Review paper

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Fibromyalgia syndrome: epidemiology, diagnosis and treatment

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Abstract

Fibromyalgia syndrome (FMS) profoundly impacts patients' quality of life with its symptoms and clinical signs. Fibromyalgia syndrome impairs daily living activities, reduces work efficiency and raises health-related costs. Although the prevalence rates vary depending on geographical location and diagnostic criteria, it is a common disorder worldwide. Females have a higher prevalence of fibromyalgia syndrome, with varied rates, and there is an increase in prevalence rates with age. Although its etiopathogenesis has not been fully elucidated, various hypotheses have been proposed that central sensitization is at the core of the process. Fibromyalgia syndrome diagnostic approaches have advanced significantly over time, moving away from pain assessments alone and emphasizing multiple clinical signs of FMS. This condition has raised physicians' and researchers' awareness of non-pain symptoms. Considering the complicated etiopathogenesis of fibromyalgia syndrome, diverse pathways connected with symptoms, and multiple clinical presentations, it becomes clear that drug and non-drug treatments should be chosen in combination.

Key words: fibromyalgia, treatment, epidemiology, diagnosis.

Introduction

Fibromyalgia syndrome (FMS) is a complex, multifactorial, chronic rheumatic disorder characterized by widespread body pain, commonly accompanied by stiffness, fatigue, sleep disturbances, cognitive impairments, and psychiatric signs. All these complex symptoms deeply affect daily life activities and quality of life and cause changes in living habits and daily routines in a considerable proportion of patients [1, 2].

In addition, FMS is a costly public health issue. Fibromyalgia syndrome patients frequently use healthcare services and utilize various medications for symptom relief. This condition substantially increases the medical costs in FMS patients [3].

Although the etiopathogenesis of FMS has not been fully elucidated and the pathophysiological framework has not been identified, numerous hypotheses addressing the function of centralization of the pain process have been suggested.

There is a decrement in pain regulation ability through the descending pathways in a subset of FMS patients, with serotonergic-noradrenergic activity appearing to be reduced. This notion is promoted by the clinical efficacy of serotonin and norepinephrine reuptake inhibitors [4].

High concentrations of excitatory neurotransmitters such as glutamate and substance P have been detected in FMS. Furthermore, dopamine dysregulation and changes in the activity of endogenous cerebral opioids have been demonstrated [5].

Peripheral changes and increased frequency of upstream stimuli can contribute to central sensitization. Genetic features, infections, neuroendocrine alterations, and increased oxidative stress are among the factors involved in the etiopathogenesis of FMS and induce the emergence of clinical signs [5, 6].

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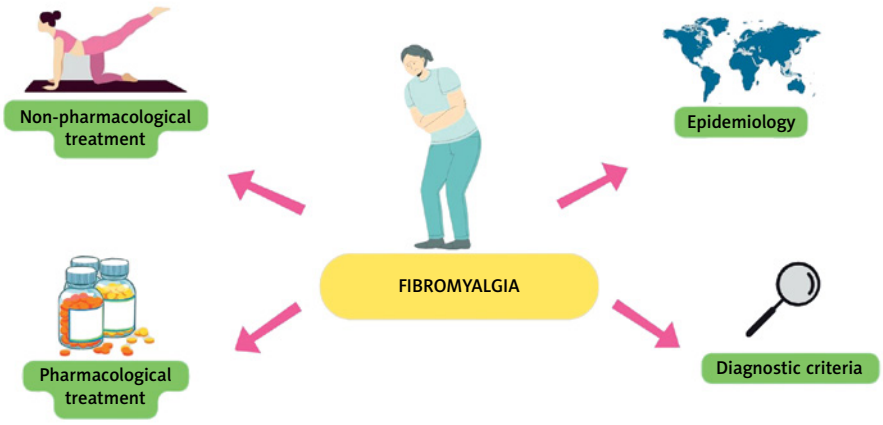

Fig. 1. Epidemiology, diagnosis and treatment of fibromyalgia syndrome.

In this review, we provide a comprehensive overview of the epidemiology, diagnosis, and treatment of FMS. In addition, we present different diagnostic criteria developed over time and their reflections. Finally, we evaluate the main pharmacologic and non-pharmacologic treatment methods in FMS management (Fig. 1).

Material and methods

A search strategy was created depending on the recommendations of Gasparyan et al. [7]. First, articles were searched on the Web of Science, Scopus, PubMed/MEDLINE, and DOAJ with the keyword combinations: "fibromyalgia and epidemiology" OR "fibromyalgia and diagnosis" OR "fibromyalgia and treatment" OR "fibromyalgia and drug therapies" OR "fibromyalgia and therapeutics". The selection of keywords was based on MeSH terms.

