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FIBROMYALGIA: EMERGING EVIDENCE ON A HIGHLY DEBATED MEDICAL ENIGMA

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Abstract: Fibromyalgia (FM) is a highly prevalent condition characterized by persistent diffuse musculoskeletal pain, often accompanied by other functional and significant psychological comorbidities. The disease is controversial since there is no clear knowledge of its causes, it lacks precise diagnostic criteria and targeted treatment protocols. All these are sparking medical debates amid physicians and scientists worldwide, with some even placing FM in the spectrum of functional somatic syndromes. This article aims to review the up-to-date literature on the pathogenesis and pathophysiology mechanisms, the clinical manifestations and diagnostic criteria, and treatment options for FM patients. We will discuss both approved and investigational agents that have shown promising effects, as well as the evidence behind non-pharmacologic treatments. It is the authors' hope that improving our understanding of this complex disease will lower the consumption of health and social resources, and alleviate the increasing burden it generates on primary and specialty care systems.

Keywords: fibromyalgia, chronic pain, pathogenesis, pharmacotherapy, alternative therapies.

INTRODUCTION

Fibromyalgia (FM) is one of the most prevalent causes of chronic diffuse pain. It is a syndrome of unknown aetiology characterized by hyperalgesia (decreased pain thresholds) and allodynia (pain with commonly inoffensive stimuli) [1]. The widespread pain is usually accompanied by a wide variety of symptoms that affect individuals' quality of life, such as tiredness, sleep disorders, memory problems, depression, functional impairment and stiffness, among others [2]. The fact that FM shares some common features with other disorders, such as chronic fatigue syndrome, irritable bowel syndrome, and dysmenorrhea, has led to the hypothesis it belongs to a spectrum of disorders characterized by central sensitisation [3]. FM often occurs simultaneously with various rheumatic diseases, such as systemic lupus erythematosus and rheumatoid arthritis, but also with neurological conditions, gastrointestinal diseases, untreated endocrine diseases, and obesity [4].

The reported prevalence of FM in the general population ranges from 1% to 5% [5], currently being the third most common reported musculoskeletal condition, after lumbar pain and osteoarthritis [6]. The condition is more common in women and, when diagnosed in line with the 2010 American College of Rheumatology (ACR) criteria, has an approximately 2:1 female-to-male predominance, which is more pronounced (6:1 to 9:1 female-to-male ratio) in hospital-based studies versus population-based studies [7].

The most common symptom of FM is chronic pain (widespread or multisite pain lasting longer

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than 3 months), often accompanied by fatigue, sleep problems, and cognitive ("brain fog") or somatic symptoms (headaches, abdominal pain, diarrhea, jaw pain, dizziness) (Table 1) [7]. Patients usually use an abundance of pain descriptors, often describing their pain as being comparable to neuropathic pain: 20–30% of patients complain about paresthesia in the upper and lower limbs, fingers and hands, or affecting the trunk [8]. When performing a full evaluation on a patient with FM, it is important to exclude other connective tissue diseases, especially early rheumatoid arthritis. Clinical examination of patients with FM is often within the normal limits, except for movement-related pain and the presence of tender points. There is no specific laboratory test for diagnosing FM, but blood tests are useful for excluding differential diagnoses.

Since 1990, when the American College of Rheumatology (ACR) first approved the criteria for FM, numerous efforts have been undertaken to create diagnostic criteria that can apprehend the clinical reality of this disease. The ACR 1990 criteria were of great aid in providing homogeneous patient population for clinical research and required the presence of chronic widespread musculoskeletal pain for a minimum of 3 months and tenderness elicited by palpation in at least 11 of the 18 tender points [10]. Two decades later, the ACR preliminary diagnostic criteria for FM eliminated the tender points criterion and adopted the Widespread Pain Index (WPI) and the Symptom Severity Scale (SSS) [11]. Improvements were further made in 2011 [12]. In 2016, an updated version of the 2010/2011 FM diagnostic criteria introduced the generalized, widespread pain criterion (pain in at least 4 out of 5 organ systems) and specified somatic symptoms including fatigue/tiredness, headache, insomnia, depression, muscle pain, muscle weakness, and abdominal pain and spasms, also claiming that a diagnosis of FM does not rule out the co-existence of other disorders [13].

