the level of the spinal cord [81].

## *Fibromyalgia and Chronic Pelvic Pain*

Chronic pelvic pain (CPP) is a non-cyclical pain, lasting at least six months, involving the pelvic region, the anterior abdominal wall below the navel, and posteriorly the lumbosacral region, with an extent of the pain such to alter the quality of life of those affected [82]. In some cases, it can be associated with the coexistence of organic conditions with endometriosis and the presence of adhesions as the most frequent [83, 84]. However, after laparoscopic surgical treatment of these associated organic conditions (i.e., endometriosis), in 30–40% of cases, a resolution of the pain was not observed [85, 86], assuming independence from the presence or absence of

organic conditions, and considering them at most as triggering elements in the context of a multifactorial genesis. Conversely, in other cases, there is no association with organic pathologies [83]. Specifically, after laparoscopic evaluation of patients with CPP, no underlying causes could be identified in 30% of cases [84]. For this reason, CPP is considered to belong to the functional somatic syndromes, being not associated with damages or pathologies of the affected tissues, and often presenting hypersensitivity to pain [83]. It affects women more than man and is related to histories of sexual or physical abuse and to states of anxiety or depression [84]. Furthermore, as with other FSS, it can coexist in the same individual with other conditions of chronic pain, such as IBS, FM, temporomandibular syndrome, and migraine [82–84].

Fibromyalgia is frequently associated with chronic pelvic pain (CPP). Depending on the studies considered, from 12 to 65% of fibromyalgia patients complain of CPP [87, 88].

Furthermore, 44% of patients with FM report vulvodynia, and 48% of these present pelvic floor hypertonicity [89]. Women with both these conditions have a greater intensity of widespread chronic pain, and they are more prone to anxiety and depression disorders. Furthermore, FM in the presence of CPP has a more severe presentation than in patients with FM alone. Conversely, patients with CPP have a higher prevalence of fibromyalgia and other FSS [83]. CPP also shares some etiopathogenetic hypotheses with fibromyalgia and other FSS, including psychosocial factors, such as histories of abuse, anxiety disorders or depression, and the central sensitization hypothesis, triggered following an insult of various nature, but which persists even after the removal of this. In consideration of these etiopathogenetic similarities, according to some authors, CPP reflects a "visceral sensitization," and could be defined as "pelvic fibromyalgia" [90].

### *Fibromyalgia and Interstitial Cystitis/Painful Bladder Syndrome*

Painful bladder syndrome/interstitial cystitis (PBS/IC) is defined by the European Society for the Study of Interstitial Cystitis as a "chronic condition of pelvic pain, pressure or discomfort perceived in the bladder and with at least one urinary symptom such as urinary urgency or increased urinary frequency" [91]. The presence of glomerulations or "Hunner's ulcers" are present in less than a third of the cases [92]. There is no precise estimate of its prevalence, but according to some studies, it affects 2% of the general population with a female–male ratio of 9:1 [91, 93]. PBS/IC is a condition frequently associated with other syndromes characterized by chronic regional or widespread pain including fibromyalgia, irritable bowel syndrome, migraine, and temporomandibular disorder [94]. Literature data have shown that 11–17% of patients with PBS/IC have FM. Nickel et al. reported the presence of FM in 17.7% of patients with PBS/CI compared with 2.6% of controls [95–97]. Hamed et al. evaluated the presence of symptoms related to the presence of PBS using the "Fibromyalgia Bladder Index (FBI)" in women with fibromyalgia [98]. The FBI presents 2 types of assessments: one aimed at assessing bladder pain and

urinary urgency (UP), and the other one at assessing urinary frequency and nocturia (FN). The mean UP score was significantly higher in the FM patient group (10.29 ± 5.61) than in controls (1.65 ± 2.65; $p = 0.001$). The FN score was also significantly higher in patients with FM (9.93 ± 5.37) compared to controls (2.95 ± 3.27, $p = 0.001$). Numerous etiological factors have been hypothesized as involved in the onset of PBS/IC, such as urinary infections, inflammatory or autoimmune processes, abnormalities of the bladder mucosa, the role of urinary toxins, or the presence of local neurological dysfunctions. However, to date, the actual etiopathogenetic mechanisms leading to the development of PBS/IC are largely unknown [99]. According to some authors, it could be considered a functional somatic syndrome or a manifestation of an FSS, also considering the frequency of association with other FSS, first of all, fibromyalgia and IBS [94, 100]. Even in this case, amongst the various pathogenetic mechanisms proposed, there is the development of central sensitization [97–100]. PBS/IC may be the result of a central sensitization in the lower spinal cord. This CS may also be triggered by other chronic pain syndromes unrelated to the bladder, which would initiate spinal sensitization with subsequent spatial expansion to the point that the bladder would also be perceived as a site of pain. Once the CS is triggered, also when the noxious stimulus is removed, the pain perceived in the organ persists, since even non-painful stimuli are perceived as such [99]. This may also explain why patients with PBS/IC have significant discomfort with very small bladder volumes compared to normal subjects, and why these patients still have pain after cystectomy [101, 102].

## *Fibromyalgia and Temporomandibular Disorders*

The term "temporomandibular disorders" refers to a set of different clinical conditions affecting the masticatory muscles or the temporomandibular joint. These are mainly characterized by the presence of joint and muscle pain, and dysfunctions such as reduced motility or joint noises are also often associated, as well as earache, headache, dizziness, or tinnitus. TMDs can be of a congenital nature, resulting from neoplasms, inflammatory processes, or trauma. However, in a percentage of cases, an underlying organic cause is not recognized, thus defining this disorder as functional TMD. In this case, the etiology is still unknown, but a multifactorial genesis is hypothesized [103]. TMD is diagnosed when the "Research Diagnostic Criteria for Temporomandibular Disorders" (RDC/TMD) are met [104]. Functional TMD is considered an FSS [52], and as with other FSS, it is often associated with symptoms such as sleep disturbances, cognitive problems, gastrointestinal disorders, and diffuse myalgias, which alter the patient's quality of life, as well as tending to coexist with other functional chronic pain conditions [105]. Some epidemiological studies have shown a strong association between FM and TMD. It is estimated that 71–94% of fibromyalgia subjects have a TMD with a component of myofascial pain [106–108]. Conversely, when temporomandibular pain has an arthrogenic origin, the prevalence of TMD in fibromyalgia sufferers drops to 19% [109–111]. Amongst those patients diagnosed with TMD, the prevalence of FM ranges from 10 to 18.4%

[112–114]. As for the other FSSs, the functional temporomandibular disorder, especially if with a myofascial component, shares some etiopathogenetic hypotheses and risk factors recognized in FM, such as the association with some polymorphisms in genes encoding for molecules involved in the transmission of painful impulse and the emotional processing of this, as well as the association with physical or emotional trauma, or with the concept of central sensitization [105].

## *Fibromyalgia, Chronic Migraine, and Chronic Tension-Type Headache*

Chronic migraine (CM) and chronic tension-type headache (CTTH) are both very common types of headache [115]. An increased prevalence of FM in patients with these types of headaches is a well-established fact in the literature [116, 117].

The prevalence of FM (diagnosed with the aid of the ACR 1990 criteria) amongst patients with migraine varies from 11% to 22% [117–119]. Furthermore, one study observed that the frequency of FM increases to 35.6% when the association with transformed migraine is evaluated (a term previously used to describe a form of CM) [119]. The frequency of FM is even higher in patients with chronic tension-type headache (CTTH) with values ranging from 35% to 59% [117, 120]. One study evaluated the prevalence of FM diagnosed by following the ACR 2010 criteria in patients with CM and CTTH. In this study, the prevalence of fibromyalgia was much higher (69.9%) in patients with CM than in those with CTTH (25.7%) [115]. It was also observed that in patients with CM more frequently than in patients with CTTH, there was an association with anxiety disorder, depression, and somatic symptoms. Conditions that, as previously stated, often coexist also in patients with FM [115]. FM also shares with CM and CTTH the pathogenetic hypothesis of central sensitization. In fact, it is believed that the cephalic allodynia reported by migraine patients may be caused by a central sensitization mechanism in the second-order neurons of the spinal trigeminal nucleus [121]. The trigeminal neurons are subjected to sensitization following the constant painful impulse transmitted by the perivascular meningeal painful fibers [122]. In addition to the cephalic level, the presence of chronic pain in extra-cephalic areas has also been reported by patients with CM, underlining that central sensitization in these patients can be widespread [115]. Furthermore, skin allodynia appears to be more severe in patients with CM than in those with recurrent CTTH [123].

## *Fibromyalgia and Multiple Chemical Sensitivity*

Multiple chemical sensitivity (MCS) is a chronic condition that has been found in 6% of adults in California [124]. Its reproducible symptoms involving multiple organ systems are caused by low levels of exposure to multiple chemically unrelated substances and improve or resolve when the chemical agents are removed [125]. Chemical avoidance has been found to be effective in 93% of patients [126].

MCS is common in patients with CFS and/or FMS. In a sample of 33 Gulf War veterans with CFS, 42% had concurrent MCS and 6% concurrent FMS [127]. Brown and Jason [128] studied 114 men and women with CFS, finding that 43.9% of them met the criteria for CFS alone, 23.7% the criteria for CFS and MCS, 15.8% the criteria for CFS and FMS, and 16.7% the criteria for all the three conditions. The CFS/MCS/FMS patients were more disabled than those with CFS alone in terms of physical functioning, general health, and bodily pain, indicating that having more than one illness exacerbates disability beyond CFS alone.

## *Fibromyalgia and Chronic Fatigue Syndrome*

Fatigue is a frequent symptom in the general population, being reported by up to 50% of the respondents to large-scale surveys [129, 130]. It is attributable to underlying systemic diseases such as diabetes, cardiopulmonary disease, or rheumatoid arthritis, but may also accompany psychiatric conditions such as depression, panic disorder, or somatization. When fatigue cannot be explained by a medical condition such as depression, cancer, infections, or inflammatory disorders, it may be due to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). In fact, a clinical diagnosis of ME/CFS can only be made when all the other possible etiologies of fatigue have been excluded [131–133]. Although considerable progress has been made, there is still no unifying construct concerning some of the major pathogenetic mechanisms of ME/CFS. Current research is investigating the involvement of the immune and adrenal systems, genetics, stress-related syndromes, and impaired neuropsychological functions. As many of the symptoms are the same as those of viral infections, some physicians have hypothesized a post-infectious etiology [134].

Genetic susceptibility is supported by the findings of one study showing that patients with exercise-induced CFS differently express certain genes that play a role in metabolism and immune responses [135], and another study has shown a correlation between specific gene mutations, ME/CFS, and some viral infections associated with CFS [136]. The fact that ME/CFS is often associated with depression has led many physicians to believe that it is a purely somatic illness [137], but there is no evidence supporting this conclusion. The risk of developing ME/CFS may be increased as much as six times by a childhood trauma, which may reduce resilience and also increase the risk of adrenal system dysfunction [138]. ME/CFS may be considered one of the central sensitivity syndromes (CSS) [54]. It is therefore possible that specific peripheral fatigue and pain pathways in ME/CFS patients are sensitized by still unknown mechanisms (infections and physical and/or psychological stressors) [139–141], continuous inputs from which maintaining the state of chronic fatigue and chronic widespread pain. Chronic fatigue syndrome (CFS) frequently overlaps with FMS [142], and therefore it is possible that the same patient may simultaneously meet the diagnostic criteria for more than one CSS. It has been estimated that between 20% and 70% of patients with FMS meet the criteria for

CFS and that 35–70% of those with CFS also have FMS [143]. Many people suffering from FMS have those symptoms generally observed in CFS. Patients who meet the criteria for both FMS and CFS have a worse overall health status [142].

## Conclusions

It is known that FMS and dysfunctional syndromes may coexist:

- FMS is not a distinctive disease entity, but a complex spectrum of problems with frequently overlapping symptoms. It also substantially overlaps functional somatic syndromes.
- The symptoms of FMS vary from patient to patient, as does their severity.
- All patients with chronic widespread pain should be assessed for FMS on the basis of their medical history (including psychosocial factors) and TPs.

In conclusion, in patients suffering from widespread pain and fatigue, it is necessary to rule out the presence of any medical condition or disease that is known to cause these symptoms.

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# Chapter 13
# Cognitive and Behaviorally Oriented Psychotherapies for Fibromyalgia


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Manuscripts on Fibromyalgia (FM) often begin by providing a description of the cardinal symptoms (e.g., widespread body pain), and a listing of common comorbid symptoms (e.g., sleep problems, problems of mood (anxiety, depression), concentration and memory problems, fatigue, and comorbid conditions [1–3]. In addition, there is often some prevalence data (e.g., 0.5–5%), [1, 4] and a statement about the economic impact (e.g., healthcare costs are three times greater than average for FM) [5, 6]. Following this description, there is often a statement to the effect that "little is known about FM" or that it is a largely "unexplained" condition. While maybe 20 years ago FM was largely "unexplained," FM is now one of most highly studied chronic pain conditions; in fact, lessons learned about FM are being used to understand other chronic pain conditions [7, 8]. The lack of a pathogen, deformity, or specific damage may make FM "unexplainable" from the perspective of the biomedical model; but through the lens of the Biopsychosocial model, there is a clear framework for understanding FM given it is the result of aberrations in central perceptual processing. That is to say, nociceptive signals must be processed centrally in a mix of biopsychosocial influences in order for the perception of pain to manifest. Cognitive and Behaviorally oriented therapies like the ones to be discussed are ideally positioned to address these biopsychosocial influences.

This chapter will explore three efficacious psychologically-informed therapies that can be used to address fibromyalgia (FM). All three share similar techniques and have their roots in traditional cognitive and behaviorally-based principles of change, but each also has important philosophical differences in how pain is considered and by what is targeted for change in the course of therapy. Cognitive-Behavioral Therapy (CBT) uses cognitive coping and behavioral skills to gain control over pain symptoms as a means of improving functional status and quality of life. Acceptance and Commitment Therapy (ACT) encourages the letting go of

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attempts to control pain and instead, emphasizes the acceptance of pain as a part of life while still engaging in valued activities that maintain quality of life. Finally, Emotional Awareness and Expression Therapy (EAET), attempts to modify or even eliminate pain entirely by exposing and resolving negative emotion trapped within memories of past traumatic or troubling events. The emotions associated with these past events feed negative affect into the processing of current pain; thus, resolving these sources of negative emotion should also diminish pain.

## Cognitive-Behavioral Therapy (CBT)

CBT is theoretically grounded in principles of cognitive and behavioral change such as operant and classical conditioning, social learning theory, and theoretical models for modifying beliefs and attributions about illness. It presupposes a dynamic interplay between biology (e.g., neurotransmitters), experienced emotions, cognition (e.g., planning and memory of past events), and one's social environment in the generation, maintenance, and resolution of illnesses [9–11]. Traditionally, CBT has utilized a therapist to help monitor the biological, psychological, and social environments of the individual. Insights derived from monitoring then provide opportunities for teaching patients methods for thinking differently or changing behaviors consistent with the promotion of healing and wellness by learning to control unwanted symptoms. While therapists may be initially involved in CBT, the long-term aim of CBT is to promote adaptive self-management for a given condition over the long term.

CBT has demonstrated efficacy for psychiatric conditions (e.g., depression and anxiety), [12, 13] as well as more traditional medical conditions (e.g., asthma, [14] obesity, [15] cardiovascular disease, [16] and insomnia) [17]. While the specific skill sets can differ across medical conditions, the underlying principles of cognitive and behavioral change remain consistent. When CBT is used to address chronic pain, it most commonly targets pain interference rather than pain intensity per se. It can also be used to address symptoms that tend to accompany chronic pain such as sleep difficulties, distressed mood, fatigue, and cognitive challenges [18]. CBT is considered the "gold standard" psychological treatment for FM [19, 20] but the specific skills that are taught may differ from therapist to therapist and in accordance with the needs of the patient.

### *Components of CBT*

Regardless of whether CBT is being used for anxiety, diabetes, or chronic pain, the therapy tends to unfold in three phases. The first phase is Rapport and Education. This phase offers the patient and therapist an opportunity to become acquainted and initiate a trusting bond. The pair exchange viewpoints and perspectives on the

illness such as its cause, its impact, and what treatments could help. This is an opportunity for education and the time to craft a common framework for working together. The second phase is Skill Building. In this phase, the therapist teaches the patient a variety of cognitive and behavioral skills targeting identified symptom-based outcomes such as reducing pain interference, reducing sleep problems, or improving mood. The therapist and patient work together so that the patient can learn the skills, practice the skills, and engage in problem-solving when the skills become difficult. The final phase is Real World application where the patient transitions from therapy to independent self-management. Typically, patients try their new skills in increasingly challenging real-world situations. The following sections provide more details about each phase.

### Rapport and Education

Clinicians and patients often bring two very different perspectives to a given condition. Clinicians may have a deep understanding of how an illness develops, gets treated, and resolves, but they rarely have first-hand knowledge of what it's like to have the illness and its impact. In conditions like FM, where there is very little that a clinician can prescribe aside from modestly beneficial medications, [8] involvement of the patient in symptom management is essential. In CBT, patients play a critical role in treatment planning, developing expectancies, setting goals, and following through with behavioral recommendations. When treating FM, clinicians learn to abandon the traditional authoritarian role and instead engage in a more "relationship-centered" process where each party brings different resources to the common goal of FM management [21]. Such a relationship offers an opportunity for both parties to share their knowledge of the condition and to get on the same page with one another for the long-term management of the condition. Two skills that are often introduced in the Rapport and Education phase of CBT include self-monitoring and goal setting. Self-monitoring provides a means of visualizing symptoms and behaviors from the past and present, whereas goal setting provides a framework for controlling symptoms in the future.

#### Behavioral Self-Monitoring

Biomarkers can be used to monitor disease progression for some medical conditions (e.g., blood pressure, glucose levels, etc.). For FM however, reliable clinically accessible biomarkers do not exist. Therefore, one form of self-monitoring involves the assessment of symptoms. One symptom cluster that is commonly monitored in FM is remembered by the acronym s.p.a.c.e. (sleep, pain, affect, cognitive problems, and energy problems/fatigue) [18, 22]. While not everyone with FM will have all the symptoms contained in s.p.a.c.e, the presence of different combinations of s.p.a.c.e. can form a personal profile and can help guide which CBT skills may be needed at any given time. To make CBT effective, monitoring of symptoms needs

to be aligned with monitoring of thinking and behaviors. For example, monitoring activities such as walking or monitoring the perception of stress in combination with monitoring pain can reveal hidden insights into how stress and walking have opposite effects on pain over time. Because our memories for complex longitudinal relationships are not very good, daily monitoring may be the only way to identify what is working and what is not for the various s.p.a.c.e. symptoms. When monitoring is used at the outset of CBT, it can serve as a baseline against which future goals can be set and then tracked for predefined improvement indicative of success.

### Goal Setting

Goal setting is composed of two parts: [1] choosing a goal and then [2] determining the criteria by which one can identify whether the goal has been met [23]. The latter consideration, identifying when a goal has been met, is often overlooked in traditional pain treatment. For example, patients often enter treatment desiring a reduction in pain. What gets overlooked is a determination of how much pain reduction will be considered a treatment success and indicative of reaching a goal. If only 100% pain elimination is the criteria for success, almost all current treatments for chronic pain are doomed at the outset. Better goals might consider 30% or 50% reductions in pain as the goal. These amounts of pain reduction have a basis in the existing literature and would be appropriate for pharmacological as well as some non-pharmacological interventions. In order to know when a goal has been reached, patients need to self monitor pain so that it will be known when a 30–50% reduction has been achieved.

### Skill Building

The specific skills for managing and controlling symptoms for any given medical condition will differ depending upon the condition. For example, a person with diabetes may need CBT to focus on glucose monitoring, diet, and activity. Someone with FM may need to focus on improving functional status, pain reduction, and sleep. In each case, the therapist helps the patient to identify and prioritize the skills to work on, teaches the skills, encourages both in-therapy work as well as homework practice, and helps the patient overcome barriers to learning and implementing the skills. The patient on the other hand, needs to be willing to self-monitor, try new behaviors, and receive constructive feedback from the therapist. While there is no single regimen of CBT that gets applied to FM, some of the more common skill sets are the following: (a) the relaxation response to promote pain reduction and reduce stress, (b) graded activation to gradually improve physical functioning, (c) managing emotional functioning, (d) reframing to improve mood through shifts in beliefs and thinking patterns, (e) behavioral sleep strategies to improve sleep and reduce fatigue, and (f) communication skills.

### The Relaxation Response

When threatened, humans become mentally aroused and physically tense. Once the threat passes, arousal and tenseness can return to normal levels (i.e., return to homeostasis). Pain is often perceived as a threat and in the case of FM, where the pain is chronic, the threat never ends and there is no natural cue to return to homeostasis. Thus, chronic tension and persistent mental arousal (i.e., hyper-arousal) become the new normal with associated deleterious effects on the body over time. Learning the relaxation response is one method of interrupting the arousal and allowing the return of ones' physiology back to homeostasis.

Teaching one's body to relax on cue is a skill that takes time and effort to master. It is different from relaxing after a threat abates; in fact, it is totally artificial in that relaxation is being called for even though the threat of pain is still present. There are many methods of taking conscious control over the relaxation response. These include progressive muscle relaxation, [24] visual imagery, [25] hypnosis, [26] biofeedback, [27] and mindfulness meditation [28]. While each approach differs in terms of methods, all can be effective in helping a given individual return to hemostasis [29].

### Graded Activation

FM not only hurts, but it can greatly interfere with productivity and self-esteem. Profound fatigue and inertia frequently thwart efforts to accomplish routine tasks. Occasionally individuals with FM will have a relatively "good day" where pain levels are lower and energy levels seem improved. On these days, there is the temptation to quickly get a lot done to catch up on tasks. Unfortunately, this over-activity can lead to symptom flares and the need for additional "down-time" for recovery. Down-time is non-productive and adds further insult to one's self-esteem. One approach to breaking this cycle of good days followed by pain flares is to use an approach called "graded activation."

Graded activation encourages individuals to base their activity upon something objective such as time rather than upon something subjective such as perceived pain intensity. For example, if someone needs to do the dishes, he/she could simply do all the dishes until the task is completed. While the task does gets done, standing for this amount of time might be too much leading to a pain flare-up. A better approach would be to pre-plan a "safe" amount of time for doing the dishes. For example, plan to do the dishes for 5 minutes regardless of whether the task gets completed or not. After five minutes, stop and rest. The rest period will not need to be long, given there was no flare-up. Resting is recovering from a "safe" amount of activity. After several minutes of rest, return to another 5 minutes of dish washing. This activity–rest–activity–rest pattern allows for the eventual completion of a given task without the burden of a flare-up. After dishwashing is completed, a second task can be started given there was no flare-up necessitating downtime for the remainder of the

day. Graded activation is a good method of gradually increasing the amount of productive time in one's day, improving self-esteem, and at the same time, minimizing the frequency of pain flare ups. Graded activation has been found to be a useful skill for a variety of chronic pain conditions including FM, [30] low back pain, [31] and arthritis [32].

## Managing Emotions

When the experience of pain is generated by the brain, it in part uses brain regions that account for emotion. Thus, one's emotional life plays a big role in determining how intensely pain is experienced. The more negative the emotion, the worse the pain. Given the generation of emotion and the generation of pain are linked, activities that either decrease negative emotions or that increase positive emotions are likely to diminish pain. A strategy common to CBT for pain is the use of pleasant activity scheduling to generate positive emotions [33].

Pleasant activity scheduling refers to helping individuals engage in daily activity that has a pleasant valiance. These activities do not need to be long in duration, expensive, or complex. Simple movie watching, writing to a friend, or eating something special for lunch are examples. In order to use pleasant activity scheduling, one must first generate a list of activities that are personally enjoyable. This task may actually prove difficult especially if activities that were previously enjoyable (e.g., before an injury) are now not feasible. Once a list is generated, it is important to schedule the activity into one's day. Scheduling is preferred to doing it whenever time permits. Many people with chronic pain use up their energy simply by getting the essentials done and the pleasant activities (i.e., emotional medicine for pain) never get used unless scheduled.

## Reframing

It is quite natural to have both negative emotions and negative thoughts when the pain becomes chronic. Experiencing the same negative thoughts repeatedly over the course of the day, however, can lead those thoughts to become automatic with this style of thinking dominating one's mind. When thinking is negative, the mind responds with emotions that are negative which as we have described above, influences pain intensity. Thus, a conveyer belt of negative thoughts leads to a boatload of negative emotions which can make the pain worse. One method of altering one's thinking is through reframing or cognitive restructuring [34]. With the help of a therapist, individuals are encouraged to identify negative thoughts when they occur. Once the thought is identified, patients are asked to evaluate whether the thought is realistic and to identify what types of emotions it engenders. If the thought is judged to be unfounded, then alternative thoughts are encouraged that are more realistic and potentially associated with neutral or more positive emotions that can diminish pain perception.

