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Efficacy of Add-On Pharmacological Therapy in Patients with Primary Fibromyalgia.

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CONTENTS

Abstract

Aim. Fibromyalgia is a chronic disorder characterized by widespread musculoskeletal pain associated with sleep disturbances, chronic fatigue, neurocognitive impairment, and other symptoms, often difficult to treat. The aim of this retrospective study was to evaluate the effectiveness of different pharmacological add-on therapeutic regimens in a cohort of patients with primary fibromyalgia over a 12-month follow-up period.

Methods. One hundred-eighty patients (mean age 53±12 years) were enrolled and evaluated at variable intervals of 3-4 months. During follow-up, at each visit, if adequate symptom control was not achieved, pharmacological therapy was intensified according to a predefined add-on strategy by adding a new drug to the pharmacological regimen initiated at baseline (even up to 4-5 drugs). The study cohort was divided into four groups according to the pharmacological strategies adopted during the first two clinical visits in naïve patients: cyclobenzaprine plus fluoxetine (C/F, 37 patients), cyclobenzaprine plus duloxetine (C/D, 48 patients), cyclobenzaprine plus other medications (C/O, 34 patients), and cyclobenzaprine alone (C, 61 patients). Disease status was assessed at each visit (T0, T6, and T12) using the Widespread Pain Index (WPI), Symptom Severity Scale (SSS), Polysymptomatic Distress Scale (PDS), and myofascial Tender Point (TPM) pain intensity, graded on a scale ranging from 0 (no pain) to 3 (severe pain). Statistical analysis was performed using non-parametric tests.

Results. During the follow-up, an overall statistically significant progressive improvement was observed in all clinical and clinimetric parameters ($p < 0.0001$), with the greatest improvements occurring in the C/F and C groups. Patients in the C/O group showed an initial statistically significant improvement of their clinical condition from T0 to T6, followed by worsening of several clinical parameters at T12. The C group (34% of patients) exhibited progressive clinical improvement with sustained clinical stability throughout the study period and did not require any pharmacological add-on therapy. Non optimal 25-OH-Vitamin D serum levels (<30 ng/mL) were observed at baseline in 69% of patients. After supplementation, a progressive statistically significant increase of vitamin D values was observed during follow-up ($p = 0.0013$). BMI was normal (18.5-24.9) in 44% of patients, overweight (25-29.9) in 38% of patients, and obesity (>30) in 17% of patients. Side effects, usually mild even if sometimes not tolerated, were collected and reported.

Conclusions. The results of this investigation demonstrate the effectiveness of an add-on pharmacological therapeutic approach in patients with primary fibromyalgia, when cyclobenzaprine alone is not enough to control the symptoms. Cyclobenzaprine monotherapy was effective in more than one-third of patients, and the initial therapeutic regimen consisting of cyclobenzaprine plus fluoxetine during the first months of treatment appeared to be the most effective strategy. These findings highlight the pivotal role of combination treatments in addressing multiple symptoms simultaneously.

Chapter 1

Fibromyalgia

1.1 Introduction and definition

Fibromyalgia, or Fibromyalgia Syndrome, is a chronic pain condition characterized by debilitating, persistent, and widespread musculoskeletal pain, associated with a wide range of symptoms including asthenia, sleep disturbances, cognitive dysfunction (commonly referred to as *fibro-fog*), muscle stiffness, chronic fatigue, memory impairment, reduced concentration, and affective disturbances. Furthermore, patients frequently report headache, irritable bowel syndrome, and urinary urgency, all of which negatively impact interpersonal relationships, occupational performance, and daily activities. These manifestations occur in the absence of any underlying inflammatory, autoimmune, or degenerative process capable of explaining the clinical picture (1-4).

Fibromyalgia may be primary or associated with inflammatory rheumatic diseases (e.g., rheumatoid arthritis, Sjögren's syndrome, spondyloarthritis, polymyalgia rheumatica, systemic lupus erythematosus, connective tissue diseases, vasculitis, osteoarthritis) as well as non-rheumatic conditions (e.g., Hashimoto's thyroiditis, hypothyroidism, hepatic or renal disease, fluid and electrolyte imbalances, anemia).