Beyond the set of criteria used, the diagnosis of FM is still challenging. To address the need to recognize FM in daily clinical practice, Salaffi *et al.* developed a six-item, user-friendly and self-administered screening tool for FM, the SImple Fibromyalgia Screening (SIFIS) questionnaire [14]. A second FM screening tool was

Table 1. Primary symptoms of fibromyalgia

Cardinal symptoms	Other common features
Pain	***Cognitive dysfunctions:***
• Generalized • Neuropathic pain, paresthesia	• Concentration difficulties • Memory problems
Fatigue	***Psychiatric symptoms: Anxiety, depression***
• Physical • Mental	***Regional pain syndromes***
Sleep disturbances	• Migraine, headache • Abdominal pain, irritable bowel syndrome • Dysmenorrhoea • Vulvodynia • Dysuria
• Insomnia • Non-restoring sleep	***Morning stiffness***
	Hypersensitivity to external stimuli
	Autonomic disturbances
	• Photophobia • Xerophthalmia, xerostomia • Feeling of instability • Raynaud phenomenon • Orthostatic hypotension

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developed based on the self-report Multidimensional Health Assessment Questionnaire (MDHAQ) [15].

In general, it is a long-term disease and subsequently lost productivity and impairment from FM are significant economic burdens to society. Patients suffering from this disease are more likely to be referred to healthcare professionals and undergo various diagnostic tests. Data indicated that, on average, a patient with FM is making 10 primary care appointments a year and, once every 3 years, is admitted to the hospital [16].

PATHOPHYSIOLOGY AND PATHOGENESIS OF FM

Nociplastic pain: Peripheral and Central Sensitization

Conventionally, pain is divided into three categories: neuropathic, nociceptive, and nociplastic pain [9]. We call "nociceptive pain" the physiological pain that occurs in the presence of a potentially harmful stimulus. There are situations in which pain loses its role as a warning signal, namely when pain continues after withdrawal of the inciting trigger or when it is activated by a usually harmless stimulus. In these cases, pain can be induced by an actual injury to the nervous system, what is referred to as "neuropathic pain", or by usually reversible alteration to the nervous system, called "nociplastic pain" [9].

Nociplastic pain is in accordance with the characterization of FM as part of the central sensitivity syndromes group, along with chronic headache, pelvic pain syndromes, temporomandibular disorders, or irritable bowel syndrome [17]. Central sensitization refers to a significant increase in pain perception, due to an intensification of neural signaling mechanisms at the central nervous system level [18]. Clinically this is often manifested as "hyperalgesia", defined as an amplified response to a regular noxious stimulus, and/or "allodynia", defined as a painful sensation to normal sub-noxious stimuli. The characteristic tender points in FM are considered to be an expression of allodynia, with patients accusing pain from stimuli that typically do not elicit pain [18].

Central sensitization refers to mechanisms involving ascending and descending neural pathways that generate increased excitability of the central nervous system neurons.

Imaging tools such as SPECT and functional magnetic resonance imaging (fMRI) scans have been employed to assess the functional changes in the central nervous system. Clinical studies based on fMRI have confirmed that, after applying the same amount of pressure stimuli, patients with FM exhibit higher neural response in the pain-related cortical areas of the brain when compared to control subjects [18]. Furthermore, a study using magnetic resonance diffusion-tensor imaging (MR-DTI) and MR imaging of voxel-based morphometry (MR-VBM) revealed a decreased volume of gray matter in the brain structure of patients with FM, when compared to healthy individuals. More precisely, the differences were noticed in the cortical and subcortical areas, which are responsible for processing nociceptive stimuli [19]. Again, based on fMRI studies, the μ-opioid receptors found in the rostral anterior cingulate cortex (rACC) showed decreased binding potential to opioids, probably the reason why opioids are usually unsuccessful in treating FM [20].