### Behavioral Sleep Strategies

Mental arousal prior to falling asleep diminishes the quality of sleep [35]. In CBT for FM, patients are encouraged to avoid arousing activities and stimulating foods prior to going to bed (e.g., watching disturbing news, watching action movies, drinking caffeinated beverages, smoking nicotine). Other behavioral changes involve the timing of sleep, using natural cues for sleep, and creating an environment that is optimal for sleep. Timing skills simply refer to going to bed and waking at a set time each day. If consistent over about 7–10 days, the body will learn a sleep/wake rhythm. As bedtime approaches, the body will learn to anticipate sleep if a regular routine is maintained. One natural cue for falling asleep is a slight decrease in core body temperature. If one is able to artificially raise the core body temperature and then allow it to return to baseline, this can serve as a natural signal to fall asleep. Taking a warm bath just prior to bedtime is one way of raising core body temperature; once out of the bath, the body begins to cool and that is the signal to fall asleep. It can also be helpful to control as much of one's sleeping environment as possible. For example, it can help to keep the room temperature cool, the room dark, and noises at a minimum. While most of these suggestions may seem obvious, it is surprising how many people with FM try to sleep in environments unconducive to sleep.

### Communication Skills

Individuals with FM do not live in a vacuum; they are part of an interpersonal environment. As FM persists, this interpersonal environment can develop tensions or become threatening and contribute to the exacerbation of negative emotion and pain. Several areas of interpersonal interaction that can become problematic for individuals with FM include the following: doctor–patient interactions, interactions with friends and family, and interactions at work.

Patients can have multiple questions for their doctors that build up between office visits. During the office visit, the doctor's agenda may not align with that of the patient, [36] leaving patients feeling rushed and unheard. Frustration and anger associated with an unsatisfying office visit can exacerbate pain. Patients may also feel conflicted about what to tell their doctors. On the one hand, patients may want a different approach from their doctor but fear annoying the doctor and putting their prescriptions and other medical benefits at risk. Similar problems can exist in relationships with family and friends. With family and friends, there might be initial offers of help when the pain is new. Over time, however, these offers can diminish in frequency and patients may start to lose close relationships feeling more and more isolated. The same phenomena tend to happen in the workplace where accommodations may happen initially but are not sustained over long periods of time making interpersonal conflicts more common. In CBT, assertive communication skills [37] are often addressed and practiced as a means of helping patients to navigate interpersonal waters and reduce negative affect associated with increased pain and diminished function.

### Real-World Applications and Self-Management

Once skills are learned and practiced with the guidance of the therapist, it becomes necessary to apply those skills under real-world conditions. For example, an individual might be able to successfully practice relaxation skills during therapy or when at home for 20 min each day; but, the real need is to be able to draw upon the relaxation response when pain peaks at work. These real-world challenges can at first be guided by the therapist but ultimately the individual will need to be able to use each skill on his/her own as the vicissitudes of life unfold. The goal of CBT is to prepare the individual to have mastery over a suite of skills that can be successfully deployed when needed.

When CBT is initiated, it often covers a broad assortment of skills. It is quite possible that only 1–2 skills will be relevant for a given individual once the formal period of therapy ends. Over time however and as life circumstances change, the other skills may begin to have relevance. The skills of CBT are dynamic. The patient is given broad training in a skill set that can be drawn upon as symptoms come and go over time.

## *Modes of CBT Service Delivery*

The traditional format of CBT is with a 1:1 therapist-patient relationship. CBT for pain can also be delivered in a group format. Anecdotal evidence suggests that there may be some added benefits to a well-conducted group approach given patients can learn from each other as well as from the therapist. Patients also tend to enjoy the group approach given it can help remove the sense of isolation that often accompanies the experience of chronic pain. CBT is a brief form of therapy typically ranging between 6–12 sessions of formal training followed by booster or follow-up sessions (usually 2–3 per year) to help maintain gains long term.

CBT for pain can also be delivered digitally via e-Health platforms over the phone, video-conferencing, or by a therapist monitored website [38–41]. Therapist-guided digital health interventions tend to share similar efficacy with traditional face-to-face therapy with the added benefits of offering greater flexibility in patient access, timing of therapy, and reduced cost [42–44].

## *Evidence Supporting the Use of CBT in the Management of FM*

In general, meta-analytic studies and clinical treatment guidelines favor the use of CBT in the context of chronic pain reduction, improving functional status, and improving mood [19, 20, 45]. Evidence from neuroimaging studies shed some light upon the mechanisms by which CBT influences pain. Volumetric studies have found that CBT partially reverses gray matter atrophy associated with chronic pain in

regions responsible for a cognitive reappraisal of symptoms [46, 47]. Similarly, resting-state studies have shown increased activity in regions associated with executive control and reappraisal of symptoms with decreased connectivity in regions responsible for negative affect (e.g., limbic regions) [48, 49]. These studies suggest that CBT enhances executive cognitive control over pain while diminishing or down-regulating the emotional contribution to pain perception.

A recent meta-analysis of randomized controlled trials (RCTs) of CBT for FM reviewed 29 RCTs representing 2509 participants. This large review concluded that CBT was superior to controls for pain relief of 50% or greater, for improvements in Health-related Quality of Life (HQOL) of 20% or more, and in reducing negative mood. Thus, this review concluded that CBT provided a clinically relevant benefit over control conditions in key symptoms and disability of FM [50].

While CBT is typically administered in combination with medications, there is some evidence that effect sizes for CBT can rival those of medications or even surpass medications for some outcomes such as improvement in functional status [44, 51, 52]. CBT for FM appears to be efficacious whether offered in an inpatient setting as part of a multidisciplinary pain program [53, 54] or as a component of an outpatient program [55, 56]. When CBT is added to standard medical treatment, patients can receive the benefits of both interventions; this might be considered optimal care given each intervention targets different aspects of FM. One study found that medical treatment combined with six 1-hour sessions of CBT resulted in twice as many patients achieving a clinically meaningful improvement in physical functioning than did the control group receiving only medications [30].

When CBT is delivered by website, it can be either in a guided format (i.e., includes a therapist or coach) or an unguided format (no therapist, content only). One RCT using an unguided CBT website found that 30% of the website sample received a clinically meaningful reduction in pain compared to only 8% of the treatment as usual group (TAU). In the same study, 31% of the website sample received a clinically meaningful improvement in functional status compared to only 6% of the TAU group [41]. Although yet to be tested, it is hypothesized that the effect size of the website group could increase further if a therapist or coach were added to the intervention (i.e., guided intervention).

## Acceptance and Commitment Therapy (ACT)

ACT is a second cognitive and behaviorally-oriented therapy with efficacy for FM but is quite different philosophically from CBT in what it targets. In CBT, the focus is on learning cognitive, emotional, and behavioral strategies for controlling symptoms of pain. In ACT, pain is accepted and attempts at controlling it would be inconsistent with this approach. In ACT, the hypothesized mechanism of change is psychological flexibility for experiencing pain followed by committed action in service of living a fulfilling life aligned with personal values (even with pain being present) [57].

ACT is thought to be a unified non-syndromal model of behavioral change, meaning that its principles can be applied to wellness as well as pathology [58]. At the core of ACT is the concept of "functional contextualism" [59] or the idea that thoughts and actions do not inherently possess meaning, but instead must derive meaning from their context. Thoughts drive actions and over time, learned relationships between thoughts and actions can become habitual or automatically paired. When made automatic, thinking can lead to action without additional consideration. Automatic thinking-behaving is not always bad. In fact, it allows for efficiency in performing routine daily tasks. When negative however, these automated thought-action pairs can persist even when it is pathological or not in the interest of the individual. ACT does not attempt to stop or change specific forms of thought; rather, ACT seeks to alter the individual's relationship with those thoughts and subsequent behavior. If the individual has clarity for living in accordance with personal values, then the impact of fleeting negative thoughts can be minimized and evaluated with curiosity rather than with threat or fear. The key to ACT is the concept of receiving and evaluating thoughts with "psychological flexibility" so that the individual can freely engage in activities that best align with one's personal values [60].

## *Components of ACT*

Six core constructs support psychological flexibility and engagement in valued activities. Each will be briefly described [58–60].

### Experiential Avoidance Versus Acceptance

In the short term, avoidance of negativity (e.g., thoughts, events, feelings, memories, and sensations) can be a form of coping in that it helps retain homeostasis by not having to engage in events that are threatening or unpleasant. Unfortunately, avoidance can be a poor long-term strategy as it can ultimately create the negative mental states one is trying to avoid (e.g., anxiety, depression, distress). Avoidant thinking is narrowly focused on methods of eluding the problem rather than on exploring the problem itself. The counter to experiential avoidance is "acceptance." When accepting a problematic situation (e.g., thought, memory, sensation, etc.) one is not simply tolerating the situation or resigning to it; but acknowledging the problem and being open to applying additional consideration to the problem rather than automatically avoiding it. Through ACT, previously avoided situations are explored with curiosity and interest (i.e., with psychological flexibility) thus broadening the potential repertoire of behavioral responses to the situation.

### Cognitive Fusion Versus Defusion

Thoughts are frequently tied to physiological events, feelings, and behavior. For example, if you arrive home and your daughter is not there, you could either conclude that she is with friends or that she's been kidnapped. Regardless of the veracity of the thought, the latter thought has the power to elicit autonomic arousal, anxiety, and phone calls to find her. If this thought occurs each time you come home and find her missing, these behaviors can get fused with this thought. When thoughts and behaviors get fused, the opportunities for flexible responding narrows, even if it is not in the interest of the individual. The counter to fusion is "defusion." With defusion, the goal is not to change the thought or its frequency, but to decrease the importance of the thought, and its power to evoke strong emotions and behaviors. Ones' relationship with the thought is what needs to change, not the thought itself. Techniques for helping individuals distance themselves from thoughts include repeatedly writing the thought or verbalizing the thought until the emotional valence of the thought diminishes. Once the emotional valence is diminished, the thought just becomes a curious neutral object with little importance to the individual.

### Attentional Rigidity to the Past and Future Versus Being Present

Most negative experiences are contained within one's memories of past events or in threatening expectancies for the future. With ACT, what matters is the "present." "Now" is the only truly experienced part of life. The past and the future are fabricated constructions often containing unnecessary and unhelpful biases. Orienting the individual to fully and openly experience the present is another path to psychological flexibility. Breathing techniques and non-contemplation methods can be used for this component of ACT [58].

### Conceptualizing Self Versus Noticing Self

Everyone has a conceptualized version of themselves. This is what is recited when asked "Who are you?" This pre-existing version of one's self likely contains a narrow range of appropriate thoughts, appropriate feelings, and appropriate behaviors that must all stay aligned with this conceptualization. Thoughts or events outside of the self-conceptualization can be highly threatening to life itself and are therefore avoided (see above experiential avoidance). An alternative to "the conceptualized self" is the "noticing self" where the self is observed by the individual on an ongoing and "present" basis. The skills used in noticing ones' self are similar to the skills one might use to notice others in an ongoing manner. Therapy skills include perspective-taking tasks, mindfulness exercises, and the use of metaphors.

### Vague, Compliant, or Avoidant Motives Versus Values

Guilt, demands for compliance, and shame can all motivate behavioral change but these methods are less effective than internally motivated desires for something that is personally valued. When activities are personally valued, both the process and the end goal can be motivating. In ACT, the use of metaphors, writing exercises, experiential learning, and self-exploration can be used to identify valued outlets to guide behavioral priorities. Identification of personal values is foundational to the successful implementation of ACT.

### Inaction, Impulsivity, and Avoidance Versus Committed Action

Retaining psychological flexibility and maintaining on course with one's values requires work, homework, and commitment to stay the course. One can know how to be psychologically flexible and one can know what they value, but knowing is not enough. In order to be successful, in the use of ACT, the individual must also be committed to applying the methods in pursuit of one's betterment.

## *Modes of ACT Service Delivery*

The traditional format of ACT is with a 1:1 therapist-patient relationship. ACT for pain can also be delivered in a group format. Recently versions of ACT have been adapted for delivery using e-HEATH platforms with outcomes consistent with traditional face-to-face delivery. ACT therapy typically ranges between 1–12 sessions for chronic diseases generally, 4–12 sessions for chronic pain, and 8–12 sessions when being applied to FM.

## *Evidence Supporting the Use of ACT in the Management of FM*

In general, meta-analytic studies and clinical treatment guidelines support the use of ACT in the management of chronic pain [61]. ACT and mindfulness-based interventions have shown small effects (i.e., Cohen's d) on pain intensity, and depression and moderate effects on anxiety and pain interference immediately post-treatment. At follow-up (i.e., 3 or 6 months post-treatment), the effect on pain intensity remained small, but the effects on depression and anxiety were both moderate with the effects on pain interference increasing from moderate to large [61].

A meta-analysis of RCTs of Mindfulness and Acceptance-based therapies specifically for FM reviewed 9 trials (750 participants total). Overall, mindfulness and acceptance-based therapies were favored over controls for all outcomes with small to moderate effects identified post-treatment for pain, depression, anxiety, sleep,

and health-related quality of life. In one study examining ACT with FM, [62] small to moderate effects were identified for pain disability, depression, and anxiety at both post-treatment and at 3–4 month follow-up. Large effects were identified for mental quality of life and pain intensity at follow-up. A second RCT compared group-based ACT to recommended pharmacological treatment and to waitlist controls [63]. This study found ACT to be superior to both controls at 6 months follow-up on measures of anxiety, depression, and pain intensity.

As with CBT, attempts have been made to make ACT more accessible by providing digital online versions of the intervention. One RCT examining online delivery of ACT found improvement of life impact of FM at both post-treatment and at 3 months follow-up (primary outcome). Post-treatment benefits on depression, sleep, and pain intensity were also large at post-treatment but showed some degradation by follow-up. Additional work is merited examining the benefits of ACT delivered digitally.

## Emotional Awareness and Expression Therapy (EAET)

A third efficacious psychologically-based therapy for FM sharing approaches with CBT is Emotional Awareness and Expression Therapy (EAET). The approach to FM taken by EAET hypothesizes that in order to reduce or eliminate FM, one must gain resolution of past trauma and life adversity given that these emotionally charged events contribute directly to the experience and maintenance of pain/symptoms.

EAET capitalizes upon finding from neuroscience that suggests the experience of pain is generated by the brain by combining and interpreting input from peripheral nociception, emotions, cognitions, and memories. Thus, unresolved negative emotional content acts as the fuel that maintains and amplifies pain processing [64]. It may be natural to avoid negatively charged content (e.g., traumatic memories, interpersonal conflicts, etc.) but as described in the section on ACT, avoidance allows these negative feelings to be preserved and to contribute to current pain experiences. EAET is a means of safely helping patients confront these previously avoided events. In therapy, patients are encouraged to (a) become aware of the negative emotions, (b) experience (rather than avoid) the negative emotions, and then (c) learn ways to more adaptively express these emotions.

### *Components of EAET*

The foundational skills guiding EAET stem from a number of existing forms of therapy that have been used successfully with other conditions. These include education, methods to reduce perceived danger, methods to increase adaptive behavior, methods to facilitate emotional processing, and methods to foster genuine communication [65].

### Education

Like CBT, EAET utilizes education about pain as a means of grounding both the patient and therapist in a common understanding of how pain works and why the approach of EAET makes sense [66]. Much of the education stems from the most recent neuroscience findings suggesting that emotions don't simply worsen pain as one entity might influence another entity; rather, emotions and pain are one in the same entity.

### Reducing Perceived Danger

Similar to ACT, EAET addresses the power of thought to elicit negative affect. Thoughts that may have once helped with coping at a time of trauma may now only be serving to keep maladaptive emotions alive. EAET utilizes techniques such as mindfulness meditation and adaptive self-statements (cognitive affirmations) to bring critical examination of thoughts into the present context where those thoughts can be examined and relieved of their power to ignite negative emotions and pain.

### Increase Adaptive Behavior

Fear of pain frequently results in patients living physically and socially restricted lives. Borrowing from the anxiety and phobia literatures, EAET utilizes "in vivo" exposure to desensitize patients to previously avoided pain/negative emotions as a means of increasing functional activity [67–69]. Linking exposure to pain/negative affect to participation in avoided activity allows for a gradual reduction in negative affect and a return of function.

### Facilitate Emotional Processing

Pain may be linked to broader avoidance of relationships, traumatic memories, traumatic events, etc. EAET utilizes expressive writing and emotional disclosure as approaches for exposing hidden negative effect [70–72]. By encouraging patients to write about affect, it "gets it out of one's head" and on to paper. Both "free writing" and "unsent letters" are techniques that can help extract these "secret" emotions. Once on paper, the emotional content becomes more objective, can be rationally evaluated, and modified. In the session, patients may engage in experiential enactments of the events surrounding the emotion. Similar to cognitive restructuring in CBT, this approach utilizes reappraisal and re-attribution to help patients work through the emotions that may be fueling pain. For individuals with a trauma history, elements of trauma-focused psychotherapies and intensive short-term dynamic psychotherapy can also benefit patients receiving EAET [73].

### Genuine Communication

Commonly, the most salient stressor in someone's life is a relationship with another individual. Often the individual needs to develop skills for changing the dynamics of the relationship which can include assertiveness communication skills and role-playing so as to build and practice a repertoire of responses for addressing the social interactions that are currently being avoided.

Finally, again consistent with some of the skills covered in CBT, patients are trained in adaptive interpersonal communication skills to both help resolve ongoing interpersonal conflicts and to prevent future interpersonal conflicts that could contribute to pain exacerbation.

## *Modes of EAET Service Delivery*

EAET has been shown to be effective in both traditional individual face-to-face formats as well as in a group format [64]. EAET is designed to be offered in 1–8 sessions and currently, online versions of EAET are being explored.

## *Evidence Supporting the Use of EAET*

The various components of EAET have been studied individually as well as in the context of an integrated intervention. A review of the history of EAET found support for the use of the various components of EAET as well as the integrated model in the context of chronic pain [64]. While EAET is a relatively new approach compared to CBT and ACT, efficacy for its use in FM has been supported by several randomized controlled trials [64, 74]. The largest of these trials compared group EAET with group CBT and a group-based educational control. Comparisons were made between baseline, post-treatment, and 6 months post treatment. At 6 months, this study found EAET to be superior to the educational control group on measures of widespread pain, cognitive difficulties, depression/anxiety, and overall FM symptoms. Thirty-five percent of the EAET group reported feeling "much" to "very much" improved compared to only 15% of the education group. Compared to the education group, the EAET group did not produce noticeable improvements in pain reduction, sleep, fatigue, or health care use. Comparing EAET to CBT at 6 months follow-up, these two active interventions performed similarly on most outcomes with EAET showing greater improvements in FM symptoms, widespread pain, and pain intensity. The numbers of patients indicating "much" to "very much" improvement for the two active therapies were not significantly different.

As stated, EAET is a relatively new intervention with promising but limited support for use in FM. Some of the caveats for using EAET in FM include the fact that most studies in FM have been conducted in relatively highly educated females by a

relatively small number of investigators raising the question of generalizability to men and other sub-populations of FM [64]. The critical ingredient to EAET is the resolution of negative emotions that drive pain; thus, EAET may be especially useful for individuals with pain who also have a trauma history. EAET is unique among the field of CBT and ACT therapies by being able to claim at least a small percentage of cases where FM appears to have completely remitted [74, 75].

## Conclusion

Fibromyalgia continues to challenge providers and patients alike. While the search for pharmacological agents for FM continues, there still exist three under-utilized psychologically based treatments for FM that possess efficacy for reducing pain and pain interference, negative emotions (anxiety and depression), and improving quality of life both immediately following treatment and longer term. The effect sizes of these interventions rival those of pharmacological agents for FM and for some outcomes, such as improvement in pain interference/functional status, the effects sizes can be large. While no single therapy for FM (pharmacological or non-pharmacological) eliminates chronic pain for the majority of users, it would seem prudent to consider greater integration of these psychological therapies into routine care given they clearly keep pace with pharmacological options but with fewer adverse events and toxicities. Improved delivery systems allowing patients digital access may also make these therapies more affordable and accessible to a broader group of patients.

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# Chapter 14
# Juvenile Fibromyalgia

**Jennifer E. Weiss and Susmita Kashikar-Zuck**

## Introduction

Chronic musculoskeletal (MSK) pain is defined as pain in the bones, joints, and tissues of the body that persists longer than 3 months [1]. With up to 40% of children and adolescents reporting MSK or limb pain, it is the third most common complaint behind headaches and abdominal pain [2]. A subset of patients with chronic MSK pain suffers from chronic widespread pain which is accompanied by fatigue, sleep disturbance, and mood changes that are all characteristic features of fibromyalgia. This chapter focuses on juvenile fibromyalgia (JFM), an idiopathic chronic pain syndrome. The negative impact of JFM on patients' daily lives has been shown to be significantly greater than that of childhood rheumatic diseases such as juvenile idiopathic arthritis (JIA) and systemic lupus erythematosus (SLE) [3] and may have long-term negative consequences on quality of life into adulthood [4].

Pediatric rheumatologists are often asked to evaluate patients for conditions associated with chronic pain such as JIA, SLE, sports-related/overuse injuries, benign hypermobility, and JFM. For some pediatric rheumatology centers, JFM or other MSK pain syndromes such as idiopathic low-back pain (LBP) form half of the new patient referrals and may account for up to 25% of their new diagnoses. Results from a recent study of 201 JFM patients enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Legacy Registry, a prospective

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**Table 14.1** Symptoms associated with juvenile fibromyalgia in the CARRA Legacy Registry *n* (%)

| | |
|---|---|
| Widespread musculoskeletal pain | 164 (91%) |
| Pain modulation with anxiety or stress | 121 (80%) |
| Pain modulation with physical activity | 117 (75%) |
| Frequent headaches | 111 (68%) |
| Pain modulation with weather change | 86 (61%) |
| Nonrestorative sleep | 94 (52%) |
| Frequent awakenings | 75 (42%) |
| Increased sleep latency | 74 (41%) |
| Numbness and tingling of extremities | 48 (32%) |
| Anxiety and/or depression | 40 (28%) |
| Hypermobility on exam | 35 (28%) |
| Subjective soft tissue swelling of extremities | 32 (22%) |
| Irritable bowel symptoms | 24 (16%) |
| Hypersomnia | 25 (14%) |

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observational registry including 160 centers across North America, found most JFM patients were Caucasian/White (85%), non-Hispanic (83%), and female (84%) with an average age of 15.4 ± 2.2 years [5]. The most common presenting symptoms of JFM patients in this study are listed in Table 14.1 and are reflective of the JFM population in general. Symptom characteristics are also similar to those reported by adult patients with fibromyalgia (FM). One notable difference was that almost one-third of the JFM patients had joint hypermobility or joint laxity (excessive range of movement in one or more joints), which is higher than the prevalence reported in FM. Joint hypermobility is quite common in the general population and while it is usually asymptomatic/benign, it is routinely found in patients with joint and back pain and JFM. Benign joint hypermobility syndrome (BJHS) is characterized by joint hypermobility with associated symptoms such as chronic MSK pain, joint instability, soft tissue injuries, osteopenia, fatigue, and anxiety. The diagnosis of BJHS is made by applying the revised Brighton criteria [6] which includes arthralgia, joint dislocation/subluxation, abnormal skin changes (i.e., striae), marfanoid habitus, eye signs (i.e., drooping eyelids), soft tissue changes (i.e., tenosynovitis) and varicose veins, uterine prolapse or hernia. The reasons for the relationship between joint hypermobility and MSK pain in children are unknown. Some have proposed that overlap with genetic connective tissue disorders (such as Ehlers–Danlos and Marfan syndromes) in which joint hypermobility is a common feature may have a link with MSK pain [7].

Making the diagnosis of JFM may be challenging for several reasons: it is based on subjective patient-reported symptoms; it is considered a diagnosis of exclusion as laboratory test results are typically normal and it has overlapping features with many other syndromes such as chronic fatigue, irritable bowel syndrome (IBS), migraine, etc. There are also no well-validated JFM criteria for the pediatric population. Families may be unaccepting of this diagnosis in their child and some physicians may also be reluctant to assign a specific diagnosis given the limited knowledge

about the underlying pathophysiology of JFM and lack of approved medications. Unfortunately, this can lead to families seeking care with multiple specialists and often undergoing many unnecessary tests in the hope that a specific disease diagnosis (and potentially a "cure") can be found. Greater knowledge and provider experience with the assessment and treatment of chronic MSK pain in children can greatly enhance their ability to provide reassurance to families along with education about the multifactorial and complex nature of pain, which may allow for earlier initiation of multidisciplinary treatment.