According to the International Association for the Study of Pain (IASP) classification, fibromyalgia is included among chronic primary pain conditions, defined as pain persisting or recurring for more than three months, associated with significant functional disability or emotional distress, and not fully explained by another medical condition (5). Within this framework, fibromyalgia represents the most prototypical clinical example of nociplastic pain, a term introduced by the IASP to describe pain arising from altered nociceptive processing despite no evidence of ongoing tissue damage or a somatosensory nervous system lesion sufficient to account for its intensity (5,6).

Fibromyalgia is currently considered a multifactorial syndrome in which pain represents only one component of a complex clinical phenotype. In addition to pain symptoms,

patients commonly present persistent fatigue, non-restorative sleep, impaired attention and memory, and anxiety-depressive symptoms, along with several functional comorbidities including irritable bowel syndrome, primary headache disorders, migraine, and bladder pain syndrome (1,2). The coexistence of these manifestations reflects the involvement of multiple neurophysiological systems and contributes to the marked clinical heterogeneity of the disease.

From a pathophysiological perspective, current evidence indicates that fibromyalgia is primarily driven by dysregulation of central pain modulation mechanisms, including central sensitization, reduced descending inhibitory pathways, and enhanced nociceptive transmission within the central nervous system (1,7). This interpretation has progressively replaced the traditional view of fibromyalgia as an extra-articular rheumatic condition or a predominantly psychogenic disorder, supporting its recognition as a complex neurobiological syndrome. The definition of fibromyalgia has evolved in parallel with advances in scientific knowledge.

The old 1990 American College of Rheumatology (ACR) criteria defined the syndrome based on widespread pain and the presence of tenderness at ≥11 of 18 predefined tender points (8). Subsequently, the 2010 ACR criteria, their 2011 modification, and the 2016 revision abandoned tender point examination and introduced multidimensional tools such as the Widespread Pain Index (WPI) and the Symptom Severity Scale (SSS), enabling a more comprehensive assessment of symptom burden and disease impact (9).

Based on the most recent scientific evidence, fibromyalgia is defined as a chronic primary pain syndrome characterized by altered central nociceptive processing and a complex interaction among genetic, neurobiological, endocrine, immunological, psychological, and environmental factors responsible for the onset and persistence of clinical symptoms (2,5,6).

1.2 Epidemiology

Fibromyalgia is one of the most common chronic widespread pain syndromes and is currently recognized as a leading cause of disability associated with musculoskeletal pain in the general population (1,2). Although its etiopathogenesis has not yet been fully elucidated, epidemiological studies have enabled a more precise characterization of its population distribution as well as its clinical and socioeconomic impact.

The prevalence of fibromyalgia in the adult population is generally estimated at 2-4%, although reported rates in the literature show considerable heterogeneity (0.2-6.6%), mainly attributable to differences in diagnostic criteria, study design, and the demographic characteristics of the populations investigated (2,10,11).

A recent systematic review confirmed a relatively stable global prevalence of approximately 2.7%, while also highlighting differences across continents and healthcare systems (10).

The evolution of the ACR classification criteria has substantially modified the epidemiological assessment of the disease. The 1990 ACR criteria, based on the presence of widespread musculoskeletal pain associated with at least 11 of 18 predefined tender points, favored the identification of clinical phenotypes characterized by prominent peripheral tenderness, resulting in a marked female predominance (8). The introduction of the 2010 ACR criteria, subsequently modified in 2011 and revised in 2016, shifted the focus toward a multidimensional assessment of symptoms, including the Widespread Pain Index (WPI) and the Symptom Severity Scale (SSS), allowing improved case identification and a more accurate epidemiological representation of the disease (9).

Fibromyalgia predominantly affects females. While studies based on the 1990 ACR criteria reported female-to-male ratios as high as 9:1, more recent epidemiological investigations using updated diagnostic criteria have described a less marked sex imbalance, with ratios approaching 2:1. This observation suggests that female predominance, although still evident, was likely overestimated by earlier classification criteria and that the condition has historically been underdiagnosed in male patients (1,2,9).