Abnormal levels of neurotransmitters have been noted in patients with FM. Increased levels of excitatory amino acids (primarily glutamate), the neuropeptide substance P (SP) and nerve growth factor (NGF) have been reported in cerebrospinal fluid (CSF) in patients with FM when compared to healthy controls [21, 22]. Alternately, low levels of serotonin and norepinephrine have been consistently detected in the CSF analysis of FM patients.

Peripheral sensitization involves a decrease in the threshold and/or an enhanced receptivity of nociceptors in the periphery. Individuals suffering from FM demonstrated a reduction in epidermal nerve fiber density in cutaneous biopsies, associated with considerable neuropathic pain – consequently, the term "small-fiber neuropathy" was adopted, meaning alteration to small myelinated Aδ fibers or unmyelinated type C peripheral fibers [9, 23].

Recently, ASIC3 (acid-sensing ion channel 3) activation on nociceptors responsible for skeletal muscle innervation in the induction phase of diffuse hyperalgesia has been suggested [18]. Studies in knockout mice revealed that muscle fatigue decreases the pH, and consequently stimulates ASIC3 on macrophages to intensify hyperalgesia in response to the insult [24]. Also, a study using a mice model of induced mechanical hyperalgesia depicted a surprising anti-nociceptive effect of intramuscular substance P against chronic mechanical hyperalgesia [25].

As previously stated, the chronic pain characteristic of FM is caused by changes in central and peripheral sensitization and researchers have been looking for biomarkers that can identify these alterations. They concentrated on substances that can affect nerve

cell growth and survival, such as nerve growth factor (NGF). NGF is known to have an important role in regulating the development, proliferation, and cellular death of sensory neurons [26], and its levels in the cerebral fluid of FM patients were indeed detected to be increased [27]. However, results are conflicting, with a recent cross-sectional study on 89 FM patients and 36 pain-free controls demonstrating no difference in plasma NGF levels between FM and control subjects [28]. To clearly establish the role of NGF in the pathophysiology of FM, further research is required.

Sleep disturbances

Sleep disturbances are commonly reported in FM syndrome. However, some published research has led to the suggestion that such abnormalities may be due to the pathology's causal components rather than its manifestations. Research has found a bidirectional link between sleep disorders and generalized musculoskeletal pain, even indicating that insomnia tends to anticipate the development of pain and has prognostic value for its start and duration [29, 30].

Electroencephalography (EEG) studies of the structural analysis of sleep support the hypothesis that sleep disturbances are one of the causes of FM. Moldofsky *et al.* published one of the first studies on this subject, showing that abnormalities of sleep caused FM symptoms, like fatigue, myalgia, increased tenderness, and reduced pain-pressure threshold [31]. The results allowed the authors to put forward a hypothesis about FM, then known as fibrositis, to be a "non-restorative sleep syndrome", in which an inciting mechanism hampers the non-REM sleep state and its recuperative activity, therefore producing behavioral disturbances and typical somatic symptoms [31].

Endocrine factors

The role of stress in exacerbating the symptoms of FM is well explained through self-reports and clinical practice questionnaires. Based on the available data, hypothalamic–pituitary–adrenal (HPA) axis dysregulation has been studied as a component in the pathophysiology of FM, influencing the body's response to stress. Despite the disparities between several studies on potential changes in plasma cortisol levels in FM patients, fluctuation in its circadian rhythm is common [32, 33].

It is well known that the hypothalamus produces corticotropin-releasing hormone, that further stimulates release of corticotropin hormone (ACTH) from the anterior pituitary gland. Finally, ACTH acts on the adrenal gland to induce cortisol production. The release of these hormones is controlled by a circadian rhythm, and cortisol levels rise rapidly shortly after waking, with a peak within 30-45 minutes. It then decreases over the course of the day until it rises again later in the afternoon. Afterwards, cortisol levels drop late at night, achieving their trough in the middle of the night [34].