## Criteria for Diagnosis

The Yunus and Masi classification criteria proposed in 1985 [8] were the only available criteria for diagnosing JFM until recently, and have therefore been most often used for clinical and research purposes. The criteria include the hallmark symptom of widespread MSK pain for greater than 3 months in 3 or more sites along with the presence of 3/10 associated symptoms: fatigue, non-restorative sleep, chronic anxiety, chronic headaches, subjective soft tissue swelling, numbness, IBS, and worsening pain due to physical activity, weather or stress. On physical examination, 5 of 18 painful tender points (heightened pain sensitivity upon palpation) are required. These criteria were based on a small study of 33 adolescents and were never formally validated. For adults, diagnosis of FM was previously made using the 1990 American College of Rheumatology (ACR) fibromyalgia classification criteria [9]. The 1990 criteria included: the presence of widespread pain defined as axial pain, left- and right-sided body pain and upper and lower segment body pain and 11/18 positive tender points. In 2010, the ACR proposed new criteria for FM [10] requiring no physical or tender point exam. The new classification was based on a Widespread Pain Index (WPI) (the number of body locations in which the patient had pain over the past week) and a Symptom Severity (SS) scale of cardinal symptoms (fatigue, waking unrefreshed, cognitive symptoms) and associated somatic symptoms of FM (such as dizziness, depression, nausea, blurred vision, etc.). The proposed new case definition and criteria include: WPI $\geq$7 AND SS $\geq$5 OR WPI 3–6 AND SS $\geq$9, symptoms present for at least 3 months, and absence of another diagnosis that would explain the pain. These criteria were modified in 2011 and 2016 allowing the WPI and SS scale to be self-reported (with adjudication by a physician for clinical diagnosis), reducing misclassification of regional pain disorders, and removing the recommendation regarding diagnostic exclusions [11, 12].

A preliminary validation study to assess the utility of the 2010 ACR criteria for a pediatric population was published in 2016 [13]. The study included 95 adolescent females ages 11–17 years with chronic pain. Of these, 47 had a clinical diagnosis of JFM by a pediatric rheumatology or pain physician (based on the Yunus and Masi criteria) and 48 had a localized chronic pain condition, such as abdominal pain, headache, limb or back pain. All patients were assessed with the WPI, and the SS scale for other associated symptoms (fatigue, waking unrefreshed, cognitive

symptoms and somatic symptoms from the ACR 2010 symptom checklist). Additionally, a standardized tender point exam was completed for all patients. When comparing the ACR 2010 criteria against the Yunus and Masi criteria, the ACR 2010 criteria were found to have an 89.4% sensitivity and an 87.5% specificity, with no additional improvement in accuracy when results of the tender point exam were included. The JFM patients, compared to the patients with localized pain had significantly more tender points, cardinal and somatic symptoms, and a great number of painful regions (WPI). The authors suggested slight modifications of the SS scale for pediatric use, eliminating a few items that adolescents did not endorse and adding simpler descriptors to enhance comprehension—e.g., adding "trouble sleeping" to the word "insomnia." This modified version of the ACR 2010 criteria, called the Pain and Symptom Assessment Tool (PSAT) is now beginning to be used in pediatric research studies [14] with additional validation efforts underway. The modified 2010 ACR FM tool offers a simple, quick and standardized approach to classifying JFM and has the additional benefit of consistency with adult FM criteria. The development of clear criteria for diagnosing JFM will greatly facilitate efficient and accurate identification of this complex condition and promote research into underlying mechanisms and treatment. However, additional validation studies in larger samples including a more diverse representation of racial/ethnic minorities and males with JFM are still needed.

## Pathophysiology

The body of literature on the pathogenesis of JFM is sparse with the majority of research being conducted in the adult fibromyalgia population. Other chapters in this book provide an in-depth discussion on the pathophysiology of FM. While more work needs to be done in JFM, the pathophysiology between juvenile and adult fibromyalgia is likely to be similar given the clustering of fibromyalgia and other chronic pain syndromes within families suggesting possible genetic linkage. Similar to adults with FM, youth with JFM show signs of altered sensory processing evidenced by lower pressure pain thresholds [15]. Changes in central nervous system (CNS) function may disrupt nociceptive processing and also underlie some of the CNS-mediated somatic symptoms of fatigue, sleep, memory, and mood difficulties [16]. In addition to potential neurobiological mechanisms related to central sensitization and "wind-up," the possible role of small-fiber polyneuropathy has also been suggested in chronic pain syndromes such as JFM in children [17, 18]. Recent studies have reported that lowered IL-6 and IL-10 signaling may play a role in the pathophysiology of FM [19]; however, results of studies looking at cytokines in FM have been inconsistent. In general, neuroendocrine, immune and inflammatory factors implicated in adult FM have not yet been investigated in JFM. Psychosocial and environmental components such as family factors, psychiatric co-morbidities, and history of trauma may also play a role, although these are more likely to be risk factors or important from an epigenetic perspective [20]. Studies that specifically focus on children and adolescents with JFM are limited but are crucial for the field to gain

a deeper understanding of how this condition unfolds and whether developmental factors such as neuroplasticity of the developing nervous system and modifiable behavioral, lifestyle, or other triggering factors early in life can potentially alter the course of the disease.

## When to Consider the Diagnosis of JFM

The diagnosis of JFM should be considered in all patients with chronic pain who also report marked functional impairment, sleep disturbance and fatigue, psychological impairments, headache, abdominal pain or other somatic symptoms that are not clearly associated with an underlying disease condition [20]. Reports of pain tend to be in the moderate to severe range (>6/10) [5]. Expressions of pain can vary from minimal outward discomfort to high levels of pain behavior and impairment. Although JFM is more common in females, it is important that the diagnosis not be overlooked in male patients since results from the CARRA Legacy Registry found males with JFM reported significantly greater functional impairment. Males were also found to have worse health-related quality of life (HRQOL) when compared to females ($p = 0.04$).

Not all patients presenting with chronic pain have diffuse MSK pain. Some pain patients may present with more localized pain and complain of pain on contact with a light touch (allodynia) or report severe pain in response to a mildly painful stimulus (hyperalgesia). In these cases, the diagnosis of complex regional pain syndrome (CRPS) should be considered. CRPS type 1 (previously called reflex sympathetic dystrophy) usually follows an injury (typically a minor fall, limb immobilization in a cast or boot, surgery, or minor medical procedure) without an identifiable nerve lesion [21]. Type 2 (rare in children) occurs following damage to an identifiable nerve. The incidence of CRPS in pediatrics is an estimated 1.2/100,000 in children 5–15-years [22]. Patients have constant pain that increases with movement resulting in them guarding and immobilizing the area which creates a viscous cycle that can lead to profound disability. Pain descriptors include burning, shooting, stabbing, or electrical. Disuse of the affected area may lead to muscle weakness and atrophy. Autonomic findings can include swelling and edema, temperature changes (affected limb is cooler), hyperhidrosis, changes in skin color, cyanosis, cold sensitivity, and mottled dry skin [21]. Psychological factors associated with CRPS include emotional distress, stressful life events, wanting to excel academically, and parental enmeshment and these can play a role in the maintenance or progression of CRPS [23, 24].

## Treatment

The goal of the treatment of JFM is to minimize the impact of pain to enable the patient to be an active participant in activities of daily living, exercise, and school, family, and social activities. Although it may seem counter-intuitive to patients who

first and foremost seek pain reduction, the focus of most pediatric treatment programs is to restore daily function along with efforts to control pain and other symptoms. In fact, research in pain treatment has shown that a return to usual activities and overall improvement in functioning precedes reductions in pain intensity [25]. A multidisciplinary, multimodal approach that incorporates the 3 Ps (physical, psychological and pharmacological interventions) has been found to be the most effective, although sometimes challenging to implement due to cost, availability of behavioral pain management specialists, and or patient/family reluctance to participate in psychological therapy [21]. The majority of pediatric rheumatologists generally treat JFM patients with education about chronic pain and guidelines for improving sleep hygiene and increasing physical activity with a graduated aerobic exercise program. While attempts are made to avoid pharmacological intervention, about half of the patients in the CARRA Legacy Registry had medications recommended such as non-steroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors (SSRIs), serotonin—norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin, and tricyclic antidepressants [5]. Patients may also be referred to a multidisciplinary pain clinic, psychiatrist, integrative medicine specialist, or physiatrist.

The recommended standard of care for JFM is intensive physical therapy (with the goal of working up to 30 min of vigorous exercise 2–3 times/week) and psychological therapies (counseling, cognitive behavioral therapy [CBT]). Multidisciplinary programs with an emphasis on intensive physical therapy have been found to be very useful [26]. Research has demonstrated that CBT, a psychological treatment that incorporates training in techniques such as deep muscle relaxation, distraction and guided imagery, activity pacing, and cognitive restructuring is effective in reducing pain-related disability and mood symptoms in adolescents with JFM [27, 28]. Results of a randomized controlled trial of an 8-session CBT program versus fibromyalgia education showed that adolescents who received CBT showed significantly greater improvement in daily functioning than those in the education condition. Pain levels showed modest reduction. CBT on its own did not lead to increased physical activity which is recommended as part of pain treatment [29]. Therefore, attention to increasing physical exercise is also needed—but can be challenging for patients with JFM because they tend to become more sedentary and deconditioned due to pain [30]. Recent developments in JFM treatment have shown promise for programs that combine CBT with specialized physical exercise using a neuromuscular training approach derived from injury prevention research [31, 32]. The exercise component of such a program is well tolerated by adolescents with JFM [33] and involves a progression of exercises that improve gait, strength, posture, and balance through training in isometric, concentric, eccentric, and full functional movements. Early results of combining CBT with neuromuscular exercise training to achieve reductions in pain and improve daily functioning are encouraging but further controlled studies are needed.

Many of the medications prescribed for FM are not licensed for use in pediatric populations [34] and there is minimal research supporting their use in JFM. Fluoxetine has been studied for use in JFM patients [35]; however, physicians must be cautious when prescribing SSRIs to teens since in October 2004 the United States Food and Drug Administration issued a “black box” warning advising of the increased risk of suicidal behavior among pediatric patients using SSRIs. Low-dose amitriptyline,

cyclobenzaprine, or pregabalin may be used to treat sleep disturbance [36, 37]. Some studies have shown the benefits of SNRIs such as duloxetine and milnacipran [38, 39] for JFM but further investigation of their safety and efficacy for use in adolescents is needed. The International Association for the Study of Pain recently convened a Presidential Task Force on cannabis and cannabinoid analgesia which may help shed light on its use for chronic pain in the pediatric population but currently, information on the efficacy of cannabinoids for treating pain in children is inadequate (Fig. 14.1).

*1. Evaluate child with chronic musculoskeletal pain*

- Complete medical and pain history
- Assess pain intensity, location, onset, duration, quality, variability, aggravating and alleviating factors
- Assess associated disability including impact of pain daily life such as sleep, school, social, emotional and physical activities
- Physical and neurological exam including appearance, posture, gait, growth parameters and vital signs
- Complete appropriate diagnostic tests

*2. Diagnose the primary and secondary causes*

- Current nociceptive and neuropathic components
- Attenuating physical symptoms
- Contributing psychological factors, social factors and biological processes

*3. Select appropriate therapies to improve overall functioning and quality of life*

Pharmacological

- Acetaminophen
- Nonsteroidal antiinflammatory drugs
- Adjunct analgesics (for CRPS)
- Opioid analgesics * consult subspecialist if required

Physical

- Graded exercise program
- Regular daily activity
- Pacing
- Heat, ice, massage, TENs

Psychological

- Relaxation strategies
- Cognitive behavioral therapy
- Teach parents adaptive responses to child's pain
- School reintegration
- Sleep hygiene

*4. Implement pain management plan*

- Provide pain diagnosis, feedback on causes and contributing factors
- Provide rationale for integrated treatment program
- Develop mutually agreed upon treatment goals
- Measure child's pain and functional improvement regularly
- Evaluate effectiveness of treatment plan
- Revise plan as necessary

**Fig. 14.1** Treatment algorithm for chronic musculoskeletal pain. *TENS*, transcutaneous electrical nerve stimulation. Adapted from: Weiss JE, Stinson JN. Pediatric Pain Syndromes and Noninflammatory Musculoskeletal Pain. *Pediatr Clin North Am*. 2018; 65(4):801–826

## Prognosis

A community-based study of (non-treatment seeking) children with widespread MSK pain showed that the majority of these children no longer had widespread pain at 1–2 years follow-up [40]. However, patients with a diagnosis of JFM seeking treatment at a tertiary pediatric rheumatology clinic tend to have ongoing symptoms [5]. A long-term follow-up study of adolescent patients with JFM found a high likelihood of continued symptoms into young adulthood and about half met adult ACR criteria for FM in young adulthood [41]. With the knowledge that many youths with JFM will remain symptomatic into adulthood, continued follow-up and monitoring through late adolescence and early adulthood with appropriate transfer to adult care may be necessary.

## Conclusion

JFM is a chronic and often disabling condition that is diagnosed primarily in adolescent females. The clinical presentation of JFM is very similar to adult FM and although relatively understudied compared to FM, progress is being made in the proper classification of JFM. Treatment approaches are available that can be very helpful in reducing pain and disability in JFM. In particular, non-pharmacologic approaches that combine cognitive-behavioral therapy with physical exercise approaches are generally found to be safe and effective. More mechanistic studies of the underlying pathophysiology of JFM and controlled studies of pharmacologic treatments are needed. With early identification and initiation of multidisciplinary care, it is possible to minimize the long-term impact of this condition on quality of life.

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# Chapter 15
# The Neuroscience of Fibromyalgia and Central Sensitization


**Daniel J. Clauw and Roie Tzadok**

## Introduction

Central sensitization, first introduced by Woolf et al. in 1983, was initially described in animal models. The term was used to describe spinal mechanisms that augment peripheral nociceptive inputs [1]. Following Woolf, more neural pathways were discovered that were capable of augmenting peripheral nociceptive or sensory input. These discoveries would manifest clinically as hyperalgesia/allodynia in animal models of nociception and on electrophysiological studies as decreased firing threshold and increased discharge of spinal nociceptive neurons. Over time, all these neurophysiologic findings indicating inadequate amplification of sensory stimulations were termed "central sensitization" [2–5]. These neural pathways were originally thought to involve only the spine and dorsal root ganglia, but over the 1980s, more works started shedding light on the importance of supraspinal structures and pathways in pain modulation and processing [6, 7].

As the concept of central sensitization became more widespread, during the following decade, it gained popularity as a possible cause of pain hypersensitivity seen in chronic pain disorders, such as fibromyalgia [8–10], irritable bowel syndrome (IBS) [11], neuropathies [12], etc. It was also becoming clear that central sensitization was associated with other symptoms, such as fatigue and sleep disturbances.

Originally, Quantitative Sensory Testing (QST) was used both in animal models and in humans to identify central sensitization. This psychophysical test, although subject to changes by distraction, mental fatigue or confusion, is a reliable way of

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assessing sensory nerve function [13]. In recent years, novel neuroimaging techniques are being used to identify and map the neurobiology of central sensitization.

Recently, the term Chronic Overlapping Pain Conditions (COPCs)has been coined by the NIH. It indicates that chronic pain disorders, such as fibromyalgia, IBS, low back pain, endometriosis, etc., all represent a spectrum of conditions with common pathophysiology related to central sensitization and overlapping clinical features. Therefore, central factors are believed to have a prominent role in the pathogenesis of these conditions [14, 15]. However, central sensitization may also be seen in conditions in which an ongoing nociceptive input (a painful stimulation) chronically exists. These subsets of patients having a primary condition (including autoimmune diseases, cancer, various types of arthritis) and central sensitization will present with features resembling fibromyalgia and therefore were previously identified as having "secondary fibromyalgia." There is little knowledge about the neurobiological basis of this type of central sensitization, because most studies of COPCs excluded individuals with the active peripheral disease. It is known, however, that this type of central sensitization is at least in part driven by the ongoing nociceptive input mentioned and that by removing it, the patient experiences an improvement in central sensitization features [16–18].

This chapter will overview the current findings regarding central sensitization and its role in the pathobiology of fibromyalgia, as well as point out open questions in this field.

## Clinical Features of Central Sensitization

Individuals with COPCs manifest pain and other symptoms related to central sensitization from early life. The nature of this pain varies over life, and what may seem to be a new episode of acute pain may just be the expression of a preexisting pain in a new area of the body [19]. This understanding led researchers to suggest that COPCs are basically a spectrum of lifelong diseases that manifest differently over time [20, 21]. A strong family history of chronic pain is also often seen in fibromyalgia patients, as well as a combination of other cognitive and physical symptoms, most commonly fatigue, mood disorders and memory disturbances [22, 23]. These findings led Kato et al. to hold twin studies, concluding that these conditions are about 50% genetic and 50% environmental [24]. The latter group (environmental triggers) may include long-term acute pain or psychological stress. Other works suggest that bacterial and viral infections and physical injuries are also predisposing factors to COPC development [25, 26].

As mentioned, fibromyalgia may be seen in association with other chronic pain syndromes and with the occurrence of up to 25% in other conditions, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [27].

A large percentage of patients with COPCs will suffer from psychiatric comorbidities as anxiety or depression [28]. This association may stem from the fact that both chronic pain and psychiatric conditions are affected by common triggers (such as stress or trauma) and their common neurobiological basis (psycho-cognitive

syndromes are triggered from the same neurotransmitters that are involved in pain transmission).

From a genetic perspective, findings of familial clusters of chronic pain conditions led to the hypothesis that they have associated with genetic factors. Gene studies showed that specific polymorphisms in the serotonin 5-HT2A receptor and dopamine receptor are more frequent in fibromyalgia patients [29, 30]. Wider genome studies indicated a linkage to the chromosome 17p11.2–q11.2 region. However, no clear, reproducible polymorphisms have been found yet, and in combination with the fact that stress, trauma and other environmental factors clearly contribute to the pathogenesis of fibromyalgia, researchers have postulated that epigenetic changes may also contribute to the pathophysiology [31]. This aspect requires further research.

Fibromyalgia patients show not the only hypersensitivity to pain but also report increased sensitivity to daily sounds [32–34], as well as to odors [35] and light [36]. These findings have led researchers to believe that chronic pain disorders are associated with inadequate general CNS sensory amplification.

## Quantitative Sensory Testing (QST) and Central Sensitization

QST is a method that involves delivering a quantifiable stimulus (i.e., mechanical, thermal, or electric) to the body with measurement of both objective and subjective responses to it.

In the general population, there is a Gaussian distribution of pain sensitivity, with most COPC patients being in the right margins of the curve, presenting hypersensitivity even outside the triggered region [20, 37–44]. The fact that hypersensitivity is also witnessed in pain-free parts of the body suggests a central mechanism.

Conditioned pain modulation (CPM) can also be demonstrated using QST, meaning the body's ability to inhibit a stimulus-evoked pain. A meta-analysis held by Lewis et al. showed that CPM is attenuated in chronic pain syndromes [45]. Following up, functional methods of neuroimaging demonstrated a network of cortical and brainstem regions comprising the CPM response in humans [46–49].

Temporal summation, the amplification of perceived intensity of pain in response to sequential stimuli, is a normal phenomenon that occurs in healthy individuals but is enhanced in patients with central sensitization [50–54]. Therefore, enhanced temporal summation may indicate persons at increased risk for central sensitization.

## Neuroimaging Studies

Neuroimaging techniques have been used to assess the brain's role in fibromyalgia pathophysiology. Recent studies demonstrate significant structural, chemical, and functional changes in brain areas related to pain processing. Structural changes have also been noted in brain regions such as were noticed in the periaqueductal gray (PAG), cingulate, and thalamus [55].

Neurochemical changes have also been identified in brain sensory processing regions such as the insula, including increased levels of excitatory neurotransmitters (such as glutamate) and decreased levels of inhibitory neurotransmitters (such as GABA) [56]. The insula was also found to be activated at increased intensities in fibromyalgia patients, which correlated with the individual patient's reported level of pain [57]. This over-activation was reduced following the administration of pregabalin.

Functional MRI (fMRI) studies have also demonstrated that fibromyalgia patients perceive sensations most individuals would categorize as mild or benign, as painful. During these episodes of experienced pain, the same brain centers and activity patterns arise as to when chronic pain-free individuals experience a noxious stimulus [58]. This indicates that individuals with central sensitization have a similar brain response to painful stimuli as controls but at lower levels of stimulus intensity.

Neuroimaging studies such as positron emission tomography (PET) showed indications of attenuated dopaminergic activity in fibromyalgia. Harris et al. also found decreased μ opioid receptor binding [59, 60]. This reduced opioids receptor availability was shown in fMRI-PET to reduce the anti-nociceptive activity of the anterior cingulate cortex [61]. These findings may explain the poor efficacy opioids show in treating fibromyalgia.

Furthermore, nuclear imaging techniques showed increased concentrations of glutamate in various brain regions of fibromyalgia patients [62]. The mechanism behind pregabalin and gabapentin's ability to ameliorate fibromyalgia pain is suggested to be related to the reduction of glutamatergic activity in the brain [63]. Brain glutamate levels may, therefore, be used to predict one's successful response to anti-glutaminergic treatment.

Similar neuroimaging methods were also used to demonstrate low levels of gamma-aminobutyric acid (GABA) in the brains of fibromyalgia patients. This finding is used to explain how moderate alcohol consumption may improve symptoms on fibromyalgia, as alcohol enhances the inhibitory neurotransmission of GABA in certain areas of the brain [64, 65].

## Immune Dysregulation in Central Sensitization

Some findings support the role of immune dysregulation in the pathogenesis of fibromyalgia and other COPCs [66]. Elevated levels of IL-8 were previously described [67], but Wallace et al. have also suggested that certain diets, as well as obesity, could contribute to a chronic low-grade inflammation in fibromyalgia patients [68].

These findings are still preliminary, and further research is required.

## Viewing Central Sensitization as a Spectrum

Wolfe was the first to use the term "fibromyalgianess," referring to it as a continuum of clinical presentations with "sub-threshold" levels [69]. He used assessment tools derived from the different versions of the American College of Rheumatology (ACR) fibromyalgia criteria (published between 2010–2016) to evaluate the extent of pain and disability in individuals with conditions such as rheumatoid arthritis, low back pain or osteoarthritis. In a series of works, these tools were found to be more predictive than objective scores of joint damage and inflammation [70–74].

Interestingly, fibromyalgia assessment tools are patient self-reported and include various tools such as the Michigan Body Map [75], Widespread Pain Index (focusing on 19 possibly painful body parts) and the Symptom Severity Index (also describing cognitive aspects of fibromyalgia). The Widespread Pain Index and Symptom Severity Index are combined for a total fibromyalgia score ranging 0–31. This score can be viewed not only dichotomously (whether a person is above the threshold to be diagnosed as having fibromyalgia), but also as a spectrum of levels of central sensitization or "fibromyalgianess." This spectrum can contribute to the management of patients with conditions associated with chronic pain.

Brummett et al. and Janda et al. both proved the practical importance of "subsyndromal" fibromyalgia when implementing the fibromyalgia score criteria on candidates for either lower extremity joint replacement or hysterectomy. It was shown that an increase in the score (between 0–31) correlated with increased needs for opiates in the first 48 hours after surgery and less likelihood for pain improvement after [76–78]. These findings were also observed in individuals whose scores were below the threshold for a formal diagnosis of fibromyalgia.

## Peripheral Nervous System Findings in Central Sensitization

There is abundant evidence that fibromyalgia patients demonstrate reduced nerve fiber density, but this finding is non-specific, and debate remains regarding its meaning [79–85].

Reduced nerve fiber density is a very non-specific finding that has now been noted in over 50 different pain and non-pain conditions [85]. in 2017, Harte et al. showed that reduced nerve fiber density could could also be induced in an animal model of central sensitization by increasing insular glutamate [86]. These findings may lead to the hypothesis that chronic pain, among other neurological conditions, therefore causes a structural reorganization of the peripheral nervous system. Although the pathophysiological significance of this finding is still not clear, it is a possible focus of interest for future research, especially considering that the available data regarding fibromyalgia pathophysiology is derived from the central nervous system.

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# Chapter 16
# Autonomic Nervous System Dysfunction in Fibromyalgia


**Manuel Martínez-Lavín**

## Introduction

Fibromyalgia is a stress-related disorder. Psychological, physical, infectious and/or autoimmune stressors are frequent fibromyalgia drivers. The autonomic nervous system (ANS) is our main stress response force. Aggregated evidence supports the notion of fibromyalgia as dysautonomia-related neuropathic pain syndrome.

## The Autonomic Nervous System

The ANS is the main regulatory system of the body in charge of maintaining essential involuntary functions, such as the so-called vital signs (blood pressure, pulse, respiration, and temperature). The ANS balances the function of all internal organs with the heart rate, intestinal motility, urination, and sexual activity, among many other variables, all regulated by the system.