Fibromyalgia can occur across all age groups, including pediatric populations; however, peak incidence is observed between the fourth and sixth decades of life. Prevalence increases progressively with age, reaching the highest levels in older adults, likely reflecting the higher frequency of chronic pain conditions, multimorbidity, and age-related alterations in pain modulation mechanisms (2,6).

From a geographical perspective, fibromyalgia shows a relatively uniform global distribution. Differences in reported prevalence across Europe, the Americas, Asia, and South America appear to reflect mainly methodological variability, differences in diagnostic strategies, and healthcare system characteristics rather than true biological or genetic differences between populations (10,11).

A further relevant epidemiological feature is familial predisposition. Observational studies have demonstrated that first-degree relatives of affected patients have a significantly increased risk of developing the syndrome, supporting the hypothesis of a complex interaction between genetic susceptibility, environmental factors, and epigenetic mechanisms (2,6).

Fibromyalgia is frequently associated with multiple comorbidities, including mood disorders, anxiety disorders, irritable bowel syndrome, migraine, sleep disturbances, chronic fatigue syndrome, and inflammatory rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, and spondyloarthritis (2,12). The coexistence of these conditions contributes to disease burden and represents a major determinant of functional impairment.

The impact of fibromyalgia on healthcare systems is substantial. Patients exhibit increased healthcare utilization, higher medication consumption, frequent specialist visits, and a significant reduction in work productivity.

Although fibromyalgia is not associated with increased mortality, it is now recognized as a leading cause of chronic pain-related disability, with major consequences for quality of life and for both direct and indirect healthcare costs (2,12).

1.3 Etiopathogenesis and pathophysiology

Despite substantial advances over recent decades, etiopathogenesis of fibromyalgia remains incompletely understood. Current evidence indicates that fibromyalgia is a multifactorial condition arising from the interaction between genetic susceptibility, environmental triggers, and alterations in central nervous system pain processing mechanisms (1,2,6).

In recent years, fibromyalgia has increasingly been conceptualized within the framework of nociplastic pain, defined by the International Association for the Study of Pain (IASP) as pain arising from altered nociception despite no clear evidence of actual or threatened tissue damage or disease of the somatosensory system sufficient to explain the pain (13). This conceptual shift has helped move beyond earlier interpretations of fibromyalgia as a purely psychogenic or functional disorder, recognizing its complex neurobiological basis. The most widely accepted pathophysiological mechanism is central sensitization, a process in which neurons within nociceptive pathways of the central nervous system become persistently hyperexcitable, leading to amplification of pain transmission (1,2,7). As a consequence, normally innocuous stimuli may be perceived as painful (allodynia), while mildly painful stimuli are disproportionately amplified (hyperalgesia). This phenomenon is driven by synaptic plasticity changes, increased glutamatergic transmission, and reduced efficacy of descending inhibitory pain pathways.

Functional neuroimaging studies have demonstrated increased activation of multiple brain regions involved in pain processing in patients with fibromyalgia, including the insula, anterior cingulate cortex, primary and secondary somatosensory cortices, and prefrontal cortex. These alterations are observed even in response to low-intensity stimuli, supporting the presence of abnormal central processing of nociceptive input (2,14).

Concurrently, impaired descending pain modulation has been consistently documented. Under physiological conditions, brainstem structures such as the periaqueductal gray, the nucleus raphe magnus, and the locus coeruleus modulate nociceptive transmission through serotonergic and noradrenergic inhibitory pathways. In fibromyalgia, these

circuits appear less efficient, resulting in reduced endogenous pain inhibitory capacity (2,7).

Biochemical studies further support an imbalance in key neurotransmitter systems involved in pain modulation. Increased cerebrospinal fluid levels of glutamate and substance P have been reported, alongside reduced levels of serotonin, norepinephrine, and dopamine. These neurochemical alterations likely contribute not only to enhanced pain perception but also to associated symptoms such as fatigue, sleep disturbances, mood disorders, and cognitive dysfunction (1,2,15). Genetic susceptibility represents an additional relevant factor in disease pathogenesis. Family and twin studies have demonstrated increased familial aggregation, supporting a heritable component.