A study on a group of patients with FM investigated the levels of corticotropin release factor (CRF) in the spinal fluid (CSF), the heartbeat rate (HRV) and general symptoms (such as pain, fatigue and depression). The results showed that the CRF levels were linked with symptoms of sensory and emotional pain, but not with fatigue symptoms. In addition, increases in HRV were correlated with elevated levels of CRF and increased pain.

These results remained significant even after additionally adjusting for age, gender, and depression symptoms [35]. Another important discovery was that women who suffered from FM and had a history of physical or sexual abuse did not present with elevated concentrations of CRF in the CSF. This suggests that FM patients may be divided into different subsets according to their different neurological characteristics. Hence, further studies are warranted to better understand the rationale behind the correlation between CRF and pain symptoms in FM. A possible pathogenic role of the growth hormone (GH)/insulin-like growth factor 1 (IGF-1) axis has also been investigated, and some studies depicted that approximately a third of people with FM have lower levels of IGF-1 than the control group [32].

Genetic aspects

Several biologic studies support that genetic factors, along with environmental causes like trauma, disease or emotional stress, can predispose individuals to develop FM [36].

Specific genes in the pathogenesis of FM include genes involved in the serotonin pathway (serotonin transporter-5-HTT and the serotonin 2A receptor-5-HT2A), the pain-related catechol-O-methyltransferase (COMT) gene and the dopamine receptor. The S/S genotype of the 5-HTT gene was more frequently reported in patients with FM than in healthy controls [37]. Lower dopamine receptor gene D4 levels were also detected in patients with FM [38]. In terms of COMT genotypes, the Met/Met and Val/Met genotypes were the most common in FM patients [39]. As for pain, exhaustion, sleep disruptions, and

stress domains, the Met/Met genotype seems to be an indicator of increased disease severity. Furthermore, individuals with the Met/Met polymorphism reported a pronounced negative attitude on days when the pain was greater, in opposite to individuals with the Val/Met or Val/Val genotype [40].

The receptor 1 gene (TAAR1), the regulator of the G-protein signaling 4 (RGS4) gene, the cannabinoid receptor 1 (CNR1) gene and the ionotrophic glutamate receptor gene AMPA 4 (GRIA4) have all also been linked to FM and can modulate nociceptive and analgesic neuronal pathways [41].

Nevertheless, in patients with FM, a hypomethylated DNA pattern was observed in genes involved in DNA repair, stress response, autonomic nervous system responsiveness and subcortical neural anomalies. In many samples, differences were observed in the genome-wide microRNA expression profiling, proposing the involvement in the pathogenesis of FM [42].

MULTIFACETED MANAGEMENT

Because FM is a complex syndrome accompanied by a wide variety of symptoms, its management should be holistic and comprehensive. Treatment should be multidisciplinary, integrating both non-pharmacological and pharmacological interventions, by shared decision-making with the patient [43]. The global approach to treating FM should focus on improving physical function, symptoms, as well as the quality of life.

Non-pharmacological management

Given that FM is a chronic condition, pain control often requires complementary auxiliary methods in conjunction with standard therapies. The EULAR 2017 revised recommendations highlight the importance of initially using non-pharmacological measures, and the only current 'strong' recommendation is in favor of low-impact physical exercise [43]. Other complementary and alternative non-pharmacologic measures investigated for the treatment of FM include water-based therapies, acupuncture, electrical stimulation, cognitive behaviour therapy and meditative movement therapies.