One striking characteristic of the ANS network is the rapidity and intensity of onset of its action and its dissipation. The ANS is activated by centers located in the spinal cord, brain stem, hypothalamus, and thalamus. These centers also receive input from the limbic area and other higher brain regions. Emotions (fear, anger, and panic), therefore, have immediate biological responses (pupil dilation, paleness, and tachycardia). The ANS may be viewed as the interface between mind and body functions in charge of the basic fight or flight reaction.

The peripheral autonomic system is divided into two branches; sympathetic and parasympathetic. These two divisions have antagonistic actions on most bodily functions, and thus their proper balance preserves homeostasis. The action of these

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two branches is mediated by neurotransmitters. Catecholamines are the sympathetic neurotransmitters. The naturally occurring catecholamines are norepinephrine, epinephrine, and dopamine. The three substances act as neurotransmitters within the central nervous system. Norepinephrine transmits impulses also in peripheral postganglionic nerve endings and exerts its effects locally, in the immediate vicinity of its release, whereas epinephrine is the circulating hormone of the adrenal medulla and influences processes throughout the body [1].

The major metabolic transformation of catecholamines involves methylation and oxidative deamination. Methylation is catalyzed by the enzyme catechol-O-methyltransferase (COMT) and occurs throughout the body, whereas oxidative deamination is promoted by monoamine oxidase and takes place mainly in the synaptic cleft. The COMT gene is located in region q11.21 of chromosome 22. This gene has abundant functional polymorphism. The better-known transition occurs in codon 158 with a guanine-to-adenosine substitution, a polymorphism that results in functional alterations of the corresponding enzyme. The val/val genotype gives rise to an effective enzyme, whereas the met/met genotype produces a "lazy" enzyme unable to effectively clear catecholamines from the system [2].

## The Autonomic Nervous System. Our Main Stress Response Force

Stress can be defined as a state of disharmony or threatened homeostasis. For human beings, a stressor could have a psychological origin (ongoing anger, anxiety, or depression) but can also originate from a biological insult (an infection, a burn, or a myocardial infarction). The term stress or stressor should therefore not be restricted to psychological events but, rather, should be viewed in an ample physiological context.

The stress response system is a delicate, dynamic system that vertebrate animals have in order to maintain homeostasis. The main components of this system are the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenal axis. These two branches closely interact with each other and have positive reverberating feedback loops at different levels. If the capacity of the stress response system to adapt is overwhelmed, chronic diseases may appear [1].

Evolution imposes new challenges on all living organisms. Human societies have become more intricate and stressed with industrialization. An example of the new defiance is the alteration in the circadian rhythm. For many thousands of years, the day and night cycles were harmonious with external cues: light, noise, and activity during the day; darkness, rest, and quietness at night. In past decades, however, industrialization has clearly disturbed this harmony. Nowadays, there can be light, activity, and noise at night. This and many other stressors of modern societies undoubtedly have an impact on human health.

## Clinical Assessment of Autonomic Nervous System Function

The function of the ANS has been difficult to evaluate in clinical practice. Changes in breathing pattern or mental stress, or even posture, alter immediately and completely the sympathetic/parasympathetic balance. This dynamic system could therefore not be properly studied by "static" tests such as the levels of circulating neurotransmitters and less so by their urinary catabolites. Bedside maneuvers to assess ANS function have included measurements of supine and standing pulse and blood pressure. Sustained drops in systolic blood pressure (>20 mmHg) or diastolic blood pressure (>10 mmHg) after standing for 3 min that are not associated with an increase in the pulse rate >30 beats per minute suggest autonomic deficit.

Opportunely, two research instruments have been recently introduced to aid in clinical research of cardiovascular autonomic function: heart rate variability analysis and the tilt table test. These two instruments have been used to study the pathogenesis of FM.

### *Heart Rate Variability Analysis*

The method is based on the well-known fact that the heart rate is not fixed but varies from beat to beat constantly. The antagonistic effects of the sympathetic and parasympathetic branches of the ANS on the sinus node harmonize the periodic components of this constant variability. Heart rate variability can be studied in the time domain, where the basic units are milliseconds. Time-domain mathematical calculations include, among others, the standard deviation of all R–R interval durations as well as the percentage of adjacent pairs of R–R intervals that differ by more than 50 milliseconds from each other in a given time period. The higher time-domain variability indexes signify more parasympathetic influx on the sinus node.

Heart rate variability can also be studied in the frequency domain using spectral analysis, where the basic units are Hertz (cycles per second). Pharmacological and clinical studies have established that the high-frequency-band spectral power reflects parasympathetic activity on the heart. These cycles of variability are harmonious with respiratory rhythm. The sympathetic division modulates less frequent oscillations through the arterial baroreceptors. Since the two branches of the ANS have antagonistic effects on the sinus node, the low-frequency-band/high-frequency-band ratio is regarded as a reflection of sympathetic activity [3].

### *Tilt Table Test*

The tilt table test is another useful tool to study orthostatic intolerance and syncope. The method is based on the physiological changes that occur after adopting an upright posture with a pooling of approximately 700 ml of blood in the lower parts

of the body. In normal circumstances, the ANS quickly compensates for this relative volume loss by increasing vascular tone and cardiac output. This mechanism avoids hypotension and inadequate cerebral perfusion. Tilt table testing examines this response in a controlled environment. With passive orthostasis, additional stress is exerted on the sympathetic nervous system by blocking the influence of muscle contraction that could increase venous return. Subjects are supine for 30 min in the first step. The subject is then tilted upright for 30–45 min at an angle of 60–80°. Pharmacological stimulation with isoproterenol is sometimes used as an additional step.

The normal responses to tilting consist of an increase in the heart rate of 10–15 beats per minute, an elevation of diastolic blood pressure of about 10 mmHg, and little change in systolic pressure. There are two types of abnormal responses. One such response is orthostatic hypotension, defined as a reduction of systolic blood pressure of at least 20 mmHg or a reduction of diastolic blood pressure of at least 10 mmHg. This hypotension may induce syncope. The other type of abnormal response is postural orthostatic tachycardia, which consists of a sustained increase of heart rate of at least 30 beats per minute or a sustained pulse rate of 120 beats per minute. Tilt table testing has been used mostly to study syncope in patients with no evidence of structural heart disease [4].

## Validated Questionnaires Assessing Autonomic Nervous System

The Composite Autonomic Symptom Score (COMPASS) 31 is a refined, quantitative measure of autonomic symptoms and is suitable for use in autonomic research and practice. COMPASS-31 assesses dysautonomia symptoms in six domains: Orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor [5].

## Autonomic Nervous System Dysfunction in Fibromyalgia. Heart Rate Variability Analysis and Tilt Table Testing

Different groups of investigators have reported abnormal heart rate variability in subjects with FM. Controlled studies in women have described changes consistent with exaggerated sympathetic activity. A meta-analysis corroborated this association [6].

Several controlled studies found that fibromyalgia patients have a deficient sympathetic response to different types of stressors. On the basis of this presented evidence, it can be safely stated that patients with FM display prominent dysautonomia when studied by means of heart rate variability analysis and/or the tilt table test.

This dysautonomia can be characterized as a sympathetic nervous system that is persistently hyperactive but is hyporeactive to stress. This apparent paradox (sympathetic hyperactivity with hyporeactivity) nevertheless agrees with the basic physiological principle demonstrating that chronic hyperstimulation of the β-adrenergic receptors leads to receptor desensitization and downregulation [7].

COMPASS questionnaire discloses prominent autonomic symptom burden in fibromyalgia patients. Fibromyalgia individuals also have genetic COMT polymorphisms associated to defective COMT enzyme [5].

## Dysautonomia May Explain the Multisystem Features of Fibromyalgia

ANS dysfunction may explain the diverse clinical manifestations of FM. It has been suggested that, due to a ceiling effect, the hyperactive sympathetic nervous system of such patients becomes unable to further respond to different stressors, thus explaining the constant fatigue and morning stiffness these patients suffer. Relentless sympathetic hyperactivity may explain sleep disorders, anxiety, pseudo-Raynaud's phenomenon, sicca symptoms, and intestinal irritability [7].

## Sympathetically Maintained Pain Concept

For many years it has been assumed that abnormal activity of the sympathetic nervous system may be involved in the pathogenesis of chronic pain syndromes. This assumption was based mainly upon the observations that the pain is spatially correlated with signs of autonomic dysfunction, with the fact that blocking the efferent sympathetic supply to the affected region relieves the pain, and with the observation that norepinephrine injections rekindle the pain.

The sympathetically maintained pain concept has strong and ample foundations in the animal model. In contrast, the clinical information sustaining this pathogenesis is mostly anecdotal and does not, in most instances, fulfill the strict evidence-based medicine criteria [8].

## Animal Studies of Sympathetically Maintained Pain

Under normal circumstances, primary afferent nociceptors do not have catecholamine sensitivity. Under pathological conditions, however, particularly after trauma, a sympathetic–afferent interaction can be established both at the peripheral and central levels.

In a rabbit model, after peripheral nerve injury, sympathetic stimulation and norepinephrine are excitatory for a subset of skin C-fibers nociceptors that express α2-adrenergic-like receptors [9]. Perhaps more germane to the pathogenesis of sympathetically maintained pain are the experimental models that have been extensively reproduced, in which sympathetic sprouting at the dorsal root ganglia becomes apparent after nerve injury and forms basket-like structures around large-diameter axotomized sensory neurons; sympathetic stimulation can activate such neurons repetitively [10].

## Fibromyalgia as a Sympathetically Maintained Pain Syndrome

The defining FM features (widespread pain plus tenderness at palpation on specific anatomical points), as well as the paresthesias that these patients have, could theoretically be explained by the pathogenesis known as "sympathetically maintained pain." This type of neuropathic pain is characterized by its frequent post-traumatic onset and by the presence of stimuli-independent pain perception accompanied by paresthesias and allodynia, which are precisely FM pain features. Different controlled studies have determined that subjects with FM have higher rates of physical or emotional trauma prior to the onset of their symptoms [11]. FM is clearly a stimulus-independent pain state since there is no underlying structural damage and inflammatory signs are conspicuously absent [8]. Most patients with FM have paresthesias [12]. The typical FM tender points reflect a state of generalized allodynia. FM patients have norepinephrine-evoked pain [13].

A prototype of sympathetically maintained pain syndrome is complex regional pain syndrome. There are important points of coincidence between complex regional pain syndrome and FM. Both conditions affect mostly females and have frequent post-traumatic onset. Both entities are characterized by stimuli-independent chronic pain, allodynia, paresthesias, and vasomotor instability. Complex regional pain syndrome may evolve into full-blown fibromyalgia [14].

Emerging genomic evidence supports the concept of FM as a sympathetically maintained pain syndrome. As mentioned above, the COMT enzyme is the main catecholamine catabolic pathway. Different groups of investigators reported that when compares to healthy individuals, subjects different COMT gene enzyme polymorphisms [15].

## Small Fiber Neuropathy and Fibromyalgia

FM pain has clear neuropathic features. It is a stimulus-independent pain associated with paresthesias and allodynia. The recent recognition of small fiber neuropathy in the majority of FM patients reinforces the neuropathic nature of the illness.

Small fiber neuropathy is a disorder of the peripheral nerves that primarily affects small somatic fibers and autonomic fibers, resulting in sensory changes and autonomic dysfunction. Damage to small somatic nerve fibers results in pain, burning, tingling, or numbness that typically affects the limbs in a distal-to-proximal gradient. Autonomic symptoms include dry eyes, dry mouth, dizziness, and bladder discomfort, among others. Physical examination reveals the presence of allodynia and hyperalgesia. Conventional electromyogram and nerve conductions studies are noncontributory. The diagnosis is based on the results of a skin biopsy showing decreased nerve fiber density and also in the abnormal quantitative sudomotor axon reflex testing. Corneal confocal microscopy is a promising non-invasive method to appraise small fiber neuropathy.

Small fiber neuropathy has been associated with many medical conditions, including diabetes, autoimmune diseases, thyroid gland dysfunction, vitamin B12 deficiency, paraproteinemia, human immunodeficiency virus infection, hepatitis C virus infection and celiac disease, among others. Nevertheless, a large subgroup of patients with small fiber neuropathy has no recognizable underlying illness. A gain of function mutations in SCN9A encoded sodium channel Nav1.7, which render dorsal root ganglion neurons hyperexcitable, are present in approximately a third of patients meeting strict criteria for idiopathic small fiber neuropathy [16].

## Small Fiber Neuropathy and Dorsal Root Ganglia Sodium Channels

Dorsal root ganglia are nodules that lie along the spinal column. They play a key role in pain perception. Dorsal root ganglia house the cell bodies of small sensory nerve fibers. Under normal circumstances, dorsal root ganglia have scant sympathetic innervations. Nevertheless, trauma and/or infection trigger sympathetic sprouting within dorsal root ganglia via nerve growth factor overexpression. Such aberrant neuroplasticity enables catecholamines and sympathetic traffic to induce sensory neuron firing. These mechanisms are the basis of the sympathetically maintained pain concept. Sodium channels play a pivotal role in this hyperexcitability. Sodium channels located in dorsal root ganglia act as molecular gatekeepers of pain detection at peripheral nociceptors. Nine sodium channel subunits have been identified (Nav1.1–Nav1.9), each with a unique central and peripheral nervous system distribution. An isoform (Nav1.7) encoded in gene SCN9A of chromosome 2q24.3 is predominantly expressed in the dorsal root ganglia pain-sensing neurons and sympathetic ganglia neurons. Different Nav1.7 mutations induce electrical hyperactivity of sensory neurons in dorsal root ganglia and, at the same time, produce hyporeactivity of sympathetic ganglia neurons [16].

## Corneal Confocal Microscopy to Study Small Fiber Neuropathy in Fibromyalgia

Skin biopsy discloses small fiber pathology in approximately half of the fibromyalgia patients. With the use of corneal confocal microscopy, our group confirmed the presence of abnormal small nerve fibers in fibromyalgia. Corneal confocal microscopy is a rapidly evolving technique. Age-adjusted normative values of corneal nerve fiber parameters are being developed. This in vivo microscopy may become a useful and non-invasive fibromyalgia diagnostic test. Different groups of investigators have confirmed the presence of small fiber neuropathy in a large percentage of fibromyalgia patients [17].

## Stress-Induced Neuropathic Pain Sexual Dimorphism. Focus on Dorsal Root Ganglia

Different studies in mice and in humans demonstrate a clear female predominance in stress-evoked neuropathic pain. Dorsal root ganglia seem to play a major role in this phenomenon. Chronic stress increases circulating prolactin levels. There is marked sexual dimorphism in prolactin receptor expression in the dorsal root ganglia and in stress-induced peripheral hyperalgesia. Epigenetic (environmental) factors may sensitize the pain pathways in women. Childhood traumatization is associated with differences in TRPA1 promoter methylation in female patients with multisomatoform disorder with pain as the leading bodily symptom. This body of evidence demonstrates that in females, physical trauma and other types of stressors can lead to neuropathic pain [10].

## Patient-Centered Fibromyalgia Therapy Based on Dysautonomia Pathogenesis

Patient empowerment through information and symptom validation is the first step for a successful fibromyalgia therapy. When feasible, the patient's family should be engaged in the rehabilitation process. The following points must be highlighted:

- Fibromyalgia is a genuine painful neuropathic pain illness.
- Ongoing stress and/or certain genetic make-up could lead to constant adrenaline over-production.
- In fibromyalgia, adrenaline harms the pain-transmitting nerves.
- In fibromyalgia, stress becomes pain.

- Persistent hyper-adrenergic state provokes insomnia, then the persistently over-active system turns out to exhaustion and fatigue ensues.
- From a philosophical point of view, fibromyalgia can be conceptualized as a failed attempt to adapt to a hostile environment. During the failing process, pain-transmitting nerves are sensitized.

In our experience, most patients agree with this fibromyalgia stress-related dysautonomia-neuropathic model. A patient-oriented fibromyalgia book may help in the information course of action.

The next therapeutic step requires important lifestyle changes. The well-informed patient and her/his family must play the leading role in the rehabilitation. The attending physician provides the tools to facilitate this transformation. Common modern bad habits worsen fibromyalgia symptoms. Frequent fibromyalgia drivers are vicious household environment, workplace dissatisfaction (unrewarding repetitive tasks, harassment, night shifts), rigid-perfectionist personality, smoking, overweight, sedentarism, and unhealthy diet, among others. These common unhealthy habits or unhealthy circumstances alter autonomic nervous system balance.

Allied healthcare personnel play a major role in fibromyalgia rehabilitation program: Ideally, the therapeutic group must include a psychologist to implement cognitive-behavioral therapy, a certified trainer in tai-chi or water-based exercise, a dietician to formulate a proper diet. Pro-active patient group therapy and work modification facilitators, when available, are also advisable. Scientific evidence supports the effectiveness of this type of non-pharmacological treatment in fibromyalgia. This type of therapy also improves autonomic nervous system performance. Medical settings without some of these multidisciplinary non-pharmacological therapies for fibromyalgia are in no way doomed to fail. Therapy should be individualized to fulfill specific patient needs [18].

## *Medications*

We must recognize the fact that current fibromyalgia pharmacological therapy is rudimentary and with low retention rates. There are not medications blocking specific fibromyalgia pain pathways. Several meta-analyses disclose that drug therapy for fibromyalgia has modest effect. Only a minority of patients experience substantial benefit. Most will discontinue therapy because of either a lack of efficacy or tolerability problems. Nevertheless, the tactful use of some drugs is often beneficial. Amitriptyline (12.5–25 mg) taken a night may ease pain and sleep difficulties. Pregabalin (150 mg bid) can be used in those fibromyalgia patients with prominent paresthesias. Dizziness, drowsiness, and weight gain are frequent side effects. Duloxetine (60 mg OD) may be used in those individuals with concomitant depression. Tramadol alone or combined with acetaminophen may ease the pain. Opioids should not be used for fibromyalgia treatment [18].

## Conclusion

FM can be viewed as a disease of modern times, as a failed attempt to adapt to a hostile environment in which the main regulatory system of the body unsuccessfully attempts to adjust to stressful contemporary lifestyles. High-risk individuals would females with defective catecholamine-degrading enzymes. Dysautonomia and painful neuropathy characterize fibromyalgia. Dorsal root ganglia may be the key sympathetic-nociceptive short-circuit site where different stressors may be converted into neuropathic pain.

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# Chapter 17
# Fibromyalgia Syndrome and Sleep

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## Sleep Physiology and Sleep Assessment

Sleep is a physiological state of mind and body characterised by a loss of consciousness and relative immobility in a recumbent posture with closed eyes. Its nature has always been obscure: in Ancient Greece, the twin brother of the God of Sleep (Hypnos) was Death (Thanatos) [1].

Sleep is non-quantal (not "all-or-none"), which is why it is studied by means of complex assessments such as polysomnography (PSG), which involves measuring brain electrical activity by means of electroencephalography (EEG), skeletal muscle tone by means of electromyography (EMG), and eye movements by means of electrooculography (EOG). PSG allows the recording of the surrogate measures of sleep continuity and sleep architecture: the former considers the duration of sleep (total sleeping time), the length of time before falling asleep (sleep onset latency), and the percentage of time spent asleep while in bed (sleep efficiency, expressed as the ratio between the length of time lying awake and the total time in bed) [2]; the latter concerns the two major phases of rapid eye movement (REM) and non-REM (NREM) sleep, and the subdivisions of NREM sleep.

Neurophysiologically, falling and staying asleep require the suppression of activity in the ascending sub-cortical arousal systems, which happens by means of inhibitory neurons in the ventrolateral pre-optic area (VLPO) of the hypothalamus [3]. Although the neuronal and molecular regulation of sleep has not yet been fully and precisely defined, it is known that adenosine plays an indisputable role in wakefulness (as is highlighted by the effect of the potent adenosine receptor antagonists

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caffeine and theophylline) and that the VLPO also undergoes major circadian modulation by the suprachiasmatic hypothalamic nucleus (our circadian clock) and orexin neurons in the lateral hypothalamus [3]. The characteristic cycling between REM and NREM sleep is due to reciprocal inhibitory connections between "REM-on" cholinergic neurons and noradrenergic (locus coeruleus) and serotonergic (raphe) neurons [4].

REM sleep (the type of sleep associated with dreaming) has a low-amplitude, mixed-frequency EEG pattern of desynchronised waves, "sawtooth" waves, slow alpha waves (8–13 Hz), and theta waves (3–7 Hz). It has been noted that alpha waves are associated with drowsy wakefulness during REM sleep, which is mainly characterised by skeletal muscle atony and rapid eye movements [5]. NREM sleep is deeper, with no skeletal muscle atony and slower EEG waves, and is conventionally divided into three stages: the lightest stage (N1) is characterised by theta waves; the intermediate stage (N2) has an EEG pattern of sleep spindles (burst-like trains of 11–16 Hz waves lasting for a total of ≥0.5 s) and K complexes (biphasic waves that last for ≥0.5 s and are usually maximal over the frontal cortex); and the third stage (N3) is mainly characterised by slow delta waves of 0.5–2 Hz [5, 6]. There may also be a deeper stage (N4) but, as it is difficult to distinguish it from N3, reference is usually made to slow-wave sleep (SWS) in general. REM and NREM sleep cyclically alternate every 60–90 minutes during a normal night: the onset of sleep coincides with SWS within the first hour, after which sleep becomes shallower up to the REM stage, before returning to SWS. However, it is interesting to note that deeper SWS ceases to occur after the first two or three cycles, and thus physiologically represents about 20% of total sleep duration.

A simpler means of monitoring sleep is actigraphy, which involves a simple wristwatch-like device with multiple accelerometers that continuously record the movements of the wearer. Its greatest advantage is that it can also be used at home but, although the results are relatively consistent with PSG-monitored sleep, its accuracy is often affected by disordered or disrupted sleep [7].

In addition to actigraphy and PSG, the assessment of sleep is critically influenced by subjective self-perceptions. The American Academy of Sleep Medicine does not recommend PSG for the routine assessment of insomnia [8] because it provides little information to confirm or exclude its diagnosis, and this has led to the validation of assessments of the self-perception of sleep. These include the Insomnia Severity Index, which assesses sleep quality, fatigue, psychological symptoms, and the quality of life as a means of detecting insomnia [9], and the Pittsburgh Sleep Quality Index, which evaluates seven clinically derived domains of sleep (quality, latency, duration, habitual efficiency, sleep disorders, the use of sleeping medications, and daytime dysfunction) in order to identify clinically significant sleep impairment [2, 10].

Sleep is physiologically fundamental: SWS is essential to restore physical and mental functions and preserve physiological function, and increasing evidence shows that disturbed sleep (too short/long duration, poor quality/continuity) is associated with a host of adverse health outcomes [11].

## Sleep Disorders in Fibromyalgia Patients

The vast majority of fibromyalgia (FM) patients complain of disturbed sleep. Epidemiological studies have reported prevalence rates of 75–90% [12–14], and a 2008 prospective study of almost 500 FM patients reported a prevalence of as much as 95% [15]. One Internet-based survey published in 2012 [16] found that only 11.2% of FM patients had no problem sleeping, whereas 63% reported two or more symptoms of sleep disorders. Another Internet survey of 2596 FM patients [13] found that, together with pain, fatigue and morning stiffness, poor-quality sleep had the greatest impact on their lives, with 79% perceiving sleeping problems as one of the most frequent factors exacerbating the symptoms of FM.

Sleep disorders were not mentioned in the 1990 American College of Rheumatology (ACR) diagnostic criteria for FM [17], but the magnitude of the problem has since been increasingly acknowledged. The Outcome Measures in Rheumatology (OMERACT) recognised disturbed sleep as a fundamental outcome measure that should be used in all clinical trials involving FM patients [18] and, accordingly, the ACR included non-restorative sleep in its 2010 Preliminary Diagnostic Criteria for Fibromyalgia and the feeling of waking unrefreshed in its symptom severity score [19]. However, there is still no patient-reported, sleep-specific outcome measure that has been specifically developed and validated for FM [20].

FM patients complain of difficulties in falling or staying asleep, difficulties in going back to sleep after waking in the night, early morning awakenings, and non-restorative sleep. They also perceive daytime napping as the only beneficial means of coping with daytime sleepiness and the symptoms of fatigue [21].

The sleep alterations reported by FM patients are not isolated but correlate with a variety of FM-associated symptoms. A study by Andrade et al. [12] reported that FM sleep disturbances correlated with many FM symptoms and characteristics, primarily pain, that patients with more symptoms reported poor-quality sleep, and the total Pittsburgh Sleep Quality Index score correlated with the number of symptoms. A meta-analysis has found that distinct sleep variables predict the severity of FM symptoms [22]. It is intuitively obvious that disturbed sleep correlates with pain intensity [14], but poor-quality sleep also affects sustained attention [23] and the speed of performing complex cognitive tasks [24]. Interestingly, it has also been found that there is an association between sleep latency and the percentage of fat mass in FM women [25]. It can therefore be said that patients with more severe FM-related sleeping problems have more severe FM, and this consequently leads to higher costs for healthcare systems [26].