Polymorphisms in genes involved in serotonergic, dopaminergic, and catecholaminergic systems have been described, including those related to the serotonin transporter (5-HTT), catechol-O-methyltransferase (COMT), and dopamine receptors. However, no single genetic variant has been identified as causative on its own (2,16). Genetic predisposition interacts with environmental factors that may act as triggering events. These include physical trauma, surgical procedures, viral or bacterial infections, chronic psychological stress, adverse childhood experiences, and other conditions associated with persistent pain. Such factors are thought to facilitate the onset of central sensitization in genetically susceptible individuals (2,6,16).

In recent years, increasing attention has been directed toward a potential role of the immune system. Although fibromyalgia is not classified as an inflammatory disease, several studies have reported modest alterations in cytokine profiles, including increased levels of pro-inflammatory mediators such as interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor-alpha (TNF-α), which may influence the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system. Substance P has been shown to stimulate the release of IL-6 and IL-8, while IL-6 may contribute to hyperalgesia, fatigue, and depressive symptoms. A role for neuroinflammation, potentially mediated by glial cell activation, has also been proposed as a contributor to the maintenance of central sensitization. However, the pathophysiological significance of these findings remains under investigation and they are not considered diagnostic markers of the disease. The complex interplay among these mechanisms is still not fully elucidated (6,17).

Sleep disturbances also play a central role in fibromyalgia pathophysiology. Patients frequently exhibit reduced slow-wave sleep (N3 stage) and increased sleep fragmentation, contributing to lowered pain thresholds, chronic fatigue, and cognitive impairment. Experimental sleep deprivation in healthy individuals has been shown to induce symptoms similar to those observed in fibromyalgia, suggesting a close relationship between sleep quality and pain modulation (2,7).

Taken together, these findings support the concept that fibromyalgia is a disorder of altered central pain processing, in which genetic, neurobiological, psychological, and environmental factors interact to produce a persistent dysregulation of nociceptive modulation systems. This integrated model currently represents the leading pathophysiological paradigm of the disease and provides the rationale for modern multimodal pharmacological strategies recommended by international guidelines (6,12).

1.4 Clinical presentation

Fibromyalgia is a chronic syndrome primarily characterized by three core symptoms: widespread musculoskeletal pain persisting for at least three months and affecting both sides of the body as well as the upper and lower quadrants, fatigue, and sleep disturbances. These features are associated with a broad spectrum of somatic and neuropsychological symptoms that significantly impair patient quality of life (1,9).

Currently, fibromyalgia is conceptualized as a nociplastic pain condition, in which altered central processing of nociceptive stimuli leads to an amplification of pain perception in the absence of a proportionate tissue injury (13). The pain phenotype is characterized by allodynia, hyperalgesia, persistence of pain after stimulus removal, and temporal summation. Pain is typically described as widespread, burning, stabbing, shooting, deep, or throbbing, and its intensity may fluctuate throughout the day, worsening with physical or emotional stress, cold exposure, sleep disturbances, or prolonged inactivity (1,9).

Another highly prevalent manifestation is fatigue, often present upon awakening, described as a persistent sensation of profound tiredness, weakness, or lack of energy, frequently accompanied by easy fatigability. Fatigue may be physical or mental and, in

the latter case, overlaps with cognitive dysfunction, including impaired attention and concentration, short-term memory deficits, slowed information processing, and executive dysfunction, collectively referred to as *fibro-fog* (18). Fatigue, reported by more than 90% of patients, is characterized by persistent physical and mental exhaustion that is not relieved by rest and substantially limits daily functioning, representing one of the main determinants of disability in fibromyalgia (19).