Physical exercise is based on aerobic/fitness programs, resistance training for increased muscle strength, and stretching exercises. A 2017 systematic review that collected data from 13 randomized controlled trials (839 patients) concluded that aerobic exercise is well tolerated among FM patients and can significantly improve health-related quality of life (moderate-quality evidence). The results found that it may also be slightly beneficial in terms of improving functionality and alleviating pain intensity (low-quality evidence) [44]. Other recommended modalities of exercise are strength training and muscle stretching programs. One trial that randomly placed 44 patients in a control group and two intervention groups (a stretching group, or a resistance group) - found that a stretching training program was the most effective in improving quality of life, reducing pain intensity and improving functional capacity, whereas resistance training proved to be the most successful modality for lessening depression [45].

Balneotherapy and hydrotherapy are attractive water-based treatment options that may be considered in the management of FM. Data suggest a moderate-to-strong association between hydrotherapy and improvements in pain and health-related quality of life, but there is no evidence for the improvement of depression and tender point count. Furthermore, a medium-to-large positive effect on pain and tender point count was reported for balneotherapy with mineral/thermal water [46].

Acupuncture therapy could provide an alternative complementary strategy for treating chronic pain conditions. It is believed that acupuncture analgesia works via pain-modulating pathways of the central nervous system and by regulating various biochemical compounds [47]. A 2019 systematic review and meta-analysis provided a comparison between sham acupuncture and real acupuncture, showing greater efficacy of the latter in terms of pain relief and quality-of-life improvement, both in the short and long term. In addition, acupuncture was more effective than conventional medicine in relieving pain [48].

Electric analgesic currents have also been used to treat FM. A 2017 meta-analysis that included 9 studies (301 patients) concluded that transcutaneous electrical nerve stimulation (TENS) does not significantly relieve pain in patients with FM, whereas electroacupuncture (a combination of electric current therapies and acupuncture) did present moderate-quality evidence to support its effectiveness for pain relief. However, neither fatigue nor quality of life improved in these patients [49]. Repetitive magnetic stimulation of the central and peripheral nervous system, a non-invasive electromagnetic therapy, is also being investigated as a relevant approach for endogenous pain modulation systems [50].

In cases that are refractory to physical exercises, electrical muscle stimulation, and other modalities, botulinum toxin type A (BonT-A) has been investigated as a possible pain relief therapy [51]. BonT-A is an injectable neuromodulator approved for the treatment of a variety of medical disorders generated by muscular overactivity, such as dystonia [52] and post-stroke spasticity [53]. However, the role of BonT-A as adjunctive therapy in FM has not been established and further studies are needed in this direction [54].

The most widely studied and implemented form of psychotherapy for FM is cognitive-behavioral therapy (CBT). By using this approach, patients learn how to identify maladaptive thoughts and develop effective mechanisms to cope with dysfunctional pain modulation [9]. FM patients receiving CBT experience superior improvements in pain, physical functioning, and quality of life when compared with patients receiving standard care. This approach is supported by data from a 2018 systematic review and meta-analysis of 29 randomized controlled trials [55]. Unfortunately, in addition to limited access to therapists with expertise in managing patients with FM, there is also a potential barrier to psychological treatments among patients with FM who are unwilling to seek out mental health services.

Tai chi and yoga are additional forms of meditative movement therapies which combine mind-body practice with low-impact movement exercises, showing some benefit in treating FM symptoms [56].

Even though multiple non-pharmacological strategies are discussed in the EULAR recommendations for the management of FM, the benefit of these complementary therapies is still debatable. The approach should be individualized based upon the patient's preferences, physical status, as well as the presence of any other comorbidities.

Pharmacotherapy

Treatment should be individualized and may incorporate both nonpharmacologic and pharmacologic therapies. In cases where proper patient education and exercise programs are insufficient for symptoms control, pharmacological therapy may be necessary.

Central nervous system-acting drugs, such as tricyclic medication (amitriptyline), serotonin-norepinephrine reuptake inhibitor-SNRI (duloxetine, milnacipran), and anticonvulsants (pregabalin) have been proposed as safe and efficient [43].