## Altered Sleep Physiology in Fibromyalgia Patients

The finding of subjective sleep complaints is consistent across studies, but discrepancies have been observed in the variables measured by means of PSG [22]: for example, Segura-Jiménez et al. [27] found no agreement between self-reported sleep patterns and actigraphy.

Neurophysiological and PSG examinations in the 1990s highlighted the fact that substantial sleep fragmentation and micro-arousals disrupt REM sleep and SWS, and that FM patients are characterised by a delayed sleep onset and poorer sleep efficiency [28–30]. Furthermore, a more recent systematic review [31] has found that the most frequent complaints among women with FM are more fragmented sleep (more time awake after sleep onset), reduced sleep efficiency, and a higher proportion of light sleep (more time in NREM stage N1 [24, 32–35] and N2 [36]).

Substantial FM sleep fragmentation was confirmed by a 2016 study [37] that compared patients with FM or primary insomnia with normal controls. In comparison with the controls, both patient groups were characterised by a shorter total time of sleep and SWS, a longer latency to persistent sleep (LPS), and more time awake after sleep onset (WASO) ($P < 0.05$ for each). Interestingly, the FM patients were characterised by more SWS (48.1 ± 32.4 vs. 27.2 ± 23.6 min; $P < 0.0001$) and a shorter LPS (58.2 ± 29.8 vs. 70.7 ± 31.3 min; $P = 0.0055$) than the patients with primary insomnia, but WASO was comparable in the two groups (107.7 ± 32.8 vs 108.6 ± 31.5 min); furthermore, the FM patients had shorter (4.64 ± 2.42 vs. 5.87 ± 3.15 min; $P = 0.0016$) but more frequent (41.6 ± 16.7 vs. 35.7 ± 12.6; $P = 0.0075$) bouts of being awake.

A careful meta-analysis published in 2017 [22] analysed the differences in PSG variables in 19 case–control studies. Estimated using pooled standardised mean values (i.e. weighted and pooled standard deviations using the calculation of Hedges' $g$), there were differences in WASO ($g = 0.81$, 95% confidence interval [CI] 0.21–1.41; $p = 0.01$), total sleep time ($g = -0.78$, 95% CI = −1.34 to −0.15; $p = 0.02$) and sleep efficiency ($g = -0.78$, 95% CI = −1.23 to −0.32; $p = 0.001$). The number of arousals during sleep was higher among the FM patients, but the difference was not statistically significant. The percentage of N1 sleep ($g = 0.55$, 95% CI = 0.15–0.95; $p = 0.01$) and SWS ($g = -0.66$, 95% CI = −1.21 to −0.12; $p = 0.02$) was significantly different, but not the duration of N2 or REM sleep. Seven studies also assessed subjective measures of sleep using the Pittsburgh Sleep Quality Index, and there were significant differences in the global scores ($g = 2.19$, 95% CI 1.58–2.79), sleep onset latency ($g = 1.75$, 95% CI 0.80–2.70), and sleep efficiency ($g = -1.08$, 95% CI −1.65 to −0.51).

Some studies have also shown reduced spindles in stage N2 sleep in comparison with healthy controls [38, 39].

It is not clear why the sleep of FM patients is so disrupted. One hypothesis is a dysfunctional circadian rhythm as FM patients may have altered melatonin profiles [40]. Another popular hypothesis is so-called "alpha intrusion" during SWS [34], which is usually seen as a marker of disturbed sleep although its exact meaning is not fully understood [41]. However, such findings are not consistent: some authors have not found any alpha wave alterations in FM patients [36, 42], and Chervin et al. [43] did not identify any alpha intrusions during NREM sleep but noted that PSG measures only showed non-specific evidence of a mild sleep disturbance such as an increased number of changes in sleep stages. Furthermore, the meta-analysis

mentioned above [22] did not find any differences in alpha wave activity between FM patients and healthy controls.

Rosenfeld et al. [44] attempted to investigate the question in a different way by using the frequency of delta and alpha events during NREM sleep and calculating the D/A ratio by dividing the total number of delta events by the total number alpha events during each patient's entire time of NREM sleep. In comparison with controls, the ratio was 95% specific for FM when ≤1, and the authors suggested that this finding was a putative marker of FM. However, most studies indicate that no sleep alteration is specific to FM patients, whose sleep pattern is similar to that of patients with primary insomnia [37], and a small study of patients with osteoarthritis or FM and healthy controls has found that subjective measurements of anxiety, depression, fatigue and sleep quality were better at distinguishing FM than objective measurements of sleep variables [45]. Disturbed sleep also affects patients with rheumatoid arthritis [46], who have a shorter total time of sleep and more fragmented sleep than healthy controls, but less daytime sleepiness and fatigue than FM patients [47].

EEG evidence of disturbed sleep is also represented by the cyclic alternating pattern (CAP) [48], made of prolonged oscillations in the arousal between two reciprocal functional states (phase A or greater arousal, and phase B or lesser arousal) that are more frequent during all phases of NREM sleep in FM patients than in controls. It is independent of the appearance of alpha wave intrusions and expresses a condition of unstable vigilance. NREM sleep is normally associated with relatively stable arousal and autonomic activities, which are expressed by stationary and homogeneous EEG patterns. A study by Rizzi et al. [49] has shown that there is an interplay between respiratory function and vigilance that not only leads to a longer average CAP cycle in patients than in controls but also to the longer duration of CAP cycles associated with periodic breathing. There is a positive linear correlation between the number of tender points, the CAP rate, and periodic breathing, which suggests that the last two variables have a considerable influence over pain in patients with FM.

Finally, breathing difficulties during sleep and parasomnias are also frequent in FM patients: one old study found that a pattern of periodic breathing was more frequent in FM patients than in controls [30]; Prados et al. [50] have shown that breathing disorders (apnoea/hypopnoea) are more frequent in males with FM; and Rosenfeld found obstructive sleep apnoea in 45% of the FM patients in his more recent study [44]. Parasomnias are undesirable physiological phenomena that predominantly occur during sleep, and can seriously disrupt sleep/wake schedules and individual functioning [51]. A particularly frequent parasomnia in FM patients is the restless legs syndrome (defined as an urge to move the legs during sleep), which is present in about 30–40% of patients [52–54]. However, the 2017 meta-analysis of PSG studies of FM patients [22] found no difference in the period of leg movement between patients and controls. The potentially shared mechanisms underlying disrupted sleep and the impulse to move the legs [55] may be the induction of inflammation markers and reduced pain thresholds.

## Mechanisms Underlying Altered Sleep in Fibromyalgia Patients

It is now common knowledge that the relationship between sleep and pain is bidirectional: chronic widespread pain disrupts sleep, and disrupted sleep may cause or worsen chronic pain [56]. The meta-analysis by Wu et al. [22] found that an increase in the number of tender points increases the difference in the percentage of SWS between patients with FM and healthy controls. On the other hand, a high proportion of insomniacs are affected by FM [57].

Moldofsky [58] was the first to show that people with fibrositis experienced objective sleep disturbances, and that the same symptoms could be induced in sleep-deprived healthy subjects. More recent studies have confirmed this finding [59] and established the idea that sleep negatively influences pain. A Norwegian longitudinal study that observed thousands of women for 10 years showed that those who had often or always experienced sleep disturbances were more likely to develop FM [60], which suggests that an intervention that improves the quality of sleep, especially by increasing the duration of SWS, may be of some help in patients with chronic widespread pain [61, 62].

Interestingly, the effects of sleep deprivation on pain can also be observed acutely: Edwards et al. [63] found that the total time of sleep on the preceding night was a highly significant predictor of the frequency of pain on the following day, and Wilson et al. [64] showed that more pain during the day predicted a shorter total time of sleep at night in patients with musculoskeletal pain. However, the concordance is not total as it has been shown that the total time of sleep and the time of being awake are not predictors of clinical pain in FM patients [65].

The neurobiological relationship between sleep and pain is elusive but seems to involve so many systems and mediators (the opioid and melatonin systems, dopamine and serotonin signalling, and so on) [66] that a detailed review would be beyond the scope of this chapter. One example is the complex relationships between serotonin, sleep and pain: the predominant functions of serotonin are to promote wakefulness and inhibit REM sleep [67], but this mechanism may also involve changes in thermal sensitivity [68]; however, chronic sleep restriction reduces the sensitivity of serotonin 1A receptors [69], and decreased serotonin levels have been found in the biological fluids of FM patients [70]. In addition, although the effect of sleep deficiency on the opioid system has not been directly tested in humans, it is known that sleep disruption impairs the endogenous pain inhibition system [66]. Furthermore, FM patients generally have a dysfunctional opioid system [71–73], but it also has to be remembered that the long-term use of opioids lengthens the latency of sleep onset, increases the duration of the stages of light sleep, and decreases the duration of SWS [74, 75].

FM has also been associated with increased levels of substance P, which may play a role in pain sensitisation [76], although investigations into the relationship between substance P and pain have led to conflicting results. It has been found that intraventricular injection of substance P in mice increases sleep latency and

awakenings [77], whereas bilateral microinjection of substance P in the pre-optic ventrolateral area of mice brain increases SWS [78]. One study has found that an infusion of substance P in healthy young men increases the latency of REM sleep, the time awake during the infusion intervals, and stage 1 sleep in the first part of the night [79], whereas another study of patients with obstructive sleep apnoea has shown that serum levels of substance P not only positively correlated with REM sleep and the duration of SWS, but were also significantly lower than in the control group [80], thus suggesting complex multifactorial effects on pain, sleep and sleeping disorders.

Endocrine function follows a circadian rhythm, and sleep disruption interferes with many hormone cycles. Most growth hormone production occurs during SWS, and so it is reduced by fragmented sleep [81]. FM patients have reduced levels of growth hormone and insulin-like growth factor 1 (IGF-1) [82, 83], and IGF-1 levels correlate with the quality of sleep but not with obstructive sleep apnoea [84]. It has also been hypothesised that there may be a relationship between FM and sex hormones [85] as FM symptoms may be induced by menopausal hormone deficits, and psychic stress and mood swings can disrupt sleep and consequently worsen FM. This is in line with the fact that the poor-quality sleep frequently reported by postmenopausal women is significantly reduced by oestrogen replacement therapy [11]. Chronic sleep disorders enhance the reactivity of the hypothalamo–pituitary–adrenocortical (HPA) axis [86], which may be manifested by increased cortisol output and may mediate greater pain sensitivity [87]. Conversely, although alterations in the HPA axis have been observed in FM patients, treatment with other key hormones (CRH, ACTH and cortisol) has led to conflicting and inconclusive results [88].

The maladaptive stress responses and lack of resilience frequently observed n FM patients [89] may be due more to alterations in the autonomic nervous system response to stress. FM patients often have a higher heart rate and less heart rate variability, both of which are markers of increased sympathetic cardiovascular activity [90]. Sympathetic activity is decreased during SWS and NREM sleep but, as is also observed in patients with insomnia, it is increased by chronically disturbed sleep [91]. This greater sympathetic response also correlates with a CAP during sleep [92]. As the number of tender points, the CAP rate, and periodic breathing all correlate with markers of sympathetic activity in FM patients [93, 94], sleep disorders (including CAP) and pain may be involved in a vicious circle in which pain increases sympathetic activation and reduces sleep efficiency, and this worsens the pain itself [95].

There is also a bidirectional relationship between sleep and immunity. The increased expression of some cytokines during the course of infection induces sleep, and the sleep disruption occurring during periods of stress is associated with a dysregulated immune system [11]. Disturbed sleep (including insomnia and excessively long sleep) increases the risk of infectious and inflammatory diseases, and women are more likely to show elevated levels of inflammation in association with short sleep duration [2]. Nocturnal sleep (particularly the SWS that is predominant early in the night) supports adaptive immunity, whereas sleep deprivation increases nitric oxide levels in the basal forebrain and frontal cortex, which is also an

important mediator of pain [2, 66]. This is especially interesting as it is currently hypothesised that FM is a dys- or autoimmune process [96] that may also be triggered by disrupted sleep.

Finally, a 2014 study [97] found that FM patients with depressive affect balance style scored significantly worse in all FM symptom domains including sleep disturbances, which suggests that FM can both exacerbate and be exacerbated by mood disorders: a negative mood and catastrophising increase pain perception and sensitisation, and poor-quality sleep predisposes to mental illnesses [98, 99].

## Treatment Options

Any intervention aimed at improving the sleep of FM patients must be multidimensional and take into account the interplay between FM symptoms and co-morbidities such as psychiatric conditions, gastrointestinal abnormalities (e.g. gastroesophageal reflux disease), sleep disorders (e.g. obstructive sleep apnoea) in a "trans-diagnostic" manner [100]. Bearing this in mind, and given the subjective nature of sleep fragmentation and the importance of first-line non-pharmacological treatment, it is crucial to consider a patient's clinical history, environmental conditions during sleep, sleeping habits and lifestyle (including chronotype characterisation) [101].

It is first necessary to insist on behavioural changes, including the adoption of good sleep hygiene practices such as avoiding exposure to artificial light, reducing the assumption of stimulants or alcohol before bedtime, maintaining a regular sleep–wake cycle, and preferring relaxing activities before going to bed (e.g. a hot bath) [102]. Mindfulness and relaxation are also extremely useful, and cognitive-behavioural therapy can improve insomnia symptoms and inflammation [66], and may therefore be particularly helpful for FM patients [103].

Exercise is the first indication in the European League Against Rheumatism (EULAR) recommendations for FM [104], and can also be exceptionally useful in FM patients with sleep disturbances. When exercise becomes habitual, it induces longer periods of NREM sleep and significantly reduces sleep onset latency and the time spent awake after sleep onset, thus leading to a significantly longer total time of sleep. These effects are mediated by multifactorial positive consequences (reviewed in [105]) that include mechanisms of pivotal importance for FM patients, such as endocrine and metabolic normalisation (growth hormone secretion increases during sleep), an improved mood and vagal modulation, and increased heart rate variability.

No safe and effective pharmacological treatment for sleep in FM patients has yet been found. The only three medications approved by the American Food and Drug Administration (FDA) are duloxetine, milnacipran and pregabalin. A PSG analysis of FM patients treated with pregabalin has shown that it decreases the number of wake/sleep bouts and increases sleep duration [106]. It improves sleep one or two days after starting treatment at all dose levels [107], and a dose of 450 mg/day is moderately efficacious on pain, global assessment, and function. The other

gabapentinoid, gabapentin, has uncertain effects on FM [108], although its extended-release form may be beneficial in terms of sleep [109]. The serotonin and noradrenaline reuptake inhibitors (SNRIs) duloxetine and milnacipran are less effective on sleep than on pain [110]: their beneficial action on sleep is mainly due to their analgesic effects [111].

The tricyclic antidepressant amitriptyline is also frequently used to treat pain and sleep disturbances in FM patients, although there is a lack of robust data in favour of its efficacy [112]. A low-dose, evening amitriptyline prescription may be given to FM patients who have significant difficulties in sleeping as it has been found to increase SWS and sleep continuity [113].

Benzodiazepines and non-benzodiazepine Z-drugs such as zolpidem and zopiclone have limited effects on sleep structure, and tend not to affect FM-related pain [104, 114]; however, they may be used in the short term.

Cyclobenzaprine, a centrally acting myorelaxant that is structurally related to tricyclic antidepressants, may be of some help in improving sleep in FM patients [115] but, as side effects are fairly common, a very low dose of ≤4 mg/day should be used in patients affected by FM and non-restorative sleep [116].

Gamma-hydroxybutyrate is a short-chain fatty acid that acts as a neuromodulator/neurotransmitter and plays a role in stimulating the release of growth hormone. Its marketed pro-drug, a sodium salt called sodium oxybate, has been approved by the FDA for the treatment of narcolepsy and has been found to have consistently positive multidimensional effects on FM patients, including that of improving sleep [117, 118]. A 14-week phase III trial [117] showed that it improved the quality of sleep (as assessed using Jenkins' Sleep Scale) by 20% at a dose of 4.5 g, and by 25% at a dose of 6 g in comparison with placebo (0.5%). Interestingly, there was also a ≥30% pain reduction (42.0% at a dose of 4.5 g, and 51.4% at a dose of 6 g) in comparison with placebo (26.8%), thus supporting the view that improving sleep is a key means of controlling FM-related pain. The 1-year extension trial highlighted its longer-term efficacy and tolerability (serious adverse events were experienced by 3.6% of the patients) [119].

Melatonin is the main hormone secreted by the pineal gland when stimulated by darkness. It is frequently prescribed for the treatment of insomnia at a dose of 3 mg/day, which may also have interesting analgesic effects as the administration of melatonin attenuates the development of neuropathic pain following nerve injury in animal models [66] and, in FM patients, may not only help sleep but also reduce pain by increasing endogenous pain inhibition [120, 121].

Cannabis and cannabinoids are other potential means of treating sleep disturbances, although reading the Literature it is extremely difficult to differentiate the results of administering cannabis or pure synthetic cannabinoids. Cannabinoids may help to improve sleep in the case of medical conditions associated with sleep disturbances [122]. Nabilone, a pure synthetic analogue of delta-9-tetrahydrocannabinol (THC), is not very beneficial on pain or the other symptoms of FM, but it may have some effect on sleep; however, it has a number of side effects that may hinder its long-term use [123, 124]. Extracts of the whole cannabis plant may be more effective in treating FM-related chronic pain and sleep

disturbances [125] and is specifically recommended for treating FM-related sleep disturbances in the 2012 Canadian Guidelines for Diagnosis and Management of Fibromyalgia [126] and the 2017 indications of the National Academies of Sciences, Engineering and Medicine in the United States [127]. However, although open studies have led to promising results [128, 129] and patients advocate its use [130], there is still a need for methodologically well-conducted studies and further data.

## Conclusions

It is very important to assess and treat sleep disturbances in patients with FM. Their extremely high frequency has led to them being included in all of the most recent diagnostic criteria, even in the absence of PSG abnormalities or disease-specific subjective disturbances. They have a significant impact on the patients' quality of life and correlate with many of the symptoms of FM, mainly widespread pain, mood disorders and fatigue. Sleep disturbances have a complex, bidirectional relationship with the other pathophysiological manifestations of FM, which means that physicians should specifically address them by means of both pharmacological and non-pharmacological interventions because, if correctly treated, this can have a positive effect on the patients' symptoms and overall quality of life.

A comprehensive anamnestic and instrumental (e.g. PSG) assessment can help to identify the most appropriate therapeutic approach, which should always be multidisciplinary, multimodal (combining pharmacological and non-pharmacological physical, cognitive, environmental and educational approaches), and tailored to the needs of individual patients [131]. In the absence of any safe and effective pharmacological treatment for FM-related sleep disturbances, the first-line treatment options are correct sleep hygiene, exercise, and a healthy lifestyle.

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# Chapter 18
# Clinimetrics of Fibromyalgia Syndrome


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## Introduction

Over the last 10 years, clinimetrics (the science of developing and validating means of quantitatively measuring clinical parameters) has made it possible to acquire new insights into the diagnosis, prognosis and monitoring of patients with chronic musculoskeletal diseases by transforming the experience gained in everyday clinical practice into measurable variables.

Defining the mainly articular symptoms of rheumatological diseases and understanding their underlying pathophysiological mechanisms has allowed the development of appropriate clinimetric scales for assessing clinical trial outcomes [1], but the complexity of the symptoms of fibromyalgia syndrome (FM) and their multisystem origins means that it requires multidisciplinary composite treatment [2]. These symptoms include fatigue, sleep disturbances, psychological and cognitive alterations, and regional idiopathic pain syndromes, and so it is difficult to develop and validate reliable patient-reported outcome (PRO) measures that are capable of accurately reflecting therapeutic effectiveness. Easier to use and less expensive than physician-observed disease activity and process indices, PRO measures include physical function or disability, pain, and general health status scales, side effects, medical costs, adherence to treatment, satisfaction with care, assessments of the quality and ease of doctor/patient communication, changes in lifestyles, and participation in rehabilitation programmes. However, given the many aspects of FM, outcome measures were often borrowed from studies of pain, neurology and psychiatry, which could only distinguish treatment responses in specific symptom domains [3],

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whereas it is important to consider all of the domains that FM clinicians and patients consider to be important [4], but the substantial lack of standardisation and disease-specific outcome measures prevented any clear evaluation of treatment effects until not long ago.

An attempt to include the patients' perspective was made by the OMERACT (Outcome Measures in Rheumatology) Fibromyalgia Syndrome Workshop [5], which included a set of core symptoms (pain, tenderness, patient global status, fatigue, the health-related quality of life [HRQL], physical function, disturbed sleep, depression and anxiety, and cognitive dysfunction) in the appropriate outcome domains. This aim of this chapter is to review the literature concerning the clinimetric properties of PRO instruments designed for FM, together with their advantages and limitations.

## Assessing Pain

Chronic generalised pain is a core feature of FM [6], and has now been recognised is an entity in itself and is no longer considered just a symptom of injury. The assessment of chronic pain in clinical practice involves documenting pain intensity, location, quality, and onset/duration, functional ability and psychosocial factors [7], as well as its underlying subjective motivational-affective and cognitive aspects. The instruments used to assess pain include mono- and multidimensional scales, with self-reporting being favoured because it makes regular reassessments easier.

### *Monodimensional Scales*

Although not really suitable for measuring the chronic pain of FM patients, monodimensional scales can be administered simply and more quickly than multidimensional scales in everyday clinical practice. However, they only measure the one dimension of pain intensity [7].

One of the most frequently used is a continuous visual analogue scale (VAS) [8] based on a single 10 cm horizontal line that usually has the statements "No pain" at one end and "Worst pain imaginable" at the other. It is reproducible, devoid of semantic problems, has a high degree of resolution, and allows patients a theoretically infinite number of choices, thus making it more precise than other categorical scales. It has also been shown to have good psychometric properties: it is a reliable and valid means of measuring the intensity and severity of both acute and chronic pain; it can be easily understood even by elderly subjects, and it can be easily administered by healthcare personnel (it can even be administered verbally) [9].

However, it has been reported that it leads to 7–16% higher failure rates than those reported for verbal rating scales (VRS) or numerical rating scales (NRS) [10, 11], and a number of particularly elderly or poorly educated patients find it

difficult to express the intensity of a sensation on an analogue scale as it requires a cognitive process that is certainly more complex than simple verbal expression. The need to draw a cross at, or slide a cursor to the desired point also involves good motor coordination and visual acuity [12, 13], and there is evidence showing that the visuospatial abilities required are more affected by age than the lexical abilities required to use a VRS [14]. A 0–10 NRS may be more practical, as it is easier to understand for most people and does not require clear vision or manual dexterity [15–17].

Pincus et al. [18] found that a circle with 21 numbers and an arithmetic scale has at least three advantages over a 10 cm horizontal line: (1) it can be scored without using a ruler, thus saving about half the time; (2) it does not require the exact reproduction of 10 cm line when printing or photocopying questionnaires, thus avoiding the problem of the minor distortions; and (3) patients seem to understand more clearly how to respond (some patients write words or even sentences when presented with a line) [7].

The simplest VRS is an ordinal scale with 5–7 defined categories of pain in an ascending sequence from less severe to greater pain. However, although it is simple and rapid to administer, it is not very sensitive in detecting small changes, and it is not possible to quantify the extent of the differences between the descriptive categories of pain.

Understanding may be improved by adding markers to form a graphic rating scale (GRS), such as a horizontal line anchored at both ends ("No pain" and "Worst pain imaginable") and graded 0–10 (or 0–100) by means of vertical bars of increasing height. Studies in other fields of medicine indicate that the anchors improve reliability and sensitivity, and do not necessarily lead to excessive marker bias (i.e. the tendency to be drawn towards the markers when completing the scale) [7].

Another alternative is a descriptive verbal scale (DVS) consisting of a list of adjectives describing different levels of pain intensity, which is sometimes used when patients find it difficult to translate their pain experience into a number. The scales have to have a sufficient number of adjectives to reflect the gradations between the two extremes of "no pain" and "severe pain" (usually 4–5), and the patients are asked to select (in a questionnaire or verbally) the one that best describes the intensity of their pain. However, these scales have a number of statistical drawbacks and they are usually only used for the purpose of coarse screening [14, 19].

Other scales include the Faces Pain Scale (FPS), which consists of schematic faces depicting increasing pain severity, each of which is associated with a number between 0 and 5 or 6 [20, 21]. It was originally developed for use by children, but also seems to be reliable for use by the elderly, although it is not necessarily preferable to a VRS or NRS.