Inclusion criteria

The inclusion criteria were controlled clinical trials, observational studies, reviews, and English-language papers. Repeated papers, meeting abstracts, posters, case reports/series, editorials, commentaries, scientific letters, articles written in languages other than English, and articles not directly linked to the topic were among the exclusion criteria.

Epidemiology of fibromyalgia syndrome

Clarifying the FMS epidemiology has clinical and financial benefits [8]. There are differences between the prevalence rates depending on the methodology, diagnostic criteria, and geographic location [9]. Most studies were conducted in a particular city, region, or area, and articles providing nationwide prevalence data are limited.

In Europe, nationwide FMS prevalence data were reported as 1.4% and 1.6% in France, 3.2% and 2.1% in Germany, and 2.4% in Spain [9–13]. In a meta-analysis, the total prevalence of FMS in the Eurozone was calculated as 2.64% [14].

The prevalence of FMS is higher in females, with varying rates, and it has been shown that there is an increase in prevalence rates with age [15]. In two studies conducted on adult females, the prevalence rates were 3.6% and 5.6% [16, 17].

The vast healthcare costs of individuals who regularly seek medical attention mirror the typically impaired quality of life of FMS patients. The number of consultations needed annually in FMS patients is nearly twice that of the healthy population.

Furthermore, when health cost assessments are performed, it is seen that the overall cost incurred for FMS patients is approximately three times higher than in a random sample [18, 19].

Diagnostic criteria

Fibromyalgia syndrome is a clinical mystery. Its etiopathogenesis is not fully understood; its clinical signs are nonspecific and overlap with various diseases. This makes the diagnosis difficult for clinicians. Attempts have been made to establish diagnostic criteria for this disease, and several classifications and diagnostic criteria have been published in the last 30 years [20].

The 1990 American College of Rheumatology (ACR) criteria recommend that widespread body pain is FMS's primary classification criterion and clinical feature [21]. These criteria considered widespread body pain (left and right sides of the body, above and below the waist, and the axial skeleton) and the tender points count (pain on palpation in ≥ 11 of 18 tender point sites) and did not include other FMS-related symptoms.

Despite the extensive use of these criteria, numerous criticisms have emerged over the years, particularly regarding the overemphasis on widespread body pain and the neglect of different symptoms such as fatigue, stiffness, and sleep disturbance. Another contentious topic has been searching, identifying, and counting tender points because many physicians lack the necessary education and clinical experience [22].

With the publication of the ACR preliminary diagnostic criteria for FMS in 2010, the tender point assessment was removed from the FMS diagnostic process [23]. The 2010 ACR criteria considerably aided the diagnostic process by removing the ambiguity caused by the tender point assessment's subjectivity.

According to the ACR 2010 criteria, FMS can be described as chronic widespread pain with somatic symptoms. The Widespread Pain Index (WPI) and Symptom Severity Scale (SSS) are recommended as diagnostic criteria. These criteria were revised in 2011 to streamline the diagnostic procedure and make it easier to conduct epidemiological studies [24].

The WPI covers 19 body locations, and the patient must show where he or she had pain in the previous week. Each painful area receives one point. Thus, the maximum score is 19.

The SSS is calculated by considering fatigue, sleep disorders, cognitive signs, and somatic complaints. Each symptom is scored between 0 and 3 based on intensity or quantity. A patient with WPI ≥ 7 and SSS ≥ 5 or WPI 3–6 and SSS ≥ 9 meets the diagnostic criteria. The American College of Rheumatology revised the diagnostic criteria in 2016 and reported the following criteria:

1. Generalized pain is defined as pain in at least four of five locations.
2. Symptoms present at a similar intensity for at least 3 months.
3. A WPI ≥ 7 and SSS ≥ 5 or a WPI of 4–6 and SSS ≥ 9.
4. An FMS diagnosis is valid regardless of previous diagnoses [25].

In the 2016 ACR diagnostic criteria, it has been clarified that FMS criteria are valid in the existence of other clinically important diseases.

The Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks (ACTTION) – American Pain Society (APS) Pain Taxonomy criteria (AAPT) set up an international FMS study group and recommended core diagnostic criteria:

1. Multisite pain.
2. Moderate to severe sleep disorders or fatigue.
3. Clinical signs must have been present for at least 3 months [26].

Despite all these diagnostic criteria, one of the main problems is the difficulty in identifying FMS-specific biomarkers. While research is ongoing, it is evident that there is still a long way to go in this field [27].