Low doses of the classic tricyclic antidepressants amitriptyline are the preferred initial therapy for FM, particularly due to their good efficacy in pain reduction, as well as low costs when compared to newer drugs [57]. Patients should be started on very low doses (5 to 10 mg), which are further increased every two weeks (by 5 mg) until a dose of 20 to 30 mg is reached, this being the typical maintenance dose in most patients. The dose can be increased up to 50 mg/day if needed, but, at this dose, the risk of possible side effects may outweigh the benefits. Nishishinya *et al.* demonstrated that amitriptyline 25 mg/day does have a significant therapeutic effect on pain, sleep and fatigue at 6–8 weeks of treatment, but without finding any additional benefit for doses of 50 mg/day [58].

Duloxetine and milnacipran are serotonin-noradrenaline reuptake inhibitors (SNRIs). Both duloxetine and milnacipran have proved to be more effective than placebo in treating FM pain; however, amitriptyline was superior to duloxetine and milnacipran in improving pain, sleep disturbances and fatigue [57]. Amitriptyline and the SNRIs, duloxetine and milnacipran, are first-line options for treating FM, but a significant number of patients drop out of treatment because of intolerable side effects (nausea, dry mouth, constipation, decreased appetite, somnolence, hyperhidrosis, and agitation) [9, 43].

The serotonin-norepinephrine reuptake inhibitor (SNRI) duloxetine and milnacipran represent an alternative for patients who do not respond or cannot tolerate amitriptyline, or may even be preferred as first-line therapy in FM patients suffering prominent fatigue or depression [59]. A 2013 systematic review and meta-analysis that included 6038 patients showed that both drugs are superior to placebo in treating FM pain [60]. The usual starting dose for Duloxetine is 30 mg/day and then is progressively increased to 60 mg/day (recommended dose). Milnacipran therapy is started at a dose of 12.5 mg/day and is steadily increased to 100 mg/day (50 mg twice daily). However, despite administering the recommended doses, a high percentage of patients on SNRIs discontinue the drugs due to a relatively high frequency of side effects, such as headache, nausea, constipation, and dry mouth [9, 43].

Pregabalin (PGB) is an alpha2-ligand that modulates neural calcium channels to block the release of pain neurotransmitters and has gained reliable evidence of benefit in FM treatment, primarily in patients with marked sleep disturbance [61]. In June 2007, Pregabalin emerged as the first drug approved by the FDA for the treatment of FM [61]. The treatment is usually initiated at a dose of 75 mg/twice a day and

is further escalated until a recommended dose of 300 to 450 mg/day is achieved. Various side effects, such as dizziness, somnolence, edema, or dry mouth, can often lead to withdrawal from treatment [62].

The first-line therapies and the dosing strategies commonly used in treating patients with FM are summarised in Table 2.

Cyclobenzaprine, another similar tricyclic medication, can be used as an alternative initial agent in individuals with mild symptoms, but it is believed to have minimal or no effect on treating depression. A meta-analysis of 5 randomized, placebo-controlled trials concluded that patients receiving treatment with cyclobenzaprine were 3 times more likely to experience an overall improvement, including alleviation of pain reports, but there was no positive impact on fatigue or tender points [63]. Mild side effects were common and included somnolence, dizziness, xerostomia, constipation, nausea, and heartburn.

The use of opioids analgesics in the treatment of FM is controversial, with tramadol being the only opioid with slight evidence supporting its use in FM treatment [64].

Data is showing that long-term use of other opioids may negatively impact the outcome, due to the wide range of dose-dependent side effects: acute myocardial infarction, sexual dysfunction, opioid abuse and addiction, psychological and sleep disturbance. Despite FM guidelines advising against the use of opioid analgesics, epidemiologic studies show that long-term opioid therapy is commonly prescribed in FM treatment [43, 65].

Nonopioid analgesics, such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), are often prescribed as adjuncts to FM treatment, even though studies have failed to show their efficacy [66]. There is some low-quality evidence on the utility of NSAIDs in short-term improvement of pain when used in conjunction with other FM therapies. However, NSAIDs should not be considered as an option on a long-term basis due to their possible adverse side effects [43].