Finally, there are VAS based on numbers, descriptive words or colours [16, 20–24]. These include the Visual Numerical Scale (VNS), in which each number is associated with multiple visual cues such as the height and shading of the bars; Gracely's Anchored Logarithmic Scale, a modified version of a continuous pain VAS in which descriptive anchors are spaced along its length in such a way as to represent logarithmic changes in pain intensity on the grounds that many sensory

responses are inherently logarithmic rather than linear; the Analogue Chromatic Continuous Scale (ACCS) of Grossi et al., which has proved to be more sensitive than a VAS and is very useful in clinical practice as it allows greater discrimination of degrees of pain; and pain thermometers or rulers in which words describing different levels of pain are aligned with a thermometer, combined with schematic faces depicting increasing pain severity, or associated with numerical options. All of these facilitate the communication of pain severity, particularly in the case of patients with diminished cognitive abilities or difficulties in thinking abstractly. For example, it has been shown that thermometer scales are the easiest to understand and preferred by older patients, for whom they are recommended [25, 26].

## *Pain Location*

The topography of pain is extremely important as the latest diagnostic criteria underline the concept of widespread pain [27, 28]. The location of the pain can be marked on simple diagrams or drawings of the front and back of a human body, as in the case of the Regional Pain Scale (RPS) [29, 30], which considers 19 non-articular sites, and the Self-Assessment Pain Scale (SAPS). which considers 16 non-articular sites and asks patients to indicate "the amount of pain and/or tenderness you have experienced in the last seven days" in each of a series of site descriptions accompanied by four boxes labelled 0 = none, 1 = mild, 2 = moderate and 3 = severe (the total score can range from 0 to 48, but is transformed to a scale of 0–10).

## *Multidimensional Scales*

Although the prevalence of the use of a simple 10-cm NRS may be justified by the overriding need to assess pain simply and quickly in clinical practice, the biopsychosocial view of FM [31] highlights the incompleteness of one-dimensional "biological" evaluations of chronic pain that often fail to reflect a patient's symptoms fully [32, 33]. This has led to the development of a number of multidimensional pain questionnaires that not only cover the key dimensions of pain, but also include other aspects of the pain experience and its consequences [4] such as the quality and quantity of pain, and the patient's psychological and functional status.

The complete McGill Pain Questionnaire (MPQ) is one of the most widely tested of these and can provide detailed information concerning the characteristics of FM-related pain. It includes questions concerning changes in pain over time, and classifies pain intensity as "mild", "discomforting", "distressing", "horrible" and

"excruciating" [34, 35]. However, its length may limit patient acceptance because it is complex (78 pain adjectives divided into the four major categories of sensory, affective, evaluative, and miscellaneous sensory pain) and takes 15–20 min to complete. Its Short-Form (SF-MPQ) is a 15-item self-report scale that contains just three components [36].

The self-administered Wisconsin Brief Pain Questionnaire (BPQ) [37] assesses pain history, worse pain, usual pain, and pain now using a drawing of a human figure that is shaded to indicate pain, pain intensity, the relief provided by medication, and pain interference (0 = none, 1 = a little, 2 = moderate, 3 = quite a bit, 4 = extremely).

The Brief Pain Inventory (BPI) was developed to provide information about pain intensity, the extent to which pain interferes with function, pain relief, pain quality, and the perceived cause of pain using simple, unambiguous, non-linguistic 0–10 NRS. As the level of pain may vary during the day, patients were asked to assess their pain at the time of completing the questionnaire (pain now), and the worst, least, and average pain felt during the previous week or 24 hours [38].

The 61-item Multidisciplinary Pain Inventory (MPI) is a more generalised measure of chronic pain and its impact that is divided into three sections: the impact of pain on the patient's life, the reactions of others to the patient's communication of pain, and participation in everyday activities. Its 13 seven-point numerical scales measure pain severity and interference; life control, affective distress, and support; punishing, solicitous and distracted responses to the communication of pain; and household chores, outdoor work, activities away from home, and social and general activities. It has proved to be reliable and valid in assessing both chronic pain and FM-related pain [39, 40].

The Chronic Pain Grade (CPG) questionnaire [41–43] has seven items: three (1–3) assess current, worst and average pain intensity over the previous six months using an 11-point rating scale (0 = no pain; and 10 = the worst pain possible); one assesses the number of days on which the patient has been prevented from doing his or her usual (work, school or housework) activities over the previous six months; and the last three (5–7) assess disability over the previous six months. The extent of interference with everyday activities, the ability to work (including housework), and the ability to participate in recreational, social and family activities are all assessed using 11-point rating scales (0 = no interference and 10 = unable to participate in any activity). Chronic pain is classified as grade I (low disability–low intensity), grade II (low disability–high intensity), grade III (high disability–moderately limiting) or grade IV (high disability–severely limiting), and there are also numerical self-rating scores for characteristic pain intensity (the average 0–10 rating of pain now, average pain, and worst pain multiplied by 10 to give a score out of 100) and disability (the average of the three 0–10 interference ratings multiplied by 10 to give a score out of 100). The CPG also asks how many days pain prevented the patient from carrying out his or her usual (work, school or housework) activities. It is brief and easy to complete, thus making it attractive to patients.

## Assessing Fatigue

Fatigue is not only a prevalent symptom of FM but also involved in almost all chronic systemic rheumatological, oncological and other conditions [44]. This means that there are many validated fatigue questionnaires that have been used to assess FM patients, although there is still no agreement as to which should be preferred [45].

The 12 items of the observer Fibromyalgia and Chronic Fatigue Syndrome Rating Scale (FibroFatigue Scale) [46] measure pain, fatigue, muscle tension, difficulties in concentrating, declining memory, sadness, irritability, sleep and autonomic disturbances, headache, irritable bowel syndrome, and the subjective experience of infection. Its excellent inter-rater reliability makes it capable of monitoring symptom severity and changes during treatment in patients with chronic fatigue syndrome and FM, and effectively measuring functional disability in FM patients [47, 48].

The relatively short and easy to administer Multidimensional Assessment of Fatigue (MAF) scale assesses the subjective elements of fatigue by means of 16 items covering the severity and timing of fatigue, distress, and the extent to which fatigue interferes with everyday activities (14 assessed using a 10-point NRS, and two by means of multiple-choice responses). Fifteen of the items are used to establish a global fatigue index ranging from 1 (no fatigue) to 50 (severe fatigue) [49].

The Multidimensional Fatigue Inventory (MFI) [50] assesses the five dimensions of general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue on the basis of four statements with five possible responses to each (range "yes, that is true" to "no, that is not true"), leading to a global fatigue score that 20 to 100 (higher scores indicate greater fatigue). Its psychometric properties are well documented, and it is often used to assess patients with rheumatic disorders [51].

The 13-item Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale uses five-point Likert-type rating scales (0 = "not at all"; 4 = "very much") to investigate the severity of fatigue monodimensionally [52]. The sum of the individual items gives a total score ranging from 0 (maximum fatigue) to 52 (no fatigue). It is frequently used to measure cancer-related fatigue and has also been used in patients with primary Sjögren's syndrome or rheumatoid arthritis (RA) [53, 54].

The brief and easy to administer Fatigue Severity Scale (FSS) [55] has nine items (such as "I am easily fatigued" and "Exercise brings on my fatigue") with 7-point responses. The initial validation study found a high degree of internal consistency that clearly distinguished patients from controls, and moderately correlated with a single-item fatigue intensity VAS. A clinical improvement in fatigue was associated with lower FSS scores in all of the patients.

## Assessing Sleep

FM patients frequently report sleep disturbances [56], and it has been shown that the symptoms of disordered sleep predict higher levels of pain and reduced physical functioning. It has also been shown that the sleep disturbances associated with

FM and insomnia do not correlate with polysomnographically revealed alterations (as described in the chapter on sleep), and so it is critically important to assess the self-reported changes in sleep patterns associated with FM treatments [57–59].

The 12-item Medical Outcome Study Sleep Scale (MOS-SS) is designed to evaluate the key constructs of sleep by means of subscales for sleep disturbances (four items), the quantity of sleep (one item), snoring (one item), awakening with a headache or shortness of breath (one item), the adequacy of sleep (two items), and drowsiness (three items) [60]. It is also possible to generate a 9-item Sleep Problems Index on the basis of the four sleep disturbance items, the two sleep adequacy items, two of the somnolence items, and awakening with a headache/shortness of breath, with higher scores indicating greater sleep impairment. This index is often used as an indication of the quality of sleep in clinical trials. The MOS-SS has positive psychometric properties in a broad range of patient populations, including patients with neuropathic pain [61, 62].

The 19-item Pittsburgh Sleep Quality Index (PSQI) retrospectively measures sleep disturbances and the quality of sleep [63]. It distinguishes good and poor sleepers and allows a brief and clinically useful assessment of multiple sleep disturbances. The 19 items generate seven component scores that measure a range of sleep quality-relate domains, including sleep duration and latency, the frequency and severity of specific sleep-related problems, and the perceived impact of poor sleep on daytime functioning, the sum of which (range 0–21) provides a global measure of the quality of sleep (>5 indicates disturbed sleep). This index is probably the most widely used general measure of sleep as it is flexible, it covers multiple dimensions of the quality of sleep, and it has proved to be a valid and useful instrument for chronic pain research and FM patients.

The Pittsburgh Sleep Diary (PSD) [64] quantifies various daytime and sleep/wake parameters that are subjectively self-reported at bedtime and during wake time, together with their timing and duration. The bedtime component consists of six general items: the timing of meals; caffeine, alcohol and tobacco consumption; the use of medications; and the timing and duration of periods of exercise and napping. The daytime component records data concerning the time of going to bed and "lights out"; sleep latency; the time and method of final waking; the frequency of nightly awakenings and the reasons for them; the time spent awake after the onset of sleep; the quality of sleep; and mood and alertness upon final wakening. The daytime questionnaire also makes it possible to calculate standard continuity parameters.

The Insomnia Severity Index (ISI) [65] is based on self-reports and measures a subject's perception of insomnia. Its seven items generate total scores ranging from 0 to 28, which it is recommended to interpret as "no clinically significant insomnia" (0–7), "sub-threshold insomnia" (8–14), "moderate clinical insomnia" (15–21), or "severe clinical insomnia" (22–28). A cut-off level of 14 is optimally sensitive (94%) and specific (94%) for distinguishing adults with and without a diagnosis of primary insomnia.

## Assessing Psychology and Behaviour

The psychological and behavioural characteristics of a patient may influence pain, functioning and the quality of life, and also provide an insight into the impact that pain, fatigue and other symptoms has on his or her psychological health [5]. Anxiety and depression can have a major impact on a patient's quality of life [66–68], there are various means of making a psychological evaluation [7].

The Zung Self-rating Depression Scale (ZSDS) [69] consists of 10 positively worded and 10 negatively worded questions concerning depressive symptoms that generate scores defining four categories of severity: <40 = within normal limits or no significant psychopathology; 40–47 = minimal to mild depression; 48–55 = moderate to marked depression; and > 56 ¼ severe to extreme depression.

The 20-item Centre for Epidemiologic Studies Depression Scale (CES-D) [70], which has been validated in mixed samples of cancer patients and reference groups of healthy controls, uses a 4-point scale to reflect the frequency of experiencing each symptom (0 = none of the time; 3 = all of the time); a cut-off value of 19 is usually used to indicate a need for the further assessment of depressed patients with pain.

The Hospital Anxiety and Depression Scale (HADS) [71] investigates the level of anxiety and depression during the previous week on the basis of seven items for anxiety (HADS-A) and seven for depression (HADS-D). Subjects rate each item on a 4-point scale (0–3), with higher scores being associated with a greater likelihood of the presence of a depressive or anxiety disorder. The 7-item depression scale (scored 0–21) principally measures anhedonia, which is generally considered to be the core characteristic of major depressive disorder, and the 7-item anxiety scale (scored 0–21) principally measures the symptoms of generalised anxiety disorder. Analysis of the two scores obtained from a second sample in the same clinical setting has shown that a score of 0–7 on either scale can be regarded as being in the normal range, whereas a score of 8–10 suggests the presence of a mood disorder, and scores of >11 indicate it is probably present. The HADS can be completed in only 2–5 minutes.

The clinician-administered Hamilton Rating Scale for anxiety (HAM-A or HARS) has 14 items that are each rated using a 5-point scale (0 = no symptoms; 4 = severe, grossly disabling symptoms). The total score can range from 0 to 56, and it has been suggested that clinically significant anxiety is indicated by a score of >14 [72].

The clinician-administered Hamilton Rating Scale for Depression (HAM-D) [73, 74] is probably the most widely used observer-rated scale for depressive symptoms. The original had 21 items, but Hamilton suggested that only the first 17 should be scored because the last 4 were infrequent or described only certain aspects. The items are scored 0–4 if the severity of the symptoms can be quantified or 0–2 if the symptoms are less easy to assess reliably. The greatest severity is therefore indicated by a 2 or 4, and the total score of the 17-item scale ranges from 0 to 50.

The Somatic Symptoms Checklist (SSC) [75] was originally designed and validated as a means of screening for somatisation disorder. It consists of six questions concerning the occurrence of symptoms (plus one concerning menstrual cramps for females) with "yes" or "no" answers (e.g. "Have you ever had trouble breathing?"). The sum of the item scores is therefore the same as the total number of reported somatic symptoms. One item ("Have you ever had difficulties swallowing or had an uncomfortable lump in your throat that stayed with you for at least an hour?") has since been excluded because of the high proportion of missing answers.

The Illness Attitudes Scale (IAS) [76] consists of two subscales: an 11-item health anxiety subscale (e.g. "Are you worried that you may get a serious illness in the future?") that is scored using 5-point scales (0–4), with the total score ranging from 0 to 44, and a 6-item illness behaviour subscale (e.g. "How often do you see a doctor?") that is scored using 5-point scales (0 = Never; 4 = Most of the time), with a total score ranging from 0 to 24.

The Beck Depression Inventory (BDI) [77], a self-report questionnaire consisting of 21 questions with multiple-choice answers, is one of the most widely used means of measuring the severity of depression in various settings. Designed for adults aged 17–80 years, the questions relate to depressive symptoms such as hopelessness and irritability, physical symptoms such as weight loss, fatigue, and a lack of libido, and cognitive aspects such as guilt and feelings of being punished. A score of >9 indicates the presence of at least minimal symptoms of depression. The 13-item BDI-Short Form is also widely used, but is only moderately specific and has a lower level of inter-rater reliability.

The 50-item Four-Dimensional Symptom Questionnaire (4DSQ) [78] is a self-rating means of measuring distress, anxiety, depression, and somatisation that evaluates the psychological and psychosomatic symptoms experienced during the previous week. The distress scale (16 items scored 0–2) considers the symptoms of general psychological distress, the most basic general expression of psychological suffering; the anxiety scale (12 items with a total score of 0–24) concerns the irrational fears, panic and avoidance characteristic of most anxiety disorders; the depression scale (six items with a total score of 0–12) measures severe anhedonia and depressive cognition (including suicidal ideation); and the somatisation scale (16 items with a total score of 0–32) measures a series of "psychosomatic" symptoms of bodily distress and somatoform disorders. It is recommended to use two cut-off values to indicate low, moderate and high levels of symptoms.

The Symptom Checklist (SCL-90) [79] is a psychopathology state measure divided into the eight dimensions of anxiety, depression, agoraphobia, somatic symptoms, sleeping disorders, distrust and interpersonal sensitivity, anger, and hostility, and provides an overall picture of a patient's symptoms and their intensity at a specific time point. Its 90 items can be completed no more than 12–15 minutes, and the total score reflects general psychoneuroticism or psychological distress.

The 30-item Rotterdam Symptom Checklist (RSCL) [80] has been extensively used in clinical trials. Some studies have found that it has a four- or five-factor structure, but it has also been suggested that it has a composite two-factor psychological and somatic structure.

## Generic Instruments

### *Health-Related Quality of Life (HRQL)*

Generic measures can generate scores for different components of health and the HRQL, or operational definitions of various constructs expressed by a single index value. FM patients complain of quite disabilities in everyday activities that are as severe as those reported by patients with RA, and the healthcare costs associated with the condition reflect their generally poor quality of life [81–84]. It has therefore become increasingly important to consider the HRQL when making decisions about resource allocation and the pharmacological treatment of patients suffering from chronic and disabling pain. The two main approaches to measuring a patient's perceptions of HRQL are based on the use of generic questionnaires to provide an overall picture, and the use of more specific instruments to investigate aspects relating to a specific disease or patient group [66]. In clinical practice, HRQL questionnaires can identify a patient's needs and evaluate the effectiveness of treatment. However, although generic instruments are not age-, disease- or treatment-specific (and therefore suitable for patients and the general population) [85], they are sensitive to any change in health [86] and may therefore actually obscure a more specific outcome of interest. Furthermore, some of the questions may be irrelevant or inappropriate, or the desire to ensure that a questionnaire does not take too long to complete may lead to too few questions investigating a specific area.

The 36-item Short Form Health Survey Questionnaire (SF-36) is a generic health questionnaire whose eight scales measure different aspects of health: [87–89] (1) physical functioning (10 items), or the extent to which health interferes with such activities as self-care, walking, bending, lifting, climbing stairs and other moderately vigorous activities; (2) social functioning (2 items), or the extent to which health or emotional problems interfere with everyday social activities; (3) physical role functioning (four items), or the extent to which health interferes with working activities; (4) emotional role functioning (three items), or the extent to which emotional problems interfere with working or other daily activities; (5) mental well-being (five items), or general mental health (including anxiety, depression, behavioural/emotional control and general positive affect); (6) vitality (four items), or feeling energetic and enthusiastic rather than tired or worn out; (7) bodily pain (five items), or pain intensity and its effect on normal indoor or outdoor working activities; and (8) general health perceptions (five items), or a subjective assessment of one's current or future health and resistance to illness. The questionnaire also has a single-item measure of health transition that is not included in the multi-item scales. The eight scales are weighted on the basis of a normative algorithm, and total scores range from 0 to 100 (higher scores reflect better quality of life). Other algorithms have been developed to calculate a Physical Component Summary Scale Score (PCS) and Mental Component Summary Scale Score (MCS), which are more

precise, reduce the number of statistical comparisons required and remove the floor and ceiling effects associated with some of the subscales. It takes about 15 min to self-complete the questionnaire, although most elderly patients prefer a standard interview.

The SF-36 has proved to be reliable and valid, and it has been used in a wide range of descriptive studies and clinical research trials involving FM patients [90–92], who show significant impairment on all of the eight scales, the PCS and the MCS [66]. As may be expected given the core features of FM, the dimensions that are usually affected are mental health, social functioning, vitality, bodily pain, and general health [93].

The Sickness Impact Profile (SIP) groups 136 items into 12 dimensions of everyday activities (walking, bodily care and movement, mobility, social interactions, emotional behaviour, alertness, communication, home management, recreation and pastimes, sleep and rest, eating, and work) [94, 95], which are assessed at the time of the interview. The items are weighted on the basis of the severity of dysfunction implicit in each statement. The dimension scores are added together, and the result is expressed as a percentage of the maximum possible score. There are also three summary scores: the total score of all domains, a physical score (walking, bodily care and movement and mobility), and a psychosocial score (social interactions, emotional behaviour, alertness and communication). Higher scores indicate greater dysfunction. The SIP can be self-administered or administered by an interviewer but, although it is easy to administer and score, it takes about 30 minutes to complete.

The aim of the Nottingham Health Profile (NHP) is to offer primary healthcare providers a brief indication of a patient's perceived emotional, social, and physical health problems [96–98]. The original was divided into two parts, but only the first part is now used: this consists of 38 yes/no items that can be grouped into six domains (physical mobility, pain, sleep, social isolation, emotional reactions and energy). The questions are based on statements generated by large-scale surveys of randomly selected members of the general population and are weighted on the basis of the perceived severity of the dysfunction. Scores range from 0 (no problems or limitations) to 100 (all problems are present); and there is no summary score. The total of all of the weighted scores in a given domain lies on a continuum ranging from 0 (optimal health) and 100 (worst health).

The self-administered European Quality of Life Measure (EQ-5D) was designed to measure health outcomes [99–101] by providing a simple descriptive profile and single health status index value for use in clinical and economic evaluations of healthcare and population health surveys. It consists of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each of which has three levels (no problems, some or moderate problems, and extreme problems) that can theoretically give rise to 243 possible states of health. It is cognitively simple, can be completed and takes only a few minutes to complete suitable for use in postal surveys, clinics and face-to-face interviews.

### *Disease-Specific Measures*

Disease-specific measures are designed to assess individual diagnoses or patient groups frequently with the aim of measuring treatment responses or clinically relevant changes in status. Broad FM-specific measures include the Fibromyalgia Impact Questionnaire (FIQ) or Revised Fibromyalgia Impact Questionnaire (FIQR), the Arthritis Impact Measurement Scales 2 (AIMS2) and the Health Assessment Questionnaire (HAQ), which cover general functional aspects of the condition, with specific reference to changes or states that are of particular concern to patients, and therefore considerably overlap generic measures.

The 10-item FIQ is a self-administered assessment and outcome instrument designed to measure the components of health that are thought to be most affected by FM [102, 103]. Item 1 consists of 11 questions about physical functioning that are rated using a 4-point Likert-type scale; items 2 and 3 ask the patient how many days they have felt well and how many days they have been unable to work (including housework) because of FM symptoms; and items 4–10 are 10-point horizontal linear scales on which to mark the level of working difficulties, pain, fatigue, morning tiredness, stiffness, anxiety and depression. All of the questions refer to the previous seven days and, as each item has a maximum score of 10, the maximum total score is 100. The score of most FM patients score is about 50, whereas those with severe disease normally score > 70. The questionnaire, which takes about five minutes to complete, has been widely used to measure outcomes in FM studies, but it is rarely used in clinical practice mainly because clinicians perceive it as being difficult to administer and score, consider it clinically irrelevant, or are simply unfamiliar with it. Other potential problems are that it may underestimate disease impact and inadequately assess the effect of treatment in patients with mild symptoms [29].

The FIQR was developed in an attempt to overcome these limitations without affecting the essential properties of the original [104]. Its 21 individual questions, all of which refer to the previous seven days, are rated using 11-point numeric rating scales (0–10, with 10 being “the worst”). The revised questionnaire is divided into three linked domains: (1) function (nine questions vs. 11 in the FIQ); (2) overall impact (two questions, the same as in the FIQ, but they now relate to the overall impact of FM on function and symptom severity; and 3) symptoms (10 questions vs. seven in the FIQ). The symptom domain has four new questions concerning memory, tenderness, balance, and environmental sensitivity. The FIQR is much easier to score than the FIQ: the total function score (range 0–90) is divided by three, the total overall impact score (range 0–20) is not changed, and the total symptoms score (range 0–100) is divided by two, after which the sum of the three modified domain scores gives the total FIQR score. The weighting of the three domains of the FIQR is different from that of the FIQ as 30% of the total score is attributed to “function” (10% in the FIQ) and 50% to “symptoms” (70% in the FIQ), whereas that of “overall impact” remains the same and, like that of the FIQ, the maximum total score of

the FIQR is 100. In comparison with the FIQ, the FIQR takes about half the time to complete.

The 78-item AIMS2 and its 26-item short form are widely used disease-specific means of assessing the severity of arthritic pain and the extent to which it has affected the health of rheumatology patients in the previous month [105, 106]. The areas considered are mobility, walking and bending, hand and finger function, arm function, self-care, household tasks, social activity, family support, arthritic pain, work, tension and mood, and respondent are asked to assess: (1) the degree to which they are satisfied; (2) the impact of the disease; and 3) the areas in which they would like to see improvements. They are also asked to summarise their perceptions of their current, future and overall health, and describe any existing medical problems that may affect their health.

The most widely used form of the Stanford Health Assessment Questionnaire (HAQ) is a self-administered 20-item questionnaire that investigates difficulties in eight activities of everyday life (dressing and grooming, rising, eating, walking, hygiene, reach, grip and outside activities) [107] during the previous week using 4-point scales ranging from 0 (no difficulty) to 3 (unable to do). The final score is the average of the eight category scores and ranges from 0 to 3, with higher scores representing greater disability. DeWalt et al. have analysed the number of symptoms and quantitative pain, fatigue and functional disability scores (including the ratios between pain and physical function scores and between fatigue to physical function scores) in order to investigate how such scores can help to identify patients with FM. They studied 78 consecutive FM patients and 149 RA controls over a period of two years, and found that the former had significantly higher pain/physical function and fatigue/physical function ratios, and reported significantly more symptoms [108].

The self-administered Fibromyalgia Assessment Status (FAS) [29] questionnaire is a short and easy to complete means of assessing non-articular pain (SAPS range 0–10), fatigue (range 0–10), and the quality of sleep (range 0–10) that provides a single composite measure of disease severity (range 0–10) that can be calculated by adding the three subscores and dividing the result by three. All three measures are printed on one side of a sheet of paper for rapid review (Fig. 18.1) and can be quickly scored by a healthcare professional without a ruler, calculator, computer or website. Our own data suggest that it is a reliable, valid and responsive disease-specific means of assessing the effects of treatment on FM patients that can be used in everyday clinical practice as well as in clinical trials [29]. The modified 2019 version [109] was developed in order to improve patient understanding and the feasibility of the questionnaire itself, and reduce systemic variability. Patients are asked to indicate their feeling of chronic pain in 19 body regions illustrated by a drawing using a simplified scoring system that considers only its presence (score 1) or absence (score 0): the final score ranges from 0 to 39. It should allow physicians to obtain reliable information concerning the course of the disease, and be sufficiently sensitive to raise a red flag in the case of deterioration, although this now needs to be fully evaluated in other settings [109].