The nociplastic pain concept was proposed to characterize a range of chronic pain disorders that had not previously been captured by pain entities involving nociceptive and neuropathic pain [28].

Nociplastic pain is described as pain caused by changed nociception, but there is no evident indicator of current tissue injury at peripheral structures that induce nociception, and impairment or damage in the somatosensory system.

The nociplastic pain concept is intended to clarify a group of disorders with similar characteristics, such as fibromyalgia syndrome, complex regional pain syndrome, non-specific chronic low back pain, and irritable bowel syndrome [29, 30].

The pathophysiological pathway suggested in the emergence of this pain type is the change of pain modulation and exaggerated pain processing in the central nervous system [31]. One of the notable nociplastic pain features in FMS is the inconsistency of pain distribution during the course of the disease, which does not match the neuroanatomical distribution.

It is still difficult and not always possible to distinguish between nociceptive, neuropathic, and nociplastic pain. Although physical examination, quantitative sensory tests, laboratory examinations, imaging methods, and several questionnaires are suggested for pain discrimination, there are difficulties in obtaining precise results [30, 32].

Recently, a new diagnostic tool called nociplastic-based fibromyalgia features was created to distinguish FMS patients from individuals with chronic non-inflammatory pain. This diagnostic tool is based on nociplastic pain characteristics rather than documenting and quantifying FMS-related symptoms and pain sites and differs from existing symptom-focused criteria. With all these features, it is claimed that early diagnosis is achievable before the symptom spectrum arises [33].

Treatment

Fibromyalgia syndrome treatment aims to reduce pain, improve quality of life, and alleviate FMS-related

psychosocial symptoms. Fibromyalgia syndrome symptoms impair functional capacity in daily life and result in biopsychosocial losses. Optimum FMS management should be established in a multimodal and multidisciplinary structure concentrating on education, drugs, and comorbidity management using pharmacological and non-pharmacological techniques [34, 35].

Pharmacological treatments

Among the pharmacological treatment options, pregabalin, milnacipran, and duloxetine are FDA-approved agents [36–38]. Furthermore, different treatment options are used in clinical settings and have positive responses at certain rates.

The choice of drug therapy in patients with FMS should be based on clinical characteristics, side effects, tolerance, and treatment response. The treatment should begin with low doses and gradually increase with patient tolerance, considering the treatment response [39, 40].

Anticonvulsants

The two prominent members of this group are pregabalin and gabapentin, and they act by displaying an affinity for the α2-δ subunit of voltage-gated calcium channels in the central nervous system. The role of gabapentin in the treatment of FMS is unclear, and there are conflicting results [41, 42].

In a Cochrane review evaluating the effect of pregabalin on FMS-related pain, it was concluded that the molecule has positive effects on pain. However, specific adverse events, particularly dizziness, sleepiness, weight gain, and peripheral oedema, were more frequent in the drug group. There was no difference in terms of serious adverse effects [43].

A randomized, double-blind, multicenter, controlled study was conducted in Japan. This study revealed that pregabalin, at doses of up to 450 mg/day, was efficient for pain relief in FMS. The pregabalin group had no considerable tolerance issues and improvement was detected in sleep and functioning indicators [44]. A multicenter, international, randomized controlled study revealed that the ideal effective dose for managing FMS is 450 mg/day [45].

Serotonin–noradrenaline reuptake inhibitors

Serotonin–noradrenaline reuptake inhibitors (SNRIs) act on FMS symptomatology through serotonin and noradrenaline, which are effective in pain inhibition pathways. Duloxetine and milnacipran are more efficient than placebo in managing FMS-related pain.

However, the cumulative effect is small, and both agents have no impact on other FMS symptoms. Duloxetine and milnacipran had higher dropout rates owing to adverse effects. The most common side effects that led to medication discontinuation were nausea, dry mouth, constipation, headache, somnolence/dizziness, and insomnia [46].

A Cochrane review that comprised 18 studies and 6,407 participants included six trials and 2,249 patients with FMS. Duloxetine 60 mg was demonstrated to be effective in relieving pain for 12 weeks. There was no effect of duloxetine at doses of 20–30 mg/day in this trial, but efficacy was shown at 60 mg/day, and there was no difference between 60 mg and 120 mg in terms of efficiency. Additionally, painful physical symptoms of depression were improved [47].

Selective serotonin reuptake inhibitors

This drug group is better tolerated than tricyclic antidepressants. citalopram, fluoxetine, escitalopram, fluvoxamine, paroxetine, and sertraline are the most widely used in clinical practice. A Cochrane review evaluated the clinical benefits of selective serotonin reuptake inhibitors (SSRIs) (citalopram, fluoxetine, and paroxetine) in patients with FMS.