Sleep disturbances are a central feature of the clinical picture and affect approximately 75% of patients. Reported abnormalities include difficulty initiating sleep, insomnia, frequent nocturnal awakenings, non-restorative sleep, difficulty returning to sleep, sleep-wake rhythm disturbances, daytime somnolence, and restless legs syndrome. Alterations in sleep architecture, particularly involving stages III and IV of non-REM sleep, are consistently described in fibromyalgia and are considered potential contributing factors to the disorder; notably, fibromyalgia-like symptoms can be experimentally induced in healthy subjects through sleep deprivation. These disturbances contribute to increased pain sensitivity and fatigue perception, establishing a self-perpetuating vicious cycle linking pain, insomnia, and exhaustion (20). Although neuropsychological testing generally reveals only mild abnormalities, these symptoms may have a substantial impact on occupational and social functioning.

In addition to the core manifestations, a wide range of associated symptoms may occur with variable expression across patients and over time. These include morning stiffness, paresthesias/dysesthesias, restless legs syndrome, tension-type headache or migraine, anxiety and depressive symptoms, prior depressive episodes, dysmenorrhea, sicca syndrome (xerostomia, xerophthalmia, vaginal and cutaneous dryness), irritable bowel syndrome, chronic pelvic pain, bladder pain syndrome with urinary urgency, Raynaud-like phenomena, and hypersensitivity to light, sound, and odors (12,13). From a psychological perspective, anxiety, depression, stress-related manifestations, and post-traumatic stress disorder are common comorbidities, although they are not considered causal factors of the disease.

Several studies showed that chronic pain, functional limitations, and sleep impairment contribute to the development of psychological symptoms, which in turn may further amplify pain perception through complex neurobiological mechanisms (9,12). Physical

examination is generally unremarkable, with no significant inflammatory or neurological findings. However, diffuse hyperalgesia and allodynia are frequently observed, reflecting central sensitization (13).

Fibromyalgia typically follows a chronic course with a fluctuating pattern, characterized by alternating periods of relative stability and symptom exacerbations triggered by psycho-physical stress. In many cases, identifiable physical (e.g., illness or trauma) or psychological (e.g., bereavement) triggering factors precede symptom onset. Although fibromyalgia does not lead to structural joint damage or reduced life expectancy, it can profoundly impair physical function, work productivity, social relationships, and overall quality of life, thus requiring a multidisciplinary therapeutic approach (1,13).

1.5 Diagnosis

The diagnosis of fibromyalgia is fundamentally clinical. To date, no specific laboratory or instrumental abnormalities have been identified for this condition (1).

In contrast to inflammatory rheumatic diseases, inflammatory markers are typically within normal ranges, and no disease-specific autoantibodies are detected. The diagnostic process is based on a careful medical history and a comprehensive physical examination, which is generally unremarkable except for the presence of widespread tenderness and/or tenderness at ≥11 of 18 specific anatomical sites, known as tender-points, as defined by the 1990 American College of Rheumatology (ACR) classification criteria (see Figure 1) (8). Tender-points are elicited by applying approximately 4 kg/cm^2 of digital pressure on specific anatomical areas. Although these criteria represented a milestone in clinical research, they had several limitations, including dependence on examiner expertise and the omission of key symptoms such as fatigue, cognitive dysfunction, and sleep disturbances (21).

To address these limitations, the ACR introduced new diagnostic criteria in 2010, which eliminated tender-point assessment and incorporated two standardized instruments: the Widespread Pain Index (WPI) and the Symptom Severity Scale (SSS) (22).

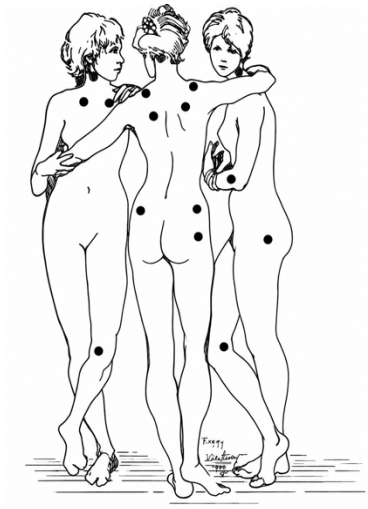

Figure 1. Location of the 18 tender points according to the 1990 American College of Rheumatology (ACR) classification criteria

The WPI quantifies the number of body regions affected by pain over the preceding two weeks, whereas the SSS assesses the severity of symptoms such as fatigue, non-restorative sleep, cognitive disturbances, and other somatic symptoms (22).