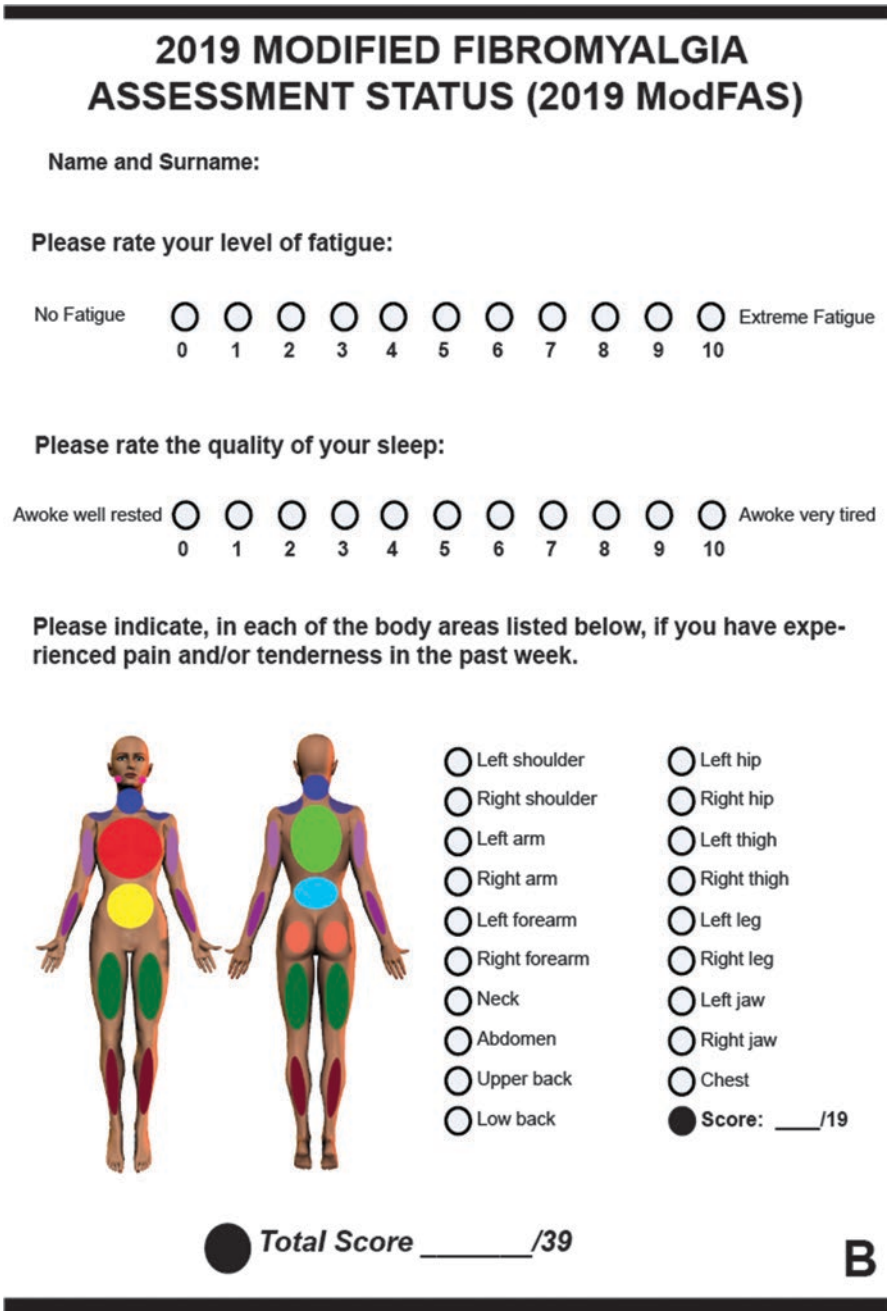


**Fig. 18.1** The Modified Fibromyalgia Assessment Status (modified from Salaffi et al., 2020 [109])

## Conclusions

Assessing health status, treatment effectiveness and disease outcomes are crucially important in everyday rheumatological practice because the results of clinical trials conducted under ideal environmental conditions and involving selected patient groups often cannot be reproduced in unselected patients.

However, developing a claim of efficacious treatment for FM is hampered by the lack of consensus concerning the primary outcome measures that should be used in clinical trials and the need for the further refinement and validation of existing measures or the development of new composite measures or response criteria that better reflect the multidimensional nature of FM and can also be used in everyday clinical practice [29]. With this in mind, it is important to try to establish cut-off points for self-administered questionnaires relating to disease severity [110] in order to determine the effectiveness of different treatments, although this is difficult because of the variety of the available instruments and the protean clinical expressions of the disease[111]. Recently, we establish optimal cut-off values for the scores of the FIQR, the modified Fibromyalgia Assessment Scale (FAS 2019mod), and the Polysymptomatic Distress Scale (PDS) in order to distinguish five levels of FM disease severity [110]. The overall median FIQR, FAS 2019 mod and PDS scores (25th–75th percentiles) were respectively 61.16 (41.16–77.00), 27.00 (19.00–32.00) and 19.0 (13.00–24.00). Reconciliation of the mean 75th and 25th percentiles of adjacent categories defined the severity states for FIQR: 0–23 for remission, 24–40 for mild disease, 41–63 for moderate disease, 64–82 for severe disease and > 83 for very severe disease; FAS 2019 mod: 0–12 for remission, 13–20 for mild disease, 21–28 for moderate disease, 29–33 for severe disease and > 33 for very severe disease; PDS: 0–5 for remission, 6–15 for mild disease, 16–20 for moderate disease, 21–25 for severe disease and > 25 for very severe disease [110].

The appropriate application of clinimetrics to signs and symptoms gives the approach to chronic diseases a modern perspective, as the benefits and risks of therapeutic options can be evaluated not only on the basis of a clinician's observations and opinions but also (and above all) on the basis of the personal preferences and wishes of individual patients. This is particularly important in the case of a disease such as FM, which has no objective signs or biomarkers and can only be diagnosed and followed up on the basis of the symptoms reported by the patients themselves.

The usefulness of clinimetrics does not end with the simplification of the collection of clinical information or the minimisation of partiality and variability in the way clinicians frame questions and record answers. Clinimetric evaluations are generally valid and reliable means of identifying patient needs, establishing therapeutic and rehabilitative priorities, and supporting the strategic planning of healthcare, and should therefore be considered an integral part of rheumatology research and the management of rheumatic diseases.

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# Chapter 19
# Concomitant Fibromyalgia in Rheumatic Diseases


**Ori Elkayam**

## Introduction

Fibromyalgia is characterized by widespread pain accompanied by somatic symptoms such as fatigue, sleep disorders and other somatic symptoms [1]. Fibromyalgia has a tremendous impact on the quality of life of the patients. It is a source of physical disability and has profound psychosocial consequences. Although most of the patients with fibromyalgia suffer from primary fibromyalgia, the syndrome is increasingly recognized in other inflammatory and non- inflammatory rheumatic diseases [2–6]. The recognition of concomitant fibromyalgia among patients with the established rheumatic disease is extremely important since it might be misinterpreted as poor control of the primary disease with management misdirected towards the underlying diseases rather than focused on the management of fibromyalgia.

This chapter will review the different aspects of fibromyalgia which is concomitant to rheumatic diseases. We will cover different aspects of the relationship between fibromyalgia and concomitant rheumatic diseases, such as the evolution of the definition of co-morbidities in the definition of fibromyalgia, the prevalence of fibromyalgia among different rheumatic diseases, the impact it might have on the management of rheumatic diseases and how fibromyalgia may mask other rheumatic diseases.

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## Classification Criteria of Fibromyalgia with Respect to Concomitant Rheumatic Disease

The first classification criteria of fibromyalgia were established in 1990 by the American college of rheumatology (ACR), with specific emphasis on the presence of widespread pain along with pain in at least 11 of 18 tender joints [7]. These criteria recognize the possible presence of a second clinical disorder that does not exclude the diagnosis of fibromyalgia [7]. These criteria were modified in 2010 with special references to the presence of widespread pain and symptom severity scales such as fatigue and cognitive syndrome. On the other hand, these criteria exclude patients who have a disorder that would otherwise explain the pain [8]. "These criteria were further modified in 2016 and reverse this exclusion, specifying the a diagnosis of fibromyalgia is valid irrespective of other diagnosis". A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses [9]. This evolution in the definition of fibromyalgia with respect to concomitant rheumatic disease is interesting and reflects the increasing recognition of the concomitant existence of these syndromes. Likewise, the symptom burden of primary and secondary fibromyalgia does not seem to differ. Wolfe et al. have studied fibromyalgia symptoms among 1525 patients with primary FMS in comparison with 12,037 patients with rheumatoid arthritis (RA), 22% of them with secondary fibromyalgia [10]. The widespread pain index, symptom severity scale, and pain, global, quality of life, and physical and mental component scores were essentially the same or only slightly different in primary and secondary fibromyalgia. Health Assessment Questionnaire-Disability Index scores were slightly higher in secondary fibromyalgia as was the painful joint count [10].

## The Prevalence of Fibromyalgia Among Rheumatic and Non-rheumatic Diseases

The presence of fibromyalgia among patients with rheumatic diseases is well known.

Comorbid FMS is reported to occur in 20–30% of patients with various rheumatic conditions. In a large North American database of over 6000 patients, FMS was identified in 21% with rheumatoid arthritis (RA), 37% with systemic lupus erythematosus (SLE) and 17% with osteoarthritis (OA) [11].

Haliloglu et al. have evaluated the prevalence of fibromyalgia among a large population of patients with a variety of rheumatic diseases [5]. The prevalence of FMS in patients with rheumatologic diseases was found to be 6.6% for RA, 13.4% for SLE, 12.6% for Ankylosing Spondylitis (AS), 10.1% for OA, 5.7% for Behcet Disease, 7.1% for familial Mediteranean fever, 12% for primary systemic sclerosis (pSS), 25% for vasculitis, 1.4% for gout, and 6.9% for polymyalgia rheumatica [5].

Duffield et al. have published a meta-analysis on the prevalence of fibromyalgia in inflammatory rheumatic diseases, which included 40 studies [12]. Of the included

studies, 29 reported data on the prevalence or impact of FMS in RA [5, 13–33]. Nine articles studied Axial Spondyloarthritis (AxSpA), with eight articles focusing on FMS in AS [5, 23, 33–38], and two papers looking at non-radiographic axial SpA [15, 35]. Lastly, six studies focused on psoriatic arthritis (PsA) patients [22, 33, 39–41]. The prevalence of FMS in patients with RA varied considerably from 4.9% [33] to 52.4% [15]. In the proportional meta-analysis, the overall prevalence rate of FMS was 21% (95% CI: 17, 25%) across all studies [12]. Including only studies with larger sample sizes ($n > 150$) reduced pooled estimate of prevalence down to 14%. In AS and axial SpA, the prevalence of concomitant FMS ranged from 4.11 to 25% and in proportional meta-analysis overall prevalence of FMS was 13% (95%CI: 7, 19%) across all studies [12]. Other studies not included in this meta-analysis reported similar results [42, 43].

The reported prevalence of concomitant FMS in PsA ranged from 9.6 to 27.2%. In proportional meta-analysis, the overall prevalence of FMS was 18% (95% CI: 13, 23%) across all studies [12].

Among patients with non-inflammatory rheumatic diseases, comorbid FMS is also reported to be high, with a prevalence of 10–17% in patients with osteoarthritis (OA). This figure is even higher for chronic spinal pain, with 25–40% of persons with chronic low back pain reporting FMS [6, 44].

FMS is also recognized as a prominent comorbidity in patients with other chronic diseases such as neurologic diseases like multiple sclerosis and Parkinson disease, endocrine disease mainly involving the thyroid as well as gastro intestinal disorders such as inflammatory bowel diseases and celiac diseases [45].

Lastly, it is important to recognize that FMS is highly prevalent in obese persons, where it is present in up to 45% of them [46].

## The Impact of Fibromyalgia on the Burden of Diseases in Patients with Rheumatic Diseases

The presence of FMS has a profound impact on the burden and management of the underlying inflammatory condition. The concept of the treat to target is widely implemented in the management of rheumatic diseases and is mainly based on the evaluation of scores of disease activity. Most of these scores rely, in part and sometimes mostly, on patients' reported outcomes. The presence of FMS may influence the scores and result in an unnecessary escalation of the anti-inflammatory treatment. In patients with RA, 19 studies reported the impact of FMS on disease activity score (DAS) [28]. All but one reported higher DAS28 among patients with concomitant FMS. Sixteen of these found statistically significant increased DAS-28 in RA patients with FMS compared with those without. The parameters that most importantly increased the DAS-28 in these patients were higher tender joint count [13, 14, 17, 24, 27–30, 47–54] and visual analog scales global scores [14, 17, 24, 28, 29, 47–49, 52, 53]. On the other hand, the swollen joint count seems to better discriminate between pain due to FMS or to the underlying inflammatory disease [5,

27, 30]. In axSpA, disease activity may be assessed using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) or Ankylosing Spondylitis Disease Activity Score (ASDAS). The BASDAI score is solely based on patient-reported outcomes and therefore is extremely influenced by the presence of concomitant FMS [55]. The ASDAS includes CRP levels and may be more objective, although most of it is also based on patients' reported outcomes [56]. Nine studies have reported the impact of comorbid FMS on disease activity in AxSpA, all using BASDAI and only two the ASDAS [5, 23, 34–38, 42, 57]. As expected, BASDAI scores were reported higher, the differences between axSpA with or without FMS being statistically significant. Two studies have demonstrated that the ASDAS can better discriminate disease activity in axSpA patients with or without FMS [23, 57].

Similar results have been reported in PsA [40, 41]. Our group has evaluated the effect of FMS on indices of disease activity in 73 patients with PsA. The Composite Psoriatic Disease Activity Index (CPDAI) and Disease Activity Index for PsA (DAPSA) were significantly higher in patients with coexisting PsA and FMS (9.23 ± 1.92 and 27.53 ± 19.23, respectively) than in patients with PsA only (4.25 ± 3.14 and 12.82 ± 12.71, respectively). None of the patients with FMS and PsA met the criteria for Minimal Disease Activity (MDA), whereas 26 PsA only patients did (43.3%, $p = 0.003$). Health Assessment Questionnaire, BASDAI, and Leeds Enthesitis Index (LEI) scores were significantly worse in patients with PsA and associated FMS [40]. Another study demonstrated that the absence of FMS was associated with the increased rate of remission [41].

Similarly, the presence of pain hypervigilance has an important impact on the report of pain in patients with OA [58].

The effect of FMS on the indices of SLE disease activity such as SLE disease Activity Index (SLEDAI), SLE Collaborating Clinic (SLICC) damage index or the British Isles Lupus Assessment Group (BILAG) has not been well studied. The systemic lupus activity measure (SLAM) does not seem to be affected by the presence of FMS [59]. The presence of FMS has been shown to affect health-related quality of life (HRQoL) in middle-aged female patients with SLE, poor sleep quality being the common independent risk factor for poor HRQoL in both middle-aged SLE patients with and without fibromyalgia [60].

In summary, the presence of FMS significantly affects the disease activity scores of the different inflammatory arthropathies. Concomitant FMS in patients with RA is associated with a higher DAS28 due to subjective parameters and with the more frequent use of biological treatments [61]. In patients with PsA, biologic drug survival was significantly low among 58 patients with concomitant FMS compared to 180 patients without FMS [62]. Similar results have been reported in axSpA, the presence of FMS significantly affecting the response to TNFα inhibitors among 192 patients with axSpA and FMS in comparison with 316 axSpA without FMS [63].

These observations raise doubt about the ability of disease activity indices to determine treatment in patient with inflammatory arthropathies and concomitant FMS. It has been suggested that in these patients, disease activity should be

determined using an objective tool such as ultrasound evaluation of joint involvement. It has been shown that in patients with RA and FMS, evaluation of disease activity by ultrasound may prevent unnecessary escalation of disease-modifying anti rheumatic drugs (DMARDs) [64]. This topic is even more relevant in PsA where enthesitis is prominent and may be confused with tender points of FMS. A recent study performed on 39 with PsA, 23 with FMS, and 39 with both have demonstrated that clinical evidence of enthesopathy was found in 43% of the patients with PsA, 51.3% of those with PsA-FMS and 50.8% of those with FMS, while US entheseal abnormalities were detected in respectively 77%, 74%, and 35%, suggesting that the use of clinical evaluation of patients with PsA and FMS may overestimate the presence of enthesitis and should be confirmed by ultrasound [65].

## Fibromyalgia Masquerading Inflammatory Rheumatic Diseases

The presence of fibromyalgia may masquerade the presence of inflammatory arthropathies. Most patients with FMS suffer from low back pain, which may have inflammatory features. We have evaluated the prevalence of axial spondyloarthritis and sacroiliitis by MRI in 99 with fibromyalgia and have demonstrated that 10.2% fulfilled the ASAS criteria for axSpA, 8% having sacroiliitis on MRI. Imaging changes suggestive of inflammatory involvement (e.g., erosions and subchondral sclerosis) were demonstrated in 15 patients (17%) and 22 patients (25%), respectively. The diagnosis of axial SpA was positively correlated with increased CRP level and with physical role limitation at recruitment [66]. Likewise, FMS may masquerade other autoimmune rheumatic diseases such as RA [67] or SLE [68].

## Conclusions

FMS is present in up to a quarter of patients with rheumatic diseases, both inflammatory and non-inflammatory. The recognition of FMS in these patients is primordial since it might artificially increase disease activity scores resulting in unnecessary escalation of treatment for the underlying disease and prevent treatment aimed at improving fibromyalgia symptoms. In these patients, evaluation of disease activity based on ultrasound findings may be more appropriate. Furthermore, patients with FMS may develop autoimmune rheumatic diseases, and the masquerading effect of FMS should be kept in mind in this population.

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# Chapter 20
# Cannabis-Based Medicines in Fibromyalgia


**Ariane Barbacki and Mary-Ann Fitzcharles**

## Introduction

Fibromyalgia (FM) is characterized by widespread chronic pain, sleep disturbance, and fatigue, as well as comorbidities including mood disturbance and hypervigilance [1]. Given this complexity and variability in symptoms, FM remains a challenge to treat effectively. In the absence of a "gold standard" treatment, cannabis-based medicines have been proposed as an option. Cannabinoids have the potential to impact many symptoms, including pain, sleep disturbance, anxiety, and mood disorders. Clearly, an agent with an impact on many symptoms could offer an advantage.

Cannabinoids have entered the therapeutic arena with great enthusiasm and have been promoted by advocacy and media coverage with the perception that they are a treatment that has been neglected by the medical community. In this chapter, we will describe the function of the human endocannabinoid system, examine the preclinical and clinical evidence for an effect in FM, discuss currently available cannabis medicines, review the potential risks and provide some practical guidance for clinical treatments.

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## The Endocannabinoid System and Preclinical Evidence

The endocannabinoid system has important effects on brain development, neurological function and serves to maintain the body in equilibrium via a "rest and respite" mechanism counterbalancing the "flight and fly" system [2]. The physiological effects are mediated by endogenous ligands signaling via the human cannabinoid receptors, found throughout the body, with two receptors ($CB_1$ and $CB_2$) identified to date, and a possible third, GPR55. $CB_1$ receptors are mostly associated with neural tissue with pain modulating effects, but also in areas sub-serving motor control, memory, and cognition [2]. $CB_2$ receptors are found peripherally on immunologic cells and musculoskeletal tissues, but with exact function needing clarification [3]. The endocannabinoid ligands are produced by the breakdown of cell membrane phospholipids and have a short half-life. They cascade in an alternate pathway to the inflammatory prostaglandin pathway with the potential to modulate pain and inflammation [4]. This complex interaction of molecules is not a simple on/off phenomenon, and is affected by the interaction between various ligands, cross-reaction with non-cannabinoid receptors, and plasticity of response dependent upon local tissue characteristics or presence of other molecules such as opioids [5].

Cannabinoids present an attractive potential for use in FM in view of preclinical studies showing effects on pain, inflammation, and calming effects [6, 7]. There are no preclinical models of FM, so any effect of cannabinoids must be extrapolated from other preclinical models. Low doses of tetrahydrocannabinol (THC) and its synthetic analogs have been shown to exert anxiolytic effects in animal models with generalized anxiety disorder and to have antidepressant-like properties [8].

## Cannabis-Based Medicines

Patients can access cannabis-based medicines in two ways. (1) Cannabis plant products are derived from the whole plant, i.e., the buds, flowers, and leaves, which contain many molecules, including non-cannabinoid molecules; (2) pharmaceutical preparations that are either plant derived or synthesized. The two cannabinoid molecules of greatest interest are $\Delta^9$-THC and cannabidiol (CBD). THC has mostly pain relieving and psychoactive properties, whereas CBD has additional tranquilizing and anxiolytic effects but with minimal psychoactive effects.

### *Cannabis Plant Products*

Herbal cannabis, derived from the plant *C. sativa,* has been called a plant of 1000 molecules, with differing molecular content for different strains of the plant, and within a strain depending upon growing conditions, method of harvesting, storage,

and preparation [9]. The leaves and flowers of the plant have the highest concentration of THC and CBD, with the concentration of THC varying from 3% to 30%, and CBD from <1% to 13% [10, 11]. Other molecules such as terpenes and phenolic compounds may work in synergy to provide a theoretical therapeutic effect named "the entourage" effect, but with only anecdotal evidence to date [12, 13].

Medical cannabis may be inhaled by smoking or vaporizing, ingested as an oil, absorbed through mucous membranes or used topically [13]. There are no directives other than anecdotal health care provider suggestions and patient report regarding the ideal method of administration, dosage, or specific product to use. With smoking not recommended due to the presence of toxic products of combustion, vaporization was believed to be less harmful until the recent emergence of severe acute lung disease related to vaping of recreational products [14, 15].

### *Pharmaceutical Cannabinoid Preparations*

There are currently four pharmaceutical cannabis-based medicines available worldwide, namely, dronabinol, a stereoisomer of THC; nabilone, a synthetic analog of THC; the oromucosal nabiximols spray, a combination of $\Delta^9$-THC and CBD, and highly purified CBD marketed as Epidiolex. Pharmaceutical preparations are regulated according to good manufacturing practices (GMP), have accurate molecular concentrations and have been studied regarding dosing, therapeutic and adverse effects. Pharmaceutical manipulation of the endocannabinoid system by other methods such as inhibition of enzymes that degrade endocannabinoids, namely fatty acid amide hydrolase (FAAH), may hold potential, although a recent trial resulted in severe illness and death in some participants [16, 17].

## Pharmacokinetics and Pharmacodynamics of Cannabinoids

Evidence for the pharmacokinetics and pharmacodynamics of cannabinoids is limited, and data are extrapolated from studies in healthy individuals. Both THC and CBD are lipophilic, resulting in low bioavailability. When inhaled, both molecules peak within a few minutes, with bioavailability in the order of 30% for both, and thereafter rapidly decline [14]. Serum levels can be erratic and influenced by the technique of inhalation, such as the rapidity, depth, and duration of breath-holding. The rapid rise in blood levels following inhalation may be an advantage for an immediate effect. Oral administration of the oil results in a more gradual and prolonged increase in serum level, with peak concentrations of THC and CBD, reached within 120 minutes. Bioavailability is lower following oral administration due to first-pass metabolism, but this route likely provides a more controlled and longer lasting effect.

Metabolism of THC and CBD is mainly hepatic, via cytochrome P450 isoenzymes. Metabolites are excreted in feces and urine. THC and CBD are highly lipophilic with high volumes of distribution, leading to a bi-phasic elimination curve: a fast initial half-life and a long terminal half-life, with the latter in the order of 24 h. Due to adipose tissue deposit, chronic daily use can prolong the elimination half-life up to 2–5 days [14]. Pharmacokinetic studies of drug-drug interactions are lacking, but with potential for effect via inhibition or induction of cytochrome enzymes. Similarly, information on pharmacodynamic interactions with other medications is also lacking, but it can be anticipated that there can be compounding effects with agents with psychotropic effects such as anti-depressants, sedatives and hypnotics. Hypertension and tachycardia due to cannabinoids could also pose a risk in the setting of cardiac stimulants.

## Clinical Evidence for Cannabis-Based Medicines in Fibromyalgia

### *Randomized Controlled Trials*

Though there have been multiple animal and human observational studies, there are only three randomized-controlled trials (RCT's) of cannabis-based medicines in FM.