There was no unbiased evidence that this drug group was more effective than the placebo group against the main clinical signs of FMS, which included pain, fatigue, and sleep disturbance. It was suggested that SSRIs could be used to treat depression in FMS patients [48].

Tricyclic antidepressants

Tricyclic antidepressants block the reuptake of serotonin and noradrenaline in the central nervous system. They are widely utilized in many countries due to their relatively low cost [49].

However, this drug group can cause some autonomic side effects by inhibiting α-adrenergic, histamine, and muscarinic receptors. Typical side effects are dry mouth, constipation, fluid retention, weight gain, difficulty concentrating, and dizziness [50].

In a meta-analysis comparing the efficacy of amitriptyline, duloxetine, and milnacipran, the methodological quality of the amitriptyline studies was rated as poor. Amitriptyline was effective against pain, fatigue, and sleep, but a similar effect on health-related quality of life was not detected.

Amitriptyline had small effects on pain and fatigue and moderate effects on sleep [51]. Amitriptyline is recommended to be used in a dose range of 10 to 25 mg/day in FMS patients under 60 years without cardiac disorders [42].

Cyclobenzaprine

Cyclobenzaprine is a centrally acting muscle relaxant and is structurally similar to amitriptyline. In a meta-analysis evaluating five randomized controlled studies, cyclobenzaprine had a partial positive effect on pain and sleep, but no effect on tender points and fatigue was detected.

Furthermore, it is a crucial handicap that 85% of the patients reported side effects [52]. It has been demonstrated that using very low dosages of cyclobenzaprine before bedtime improves pain and sleep in patients with FMS with particular sleep structures [53].

Tramadol

There is inadequate evidence from clinical trials to confirm the efficacy of opioids in treating FMS, and the EULAR recommendations do not support the use of opioid analgesics. The exception to this situation is tramadol, which is a weak opioid. Tramadol also has a mild SNRI effect and is recommended for treating FMS alone or in combination with paracetamol [54].

In a randomized, controlled, double-blind study involving participants with moderate-to-severe FMS pain, a combination of tramadol and acetaminophen was found to positively affect pain, stiffness, and quality of life in FMS patients [55].

Monoamine oxidase inhibitors

Independent of their antidepressant effects, monoamine oxidase inhibitors (MAOIs) have beneficial effects on pain and improve sleep parameters. Therefore, this drug group was considered a treatment option for patients with FMS. Moclobemide and pirlindole are selective monoamine oxidase-A (MAO-A) inhibitors. Monoamine oxidase-A, which rapidly degrades serotonin and noradrenaline, is inhibited by these drugs.

It was reported that pirlindole significantly improves pain, tender point, and patient-physician global assessment scores compared to placebo. However, positive results could not be achieved with moclobemide [56]. There are insufficient data to strongly support the use of MAO-A inhibitors in FMS.

Non-pharmacological treatment

It is well known that many patients tend to use non-pharmacological treatment options. This is due to the fact that pharmacological treatment options do not always provide adequate well-being, and patients avoid the side-effect profile. Non-pharmacological approaches aim to improve patients' physical function, activity level, overall health, and mental well-being [57].

Education

Patient education and ensuring the patient's participation in the treatment plan are essential in the long-term management of FMS, whose clinical signs fluctuate. Following a diagnosis of FMS, providing information regarding the disease's pathogenesis, treatment choices, and prognosis and discussing them with the patient can assist in alleviating health-related anxiety. The emphasis should be on FMS-related myths, efforts should be made to overcome misbeliefs, and physicians should explain that FMS is not a life-threatening disorder [58, 59].

Furthermore, patients should be encouraged to learn adequate sleep hygiene and relaxation practices, as stress, mental status alterations, and sleep disturbances are substantial triggers in FMS symptomatology.

Supporting the practice of self-management allows patients to engage in activities that improve clinical signs and develop problem-solving skills [60]. As part of FMS treatment, patient education should be utilized alongside other pharmacological and non-pharmacological treatment approaches [61].

Exercise therapy

Muscle strength decreases, and endurance is impaired in FMS patients. The main goals of exercise therapy in FMS are to reduce stress, improve muscle strength, provide proper posture, increase endurance, and restore cardiovascular endurance [62].

In fibromyalgia syndrome, exercise programs should be developed individually, started below the patient's exercise capacity, and modified based on the patient's tolerance status by increasing loads gradually. Furthermore, the personal preferences of FMS patients should be considered [63].

Aerobic exercise can be administered at different intensities and in various methods (such as walking, cycling, and aerobic dance) [64].