In 2016, these criteria were further revised to improve diagnostic accuracy and clinical applicability (9). According to the most recent revision, the diagnosis of fibromyalgia can be established when the following criteria are met WPI ≥7 combined with an SSS score ≥5, or WPI 4-6 with SSS ≥9; presence of generalized pain in at least four of five body regions; symptoms persisting for at least three months; exclusion of other clinical conditions (see also paragraph 1.6).

The diagnostic approach also requires careful differential diagnosis with a wide range of rheumatologic, neurological, endocrine, and internal medicine conditions that may present with overlapping symptoms. These include rheumatoid arthritis, systemic lupus erythematosus, polymyalgia rheumatica, hypothyroidism, inflammatory myopathies, multiple sclerosis, vitamin D deficiency, obstructive sleep apnea syndrome, and certain chronic infectious diseases (1). In cases of recent onset disease without diagnostic uncertainty regarding alternative causes of chronic pain, a basic laboratory screening is generally sufficient, including inflammatory markers, complete blood count, free T3,

free T4, thyroid-stimulating hormone (TSH), creatine phosphokinase, and liver and renal function tests, 25OH-Vitamin D. In most patients, these investigations yield normal results (1,12).

At present, no specific instrumental tests are available for fibromyalgia; investigations are performed selectively to exclude alternative diagnoses. Current international guidelines emphasize the importance of early diagnosis, as timely recognition of the disease can reduce unnecessary investigations, minimize diagnostic delay, and facilitate the initiation of a multidisciplinary management approach based on patient education, exercise therapy, and appropriate pharmacological and non-pharmacological interventions (12,23).

Finally, the diagnosis of fibromyalgia requires a patient-centered approach that considers not only pain intensity, but also the overall impact of the disease on quality of life, daily functioning, and psychological well-being (1,12).

The marked variability of symptoms, absence of specific biomarkers, and need for careful differential diagnosis often result in a prolonged diagnostic journey. Patients typically undergo multiple consultations and unnecessary investigations before a correct diagnosis is established, with an estimated doubling of primary care visits and prescriptions compared with other conditions (24). This diagnostic delay has a substantial psychological impact, as patients often feel misunderstood and receive the diagnosis only after numerous consultations and investigations, contributing to frustration and the perception of having an “invisible illness”. Fibromyalgia is associated with significant personal, familial, and socioeconomic burden. It leads to disability and dependence on family members for daily activities, contributing to stress and distress both in patients and caregivers. It also markedly reduces perceived functioning in physical, psychological, and social domains, negatively affecting interpersonal relationships and parenting. Feelings of guilt and frustration may further worsen clinical outcomes. In addition, many patients are unable to maintain employment, resulting in significant direct and indirect costs, including healthcare utilization, diagnostic testing, specialist visits, hospitalizations, non-reimbursed treatments, caregiver burden, and pharmaceutical expenses (25-28).

1.6 History, classification and diagnostic criteria

Fibromyalgia is thought to have been first recognized and studied as early as the 16th century. The first description of the condition was provided by Guillaume de Baillou in 1642, who used the term “muscular rheumatism” (29). The term “fibrositis” was later introduced by W.R. Gowers in 1904 to describe tenderness to fingertip pressure over hardened muscles attributed to inflammation of fibrous tissue (30). He also described spontaneous pain, hypersensitivity to mechanical pressure, fatigue, sleep disturbances, and symptom exacerbation triggered by cold exposure and excessive stress (30). In the same year, R. Stockman proposed a pathological basis for Gowers’ fibrous tissue inflammation theory, describing painful nodules in which connective tissue hyperplasia within inflamed tissue was observed (31). However, subsequent muscle biopsy studies failed to demonstrate evidence of inflammation, and this inflammatory hypothesis was progressively abandoned. As a result, some authors argue that these early uses of the term “fibrositis” should not be considered synonymous with modern fibromyalgia (32). In 1947, E.W. Boland, in the absence of corresponding objective physical findings, redefined the concept as “psychogenic rheumatism,” describing it as a musculoskeletal expression of functional disorders, stress states, or psychoneurosis (33). Later, in 1953, W. Graham reintroduced the term “fibrositis” to describe a pain syndrome in the absence of identifiable organic disease (34). In this context, “fibrositis” can be considered, in its later usage, conceptually close to what is currently defined as fibromyalgia. In 1968, E.F. Traut conceptualized “muscular fibrositis” or “non-articular rheumatism” as a syndrome characterized by generalized pain, fatigue, sleep disturbances, and tenderness on palpation at trigger points involving soft tissues of the neck, shoulders, elbows, carpal tunnel, palms (including Dupuytren’s contracture), and lower back pain (35).