The first RCT was a parallel design of 40 FM patients receiving either placebo or nabilone up to 1 mg twice a day, with a 4 week active treatment phase over an 8 week period with pain [visual analog pain (VAS)] and quality of life [fibromyalgia impact questionnaire (FIQ)] as primary outcomes [18]. Although both outcomes statistically improved with nabilone, neither met the minimally clinical important difference (MCID) [19, 20]. Though an improvement in a FIQ anxiety subscale was reported, interpreting differences within subscales requires caution and additional study before drawing conclusions. No serious adverse events were noted, but there were more side effects in patients using nabilone, including drowsiness (7/15), dry mouth (5/15), vertigo (4/15), and ataxia (3/15). No relative risks nor confidence intervals were provided for any result [18].

The second study was a double-blind, cross-over trial which compared nabilone (0.5 mg/day up to 1 mg/day) to amitriptyline (10–20 mg before bedtime) in 32 FM patients, with a primary outcome of sleep quality measured by the Insomnia Severity Index (ISI) and the Leeds Sleep Evaluation Questionnaire (LSEQ) [21]. The 29 patients who completed the trial received 2 weeks of each drug with a 2-week washout period between trials. Using a study per protocol analysis, both drugs improved sleep, with nabilone marginally superior to amitriptyline on the ISI (adjusted difference: −3.25; CI −5.26 to −1.24), but did not meet the MCID [22]. In addition, there was no difference between treatments using the LSEQ, though patients reported more restful sleep on nabilone. Secondary outcomes did not differ for pain, mood, or quality of life. No serious adverse events were noted, but there was a trend for more adverse events with nabilone (91 vs. 53) [21].

A third placebo-controlled trial was a 4-way cross-over trial of inhaled pharmaceutical-grade cannabis in 20 FM patients [23]. Patients inhaled three different varieties of cannabis with known THC/CBD content (THC 22%, CBD <1%; THC 6%, CBD 8%; THC <1%, CBD 9%) over 5 min, with measurement of pain at time intervals up to 3 h after inhalation. Adverse events of a drug high, coughing, and dizziness were common for all treatments, but not placebo. None of the active treatments had a greater effect than placebo on spontaneous or electrical pain, but pressure pain was improved with THC products. There was a high placebo response with a pain reduction of 30% for 11/20. More patients receiving the high THC and lower CBD content had at least a 30% reduction in spontaneous pain compared to placebo (90% vs. 55%). The magnitude of the analgesic effect correlated with the magnitude of a drug high, which was a feeling most patients disliked. The high CBD did not have a significant effect on either spontaneous or evoked pain, and CBD was noted to increase plasma concentration of THC. This small study suggests that some patients may have pain relief with high THC and low CBD inhaled herbal cannabis, especially when associated with drug high [23].

A 2016 systematic review on cannabinoids in patients with rheumatic diseases identified four trials, two of which were in patients with FM and described above [24]. These two trials were also included in a Cochrane analysis published the same year [25]. The Cochrane review assessed both studies to have a moderate risk for bias, with the quality of all outcomes according to the GRADE system assessed as very low given the indirectness, imprecision and potential for reporting bias (no study protocols were available). The evidence for effect was judged as third tier: outcomes were derived from completer analysis (rather than intention to treat) and were reported as group mean data; both studies were of short duration and included few patients. Neither reported the proportion of participants with at least 30 or 50% pain relief or who were very much improved. In addition, more participants dropped out in the nabilone groups (4/52) compared to the control groups (1/20 in placebo and 0/32 in amitriptyline). Overall, the authors concluded that there was no convincing unbiased evidence that nabilone was of value in FM patients [25].

## *Surveys and Observational Studies*

There have been several surveys and observational studies of cannabis-based medicines in recent years. These studies require scrutiny regarding quality before conclusions can be fully accepted.

Medical cannabis was added to analgesic treatment in 31 FM patients with associated lower back pain in an observation cross-over single-center study [26]. Analgesic treatment consisted of a combination opioid (oxycodone hydrochloride 5 mg and 2.5 mg of naloxone hydrochloride) two or three times daily and duloxetine 30 mg a day. Twenty-eight of the 31 patients were prescribed medical cannabis at a dose of 20 grams/month with THC to CBD content of 1:4 for a minimum of 6 months. There was an improvement in lumbar range of motion, pain (VAS), and

FM symptoms (FIQ), and decreased medication use, not further specified. The results must be interpreted with caution: it was an open-label study, did not include a control group, comprised patients younger than usually seen in FM studies (mean 33 years), had no prespecified primary or secondary endpoints, and multiple outcome measures were recorded.

An Internet-based questionnaire posted on three FM Facebook groups examined the habits of cannabis consumption by FM patients in Israel [27]. The response rate was 14% (383 of 2705), with a high risk for nonresponse and selection bias. Most patients reported improvement in pain (94%), sleep quality (93%), depression (87%) and anxiety (67%), without the use of validated measurements or assessment of the magnitude of improvement. At least some cannabis was accessed on the black market (55%), and 63% smoked cannabis with a cigarette. Furthermore, 72% of patients were driving as usual while using cannabis [27].

In a prospective observational study of 367 FM patients followed in an Israeli specialized cannabis clinic for 6 months, there was a significant reduction in pain (−4 on VAS), with an overall treatment response reported by 81% [27]. Only 57.5% of patients were included in the final analysis, leading to a significant risk of non-responder and attrition bias. Factors associated with discontinuation included older age (>60 years old) and patient concerns regarding cannabis. The authors noted that there was no significant difference between responders and non-responders at baseline and that more than 85% of non-responders were still using cannabis [27].

In order to evaluate the persistence of pharmaceutical cannabis-based medicines in the real world, a large Canadian retrospective, population-based, cohort study estimated the prevalence of continuous use for up to 1 year from the initial prescription regardless of the underlying diagnosis [28]. Using an administrative database, 5452 new users were identified. Only 18.1% were still using cannabinoids at 1 year with a median use of 31 days. Of these, 1894 patients had an underlying diagnosis of fibromyalgia, which was also identified as a predictor for continued use (HR 0.85; CI 0.79–0.9). Higher socioeconomic status, age 19–64, and substance use disorder were other predictors for continued use. Nabilone represented 97.3% of prescriptions; therefore, the results cannot be generalized to dronabinol and nabiximols. A major limitation of this study is the lack of information regarding the reasons for discontinuation and the concomitant or subsequent use of recreational or herbal cannabis. The study highlights the high rate of discontinuation of cannabinoid products once prescribed [28].

In the absence of RCT's, the development of guidelines is problematic, leading some medical groups to propose position statements. The Canadian Rheumatology Association (CRA) published a statement in 2019 on medical cannabis use in patients with rheumatic diseases, which includes FM [29]. They concluded that there was insufficient evidence about the benefits of cannabinoids, but there was evidence of harm. There may be some evidence, however for symptom relief by extrapolating data from other conditions with chronic pain. The European Pain Federation (EFIC) also published a statement in 2018 concerning cannabinoid use in chronic pain [30]. They state that cannabinoids may be considered as adjunctive therapy in patients with chronic neuropathic pain if guideline-recommended

first- and second-line therapies are insufficient. For all other patients (including FM patients) both statements recommend that cannabinoids may be considered as an individual therapeutic trial, and that the patient be well informed concerning the evidence of risks and benefits of cannabinoids. Furthermore, treatment must be discontinued if there is lack of efficacy or adverse effects [29, 30]. The American College of Rheumatology (ACR) and European League Against Arthritis (EULAR) have not yet published position statements.

## Cautions About Use of Cannabis-Based Medicine

Lacking formal study in FM cautions about cannabinoids for FM patients can only be derived from reports in other patient populations or recreational users. In view of the widespread media coverage, patients with FM are tempted to try herbal cannabis as a therapy. Furthermore, CBD specifically has been touted as a safe wellness product, even a food additive, with vigorous promotion and unsubstantiated health claims. This widespread interest in cannabis is clearly attractive to FM patients for which treatment options remain suboptimal. Patients may be self-medicating with various cannabis products believing that natural products are less harmful than pharmaceutical drugs. Much of cannabis (non-pharmaceutical) that is available on the open market is not well standardized in terms of THC/CBD content and lacking quality control. Patients may be turning to the illegal market in view of the higher cost of the legally acquired products. This raises concerns of unknown content of the product, often with THC content over 20%, and risks of contaminants including microbial products, heavy metals or intentional contamination to achieve increased psychoactive effects.

An awareness of both short- and long-term effects related to cannabis-based medicines is paramount. The most prevalent adverse effects of medical cannabis, particularly related to THC, are on cognition, executive and psychomotor function. Other than hemp oil which is almost entirely CBD, most herbal cannabis products contain some THC, which impairs short-term memory and emotional processing in a manner that may be modulated by CBD [31]. Synthetic cannabinoids have a similar negative effect on executive functions [32].

FM most commonly affects middle-aged persons, when the focus is on career, family and social development, and functionality. It is in this context that a product that impacts cognition or psychomotor function should be viewed with caution. Impairment in psychomotor function has been observed in young recreational cannabis users after acute inhalation, with effects lasting up to 5 h [33]. Driving under the influence of cannabis is concerning since even limited inhalation can impair driving ability [34]. The drug high associated with effective pain relief would likely have a negative impact on both work and driving ability. An increasing trend of impaired driving with both cannabinoids and opioids suggest that these products are either used medicinally or recreationally, are not generally perceived to impair function [27, 35]. Cannabis is associated with a five times increased risk of

having a motor vehicle accident and a two times risk of a fatal or serious accident [36, 37]. Furthermore, the delayed onset of action of oral cannabis-based medicines may prompt patients to administer additional doses resulting in more prolonged effects.

Mental health should always be a consideration for a patient with FM, with an increased prevalence of mood disorders and other mental health conditions. The use of cannabis in persons with mental health disease, especially those with severe depression, previous suicide attempts, suicide ideation and substance abuse disorders, should be strongly discouraged though this recommendation is often contested by users who claim mood benefits. In addition, cannabis use predicts psychosis vulnerability, particularly in younger persons [38]. In a systematic review of 35 longitudinal population-based studies, Moore et al. reported that cannabis increased the risk of any psychotic outcome (pooled adjusted odds ratio (OR) = 1.41, 95% CI 1.20–1.65), but findings of outcomes related to depression, suicidal thoughts and anxiety were less consistent [39]. With limited studies available, cannabis is associated with an increased rate of death by suicide (OR = 2.56, 95% CI1.25–5.27), increased suicide ideation (OR = 1.43, 95% CI1.13–1.83), and suicide attempt (OR = 2.23, 95% CI1.24–4.00), with heavy cannabis use increasing the risk of suicide attempt (OR = 3.20, 95% CI1.72–5.94) [40].

Information about the effects of cannabis in pregnancy and lactation is limited. THC crosses the placenta in rat studies, and the transfer of cannabinoids into breast milk of humans and animals has been shown [41, 42]. Therefore, cannabis use in pregnancy must be avoided.

Cardiovascular events are reported with increasing frequency for young recreational cannabis users as cannabis increases heart rate, blood pressure and myocardial oxygen demand [43]. There are case reports of the association of smoked cannabis with a spectrum of acute cardiovascular events including myocardial infarction, sudden cardiac death, arrhythmia, stroke, and transient ischemic attacks [44–46]. In a study of over two million patients admitted in the US with myocardial infarction, recreational marijuana was a significant risk factor when adjusted for demographic factors, smoking, and other substance abuse (adjusted OR: 1.031, 95% CI 1.018–1.045) [47].

## Real World Suggestions for Use of Cannabis-Based Medicine in FM

Physicians must accept that patients may wish to explore the use of cannabinoids for the treatment of symptoms of FM. It is important to maintain an open and trusting patient-doctor relationship with emphasis on shared decision-making. Physicians should inform patients of the current evidence for therapeutic and adverse effects. When considering a trial, there should be a comprehensive evaluation of current symptoms, previous and current treatments, psychosocial factors and realistic goals for treatment. Patients should be informed that a treatment trial will be evaluated for

efficacy as for any other standard medical intervention; treatment should not be expected to be lifelong; and reduction and eventual discontinuation of treatment can be anticipated when symptoms are reduced. Ideally, a pharmaceutical product should be tried prior to herbal products, although this may not be possible in many jurisdictions, and for some, the cost may be prohibitive. Any treatment with cannabis products should be prescribed and managed by a physician fully knowledgeable and responsible for the patient care, and not by a health care professional operating in a "specialist" cannabis clinic, or worse still, via a distance internet consultation with profit as the primary objective. If an herbal cannabis product is prescribed, an oil preparation for oral consumption with mostly CBD and low THC (to minimize psychoactive effects) is recommended and should be obtained from a regulated licensed medical grower/facility. Patients should be discouraged from smoking or vaping, the latter particularly until there is further clarification regarding serious lung injury. Dosing of product is not defined, but extrapolating from the dosing of nabiximols, initiation should be at 2.5 mg at night, with a gradual increase to a maximum of 20 mg a day. A time period for a trial should be prespecified, outcome goals clearly stated, and follow-up within a few weeks to assess response and dosage adjustments. Management of medical cannabis should not be in the hands of non-medical "cannabis experts." Patients can be directed to authentic sites to obtain up to date and valid information about medical cannabis (e.g., Dutch Office of medicinal Cannabis 2011; Health Canada 2016). Finally, there should be the clinical judgment of the benefit-risk profile pertinent to the individual patient characteristics.

## Conclusion

Cannabis-based medicines hold promise for a treatment option for some patients with FM, but without sufficient sound evidence. As interest in the clinical use of cannabinoids surges worldwide, evidence for efficacy and safety in FM remains scant, and clinicians rightly remain uncomfortable. Despite this lack of evidence, patients will increasingly wish to open a dialog regarding cannabis. Physicians must be as informed as possible and adhere to the principles of good medical care. The conundrum of the effect of cannabinoids can be understood for many reasons: clinical trials of herbal products lack, although the herbal product is commonly used by patients; the few available studies are of short duration; observational studies report on variable outcomes using variable measures, are often conducted in designated cannabis clinics and have attrition in numbers. Cannabinoids are diverse and cannot be regarded as a single drug. The molecular concentrations of THC and CBD of pharmaceutical and plant-based preparations differ, with the plant products containing a myriad of other molecules. In this setting of low level of evidence and increasing use, there has been a move to develop cannabis registries. While lacking the rigorous design of clinical trials, registries may provide real-world data on many aspects of cannabis use. We do acknowledge that the lack of convincing evidence

for efficacy does not necessarily mean that it is ineffective, but in this twenty-first century, the use of any remedy cannot be driven by advocacy and anecdote alone. Finally, it must be recognized that the medical cannabis industry has huge financial potential, with echoes of the cigarette and opioid industries. Irrespective of the current level of evidence for medical cannabis, buoyed by media and advocacy, medical cannabis is a current reality, and clinicians must take an active role in ensuring competent patient care.

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# Chapter 21
# The Role of Infection and Immunization in the Induction of Fibromyalgia


**Roula Qassem and Abdulla Watad**

## Introduction

Fibromyalgia (FM) is presented in approximately 2–8% of the population [1]. It is characterized by a chronic widespread musculoskeletal pain associated with tenderness of at least 11 of 18 defined points of palpitation [1]. Besides pain, fatigue, sleep disturbances, depression, concentration, and memory problems can also be noted in FM patients [1, 2].

Several studies have shown that certain environmental factors, including infections, may trigger FM [2]. Human immunodeficiency virus (HIV), mycoplasma bacteria and others were found to predict FM development. Interestingly, vaccines, which have been enormously successful in preventing infectious diseases, were also reported as a risk factor of FM [2].

The purpose of this chapter is to discuss the association between FM and both bacterial and viral infections, as well as vaccines.

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## Immunization and FM

Vaccinations are considered one of the most remarkable achievements in the medical world over the past decades due to the significant related reduction in both morbidity and mortality rate due to infectious diseases besides the considerable reduction related to financial burdens [3].

Although rare, vaccination can be associated with different adverse events. Over the past decades, many reports showed that some vaccines containing adjuvants could induce autoimmune phenomena in patients with a genetic predisposition to autoimmunity [4, 5].

Adjuvant is a substance that can be found in many environmental factors such as microorganisms (bacteria and viruses), vaccines, and silicone implants and it can trigger the development of some autoimmune diseases [6]. The origin of the word adjuvant comes from the Latin language (*Adjuvare*), which means helping, in this case, helping the immune system to produce a stronger and more effective reaction towards antigens that are part of this vaccination [4]. Aluminum is the most commonly used adjuvant in vaccines, it is highly effective in triggering the immune reaction against the injected antigens into the body, thus leading to a production of significant levels of antibodies that can protect against strains containing this antigen [7]. On the other hand, besides leading to various autoimmune phenomena, aluminum exposure can apparently damage both endocrine and nervous systems [8]. Other adjuvants included in vaccinations, such as squalene (MF59), are found in certain types of the flu vaccine, and it has also been found to be associated with an increased risk of developing autoimmune disorders [8].

## ASIA Syndrome, FM, and Vaccination

The purpose of the description of (ASIA) syndrome is to harbor under one umbrella different conditions that share clinical aspects which appear to be induced following the exposure to an adjuvant in a subgroup of subjects that are genetically prone to develop autoimmune diseases [5]. ASIA syndrome consists of 4 principal conditions including post-vaccination symptoms, siliconosis, macrophagic myofasciitis and Gulf war syndrome [5]. The latter consists of chronic fatigue and malaise, cognitive impairment, musculoskeletal symptoms, as well as post-traumatic stress disorder (PTSD) following immunization, and it has been in those soldiers that served in the Gulf war in the years 1990–1991 [5]. All these symptoms are also common in patients with FM and chronic fatigue syndrome [5].

In 2011, a registry of ASIA syndrome was established, including more than 300 patients with autoimmune/rheumatic diseases following the exposure to an adjuvant [9]. Two of the most notable diseases in this registry were CFS and FM [9]. This implies a connection between vaccines and FM [9]. It should be noted that many cases of ASIA syndrome or chronic fatigue/FM were underdiagnosed due to the

lack of knowledge concerning the relationship between these conditions and immunization [9].

In the past, the relationship between the rubella vaccine and CFS was described. Allen et al. [10] from the USA have reported a link between the level of IgG rubella antibodies and fatigue among patients with CFS after vaccination. In addition to the rubella vaccine, FM and CFS were reported after Lyme disease vaccination [10]. Analysing the Vaccine Adverse Event Reporting System (VAERS), a national vaccine safety surveillance program, patients, and their families following vaccination for Lyme disease, showed that symptoms such as persistent fatigue and arthralgia are more common in those who were vaccinated [11].

The pathogenesis of FM is not fully understood. Most probably, it is a multifactorial disease [2]. Various studies suggested several risk factors for FM, such as physical trauma, psychological trauma or hormonal disturbances [2]. Therefore, adjuvants included in vaccination may also contribute to the development of FM in people with the genetic predisposition for rheumatic diseases. Since FM is not a classic rheumatic disease as it has no classical features of an inflammatory condition such as rise in inflammatory markers and distortion of the joints, the specific mechanism behind the fact that FM is erupting by an environmental stressor such as infection or vaccination still unclear.

## Bacterial Infection and FM

Several bacterial infections have been found to be linked to FM induction. A spirochaetal infection caused by *Borrelia burgdorferi* known as Lyme disease recognized as a major confounder in the diagnosis of FM in areas where the prevalence of both Borreliosis and anxiety concerning the disease is high [2]. It is no wonder that patients suffering from FM were also diagnosed as cases of "chronic Lyme disease," given the fact that Lyme disease can lead to cognitive difficulties, diffuse arthralgia, fatigue, and impaired both memory and concentration [2].

Results from analyzing 100 patients at the Lyme Disease Center to assess the relationship between FM and chronic Lyme disease showed that Lyme disease was accountable for symptoms only in 37 out of 100 [12]. One quarter fulfilled the diagnostic criteria for FM; only three were found to have active Lyme disease, whereas 17 out of the 25 patients who referred to the clinic had a history suggestive of previous Lyme infection leading to FM [12]. The authors raised concern about misdiagnosed chronic Lyme disease and giving unnecessary antibiotic courses due to ongoing mild fatigue and malaise regardless of the adequate antibiotic treatment [12].

Another observational cohort study showed that 8% of 287 Lyme disease patients were found to have FM over a 3.5-year period [13]. Following a course of 4 weeks of Ceftriaxone, 14 out of the 15 patients continued to suffer from symptoms of FM [13].

Furthermore, certain mycoplasma species were found to induce long-lasting fatigue [14]. Through the years, various studies were attempting to declare the connection between mycoplasma infection and FM. One study conducted in 132 patients suffering from CFS and FM using a polymerase chain reaction (PCR) in blood samples from these patients found 62.9% to be positive to Mycoplasma spp. and 50% were positive for *Mycoplasma fermentans* infection, whereas healthy controls without clinical signs and symptoms, only 9.6% were positive for Mycoplasma spp. and 0% was with *Mycoplasma fermentans* (0%) infection [14]. Furthermore, it has been found that infections with a single mycoplasmal spp. were associated with less severe signs and symptoms than infections caused by more than one agent [14]. Moreover, evidence from supported reviews pointed out the improvement of symptoms in patients with CFS after antibiotic therapy for mycoplasma infection [2, 14].

*Helicobacter pylori* (HP) is a gram-negative spiral bacterium that may lead to gastric manifestations, such as peptic ulcer, gastritis, or gastric cancer, as well as extra gastric manifestations [15]. HP infection induces both local and systemic production of specific IgA and IgG [15]. Besides antibodies, the release of inflammatory mediators and molecular mimicry suggested a mechanism for extra gastric involvement [15]. Idiopathic thrombocytopenic purpura was reported as one of the HP-associated diseases [15]. A study carried out in outpatient clinic of the Physical Medicine and Rehabilitation Department showed that prior infection with HP might play a role in the etiopathogenesis of FM, showing a significantly higher rate of HP seropositivity among FM patients compared with healthy controls [15].

## Viral Infection and FM

Investigating the association between FM and viruses, a comparing study between 90 participants infected with hepatitis C virus (HCV) to 128 healthy controls and another 32 patients with non-HCV related cirrhosis was conducted [16]. While none of the controls met the American college of rheumatology (ACR) diagnostic criteria for FM, 16% of HCV patients and one cirrhotic patient were found to fulfill the diagnostic criteria for FM [16]. Moreover, HCV-infected patients had higher tender point counts [16].

To examine the prevalence of HCV infection among FM patients, 112 FM participants were screened for HCV infection in comparison with matched RA patients [17]. Additionally, they looked for evidence of FM in another 58 subjects with chronic HCV hepatitis [17]. The study found a link between FM and HCV infection suggesting to consider such an infection in FM patients even in those cases with normal hepatic enzyme levels [17].

Another study has reported abnormality of the cytokines profile in the chronic form of HCV leading to hyperalgesia, fatigue, depression, stress, sleep disturbances and other symptoms resembling an FM condition [18].

HIV has also raised a debate in its role in triggering FM. In a study examining the frequency of FM among HIV-infected patients, 29% of HIV patients fulfilled the

diagnostic criteria for FM [19]. In another study of 140 HIV-infected participants, 11% had FM while 41% of them were found to suffer from musculoskeletal symptoms [20]. Regardless of the highly active antiretroviral therapy, the overall prevalence of FM remained unchanged [20].

Although, no clear evidence was found on how HIV can lead to FM, and several hypotheses were suggested. Alteration in hypothalamic–pituitary–adrenal axis (HPA) has been seen in both HIV and FM patients, although the exact role played by the HPA alteration in the pathogenesis of FM is still incompletely understood [21]. Since insomnia is a classical manifestation in FM patients, it was also suggested as a hypothesis as well [22]. HIV infection is known to be associated with significant sleep disturbances, and these have been found to be associated with levels of pain considering the pain and stress those patients suffer from [23]. Furthermore, some highly active antiretroviral drugs are known to cause significant neuro-psychiatric side effects to include sleep disturbances [24]. Depression is prevalent among both HIV and FM patients [25]. As it is one of the characteristics of FM, it was also found that 22–45% of HIV patients suffer from a lifelong depression as well [25].

In conclusion, there is a complex interplay between viral, bacterial infection, immunization and the development of FM and CFS disorders. More efforts should be put towards clarifying and understating the relationship between adjuvant administration and FM and CFS.

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# Correction to: The Clinical Spectrum of Fibromyalgia and Its Treatment: An Overview

**Jacob N. Ablin**

**Correction to: Chapter 11 in: J. N. Ablin, Y. Shoenfeld (eds.), Fibromyalgia Syndrome, https://doi.org/10.1007/978-3-030-78638-0_11**

The original version of this chapter was inadvertently published without the co-author name. The chapter and book front matter has been corrected to include the co-author name, Shai Shtrozberg.

The updated version of this chapter can be found at https://doi.org/10.1007/978-3-030-78638-0_11



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