In a Cochrane review evaluating the effectiveness of aerobic exercise in FMS, compared to healthy controls, moderate-quality evidence suggests that aerobic exercise ameliorates FMS-related quality of life and all-cause withdrawal, while low-quality evidence suggests that aerobic exercise mildly reduces pain level, increases physical capacity, and causes minor differences in fatigue and stiffness [65].

A systematic review reported that an aerobic exercise program consisting of mild-to-moderate intensity, land- or water-based exercises two or three times a week for at least four weeks is beneficial [66].

A Cochrane review was conducted on strengthening-resistance exercise interventions. The low-quality evidence suggested that moderate- to high-intensity resistance exercises ameliorate functional capacity, pain level, and tenderness in FMS. Furthermore, low-quality

evidence suggests the superiority of aerobic exercise over resistance exercise [67].

In another Cochrane review on flexibility exercises, the effect of flexibility programs on FMS symptomatology compared to aerobic exercise was reported to be uncertain [68]. A Cochrane review included 16 studies that assessed the efficacy of aquatic exercises in FMS.

Compared to controls, low to moderate quality evidence suggests that aquatic exercises are helpful for improving clinical signs in FMS. The superiority of aquatic exercises over land-based exercises was not reported [69].

A Cochrane review examined the effectiveness of mixed exercise programs in FMS. Studies that included at least two different types of exercise (aerobic, resistance, flexibility) were evaluated. Moderate quality evidence suggests that mixed exercise programs likely ameliorate physical function, fatigue, and health-related quality of life when compared to controls [70].

Cognitive behavioral therapy

Cognitive behavioral therapy is a comprehensive treatment approach involving several interventions that help patients comprehend, recognize, and modify undesirable psychiatric and behavioral patterns.

As a result of a meta-analysis evaluating fourteen studies, it was reported that cognitive behavioral therapy improved depression and pain levels in FMS patients [71]. A Cochrane review reported a positive but minor effect on pain levels, psychological signs, and disability after treatment and at long-term follow-up [72].

Hydrotherapy and balneotherapy

A systematic review reported that various approaches of hydrotherapy could be beneficial in managing patients with FMS. A short-term effect was noted, improving pain, fatigue, and psychological symptoms [73].

A meta-analysis of ten articles on balneotherapy and eleven articles on hydrotherapy found that combining hydrotherapy with exercise offered a minor improvement in pain and quality of life. Furthermore, balneotherapy using thermo-mineral water was reported to have a moderate-to-large effect on pain and tender point count. There was a moderate effect on the quality of life but no effect on depression. However, the small sample size and risk of bias are significant handicaps [74].

Massage

A meta-analysis evaluated the effectiveness of different massage techniques on FMS. Although some favorable benefits were reported, the methodological shortcomings of the articles and the risk of bias should be considered [75].

Mind-body therapies

A Cochrane review evaluating mind-body therapies in FMS revealed that psychological intervention techniques can improve pain, physical function, and mood status compared to controls, but the quality of evidence is low. Furthermore, the efficacy of biofeedback, mindfulness, movement therapies, and relaxation-based therapies is uncertain as the quality of evidence is poor [76].

According to the results of another review, mindfulness meditation interventions can be beneficial, particularly when combined with high-evidence treatment methods [77]. A systematic review evaluating the effectiveness of meditative movement therapies in FMS suggested positive effects on sleep, fatigue, and psychiatric signs [78].

Nutrition therapy

In a systematic review assessing the efficacy of diet interventions in FMS, it was reported that a low-calorie diet, vegetarian diet and fermentable oligo-, di- and monosaccharides, alcohols and polyols (FODMAP) diet can have beneficial effects.

However, it is difficult to provide precise results due to the insufficient number of articles in this field and low-quality evidence [79]. It has been noted that there is no specific diet for FMS, and weight control and antioxidant diets may positively impact FMS symptomatology [80].

Conclusions

Fibromyalgia syndrome is a rheumatic disorder that is common all over the world. The increased scientific research on FMS over the years reflects the lack of complete elucidation of the etiopathogenesis and the growing interest in the epidemiology, diagnosis and treatment of FMS.

Fibromyalgia syndrome diagnostic approaches have evolved significantly over time, shifting away from pain-only assessments and focusing on the polysymptomatology of FMS. The complex etiopathogenesis of FMS and the fact that various mechanisms are responsible for clinical signs reveal the necessity of multidimensional treatment approaches.

Therefore, FMS management should include a combination of pharmacological and non-pharmacological treatment modalities. In addition, individual characteristics should be considered, and treatment should be individualized.

The authors declare no conflicts of interest.

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