Emerging cellular therapies that utilize stem cells, platelet-rich plasma (PRP), and other biomaterials are investigated as novel therapeutic strategies for treating several chronic pain conditions, including neuropathic pain, and additional clinical studies are necessary to validate the adjunctive role of these cell-based therapies for clinical use in FM [67].

Finally, medical cannabis treatment could have a positive effect on patients with FM, according to only a few studies that investigated its role in FM treatment [68-70]. Since medical cannabis has already been legislated in various European countries, as well as several states in the US, there will be a surge of interest in its use.

Further evidence in support of the efficacy of each agent described above is needed.

FIBROMYALGIA: WHERE DO WE STAND NOW?

In recent years, an increasing amount of medical research in regard to fibromyalgia has been conducted in the rheumatic field as well as other biomedical fields, even though its true nature is still uncertain. This article was designed to assess the importance of the complex pathophysiology of FM, as well as the multifaceted management of the disease, both in terms of nonpharmacological and pharmacological therapy. The vast clinical picture requires a combination of both therapies for good disease management and control, and it requires shared decision-making with the patient, after thoroughly educating the patient with regard to the nature of the disease and the principles of the treatment approach.

Despite the fact that the pathophysiology of FM is still unclear, the identified alterations support the theory that FM is associated with abnormalities in some pain mechanisms. The base cause of the disease is linked to aberrant pain processes suggested by somatosensory abnormalities, quantitative chemical changes in the cerebrospinal fluid, and functional neuroimaging investigations [9]. Brain imaging has provided solid evidence for this central sensitization, including an excessive pain response to experimental pain stimulus, altered structural and neurotransmitter function. The chronic pain that is characteristic of FM is caused by changes in both central and peripheral sensitisation. Also, the interaction between genetic, endocrine and environmental factors likely leads to

Table 2. First-line agents for the treatment of FM

Drug	Drug class	Starting Dose	Target dose
Amitriptyline (Off-label)	Tricyclic antidepressant	5-10 mg/day	25 mg/day, increase to 50 mg/day if needed
Duloxetine	SNRI	30 mg/day	60 mg/day
Milnacipran	SNRI	12,5 mg/day	50 mg twice a day
Pregabalin	GABAergic drug	75 mg twice a day	225 mg twice a day

central and peripheral nervous system hyperirritability.

FM is a chronic disease, meaning it can be managed rather than cured. As we mentioned previously, the general approach to treating FM should concentrate on preserving or improving function, improving quality of life, and managing symptoms. In terms of nonpharmacological therapies, exercise programs and cognitive behavioral interventions have the strongest evidence supporting their use as efficient methods for modulating pain and improving the overall quality of life. In cases where exercise and patient education are insufficient, pharmacological therapy may be necessary. However, there is no "gold-standard" pharmacological intervention for FM, and pharmacotherapy alone is usually insufficient for the vast majority of patients suffering from this condition.

Central nervous system-acting drugs, such as tricyclic medication (amitriptyline), serotonin-norepinephrine reuptake inhibitor-SNRI (duloxetine, milnacipran), and anticonvulsants (pregabalin) have been proposed as safe and efficient

Amitriptyline, duloxetine, milnacipran and pregabalin are the current first-line prescribed drugs, but an adequate response with significant clinical benefit is experienced by only a minority of patients. The majority of patients will withdraw from treatment due to a lack of efficacy or intolerable side effects.

In conclusion, fibromyalgia remains a complex syndrome that poses difficulties for diagnosis and treatment even to the experts. Most patients need combined strategies to address different aspects of this heterogeneous disorder, highlighting the role of a cohesive multidisciplinary team in assessing and managing patients with this condition. More high-quality research into both nonpharmacologic and pharmacologic therapies is needed to further improve patients' quality of life.

Conflict of interest

The authors declare that they have no conflict of interest.

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