In 1976, Philip Showalter Hench coined the term fibromyalgia (from the Latin *fibro* meaning fibrous tissue, and the Greek *myo* meaning muscle and *algia* meaning pain) to define a non-articular rheumatic condition characterized by widespread pain, fatigue, sleep disturbances, diffuse morning stiffness, emotional stress, and multiple tender points (36). In 1977, Hugh A. Smythe and Harvey Moldofsky further advanced the work of Hench by proposing one of the first structured diagnostic

approaches to fibromyalgia in their paper “Two Contributions to the Understanding of the Fibrositis Syndrome” (37). They identified non-restorative sleep and tender points as core features of the condition. However, while sleep disturbance, fatigue, and widespread pain were considered essential, no standardized methods for their assessment were proposed. In contrast, tender point count was clearly defined, requiring tenderness at 12 of 14 anatomical sites, and subsequently became the dominant diagnostic feature, while other symptoms were largely neglected (37). Subsequent studies proposed different numbers of tender points. In 1981, Yunus et al. introduced diagnostic criteria for primary fibromyalgia, while proposing the term “secondary fibrositis” for cases associated with underlying conditions (e.g., inflammatory diseases). Their criteria were the first to emphasize symptom-based diagnosis rather than exclusion alone, representing an important step toward a more comprehensive understanding of fibromyalgia. They also suggested that primary fibromyalgia should be diagnosed based on its intrinsic clinical features rather than merely by exclusion of other disorders, a concept that remains relevant today (38).

In 1987, the American Medical Association recognized fibromyalgia syndrome as a distinct clinical entity. Subsequently, the ACR established a committee to develop formal classification criteria. In 1990, the ACR published the first official classification criteria and adopted the term fibromyalgia syndrome instead of fibrositis (8) (see Table 1). Diagnosis required the presence of widespread pain for at least three months and tenderness in at least 11 of 18 predefined tender areas (tender-points), assessed by digital palpation with approximately 4 kg/cm² of pressure, corresponding to nail blanching pressure applied to the examiner’s thumb (8) (see Figure 1). Six control sites were also included in the physical examination. No distinction was made between primary and secondary fibromyalgia.

The 1990 criteria were later criticized for limited predictive validity, poor standardization of tender point examination, and lack of consideration of key symptoms such as sleep disturbances and fatigue. In addition, their reproducibility was limited, as approximately 30% of previously diagnosed patients no longer met criteria upon revaluation due to symptom fluctuation or measurement variability. Consequently, these criteria did not adequately meet the needs of clinicians, researchers, and patients.

1. History of widespread pain
Definition. Pain is considered widespread when it is present in all of the following regions: the left and right sides of the body, both above and below the waist. In addition, axial skeletal pain must be present (cervical spine, anterior chest, thoracic spine, or low back). For the purposes of this definition, shoulder and buttock pain are considered pain affecting the respective side of the body. Low back pain is considered lower segment pain.
2. Pain on digital palpation in at least 11 of the 18 tender points
Definition. Pain on digital palpation must be present in at least 11 of the following 18 tender points. **Occiput:** bilateral suboccipital muscle insertions. **Low cervical region:** bilateral anterior aspects of the intertransverse spaces at C5-C7. **Trapezius:** bilateral midpoint of the upper border. **Supraspinatus:** bilateral origins above the medial border of the scapular spine. **Second rib:** bilateral second costochondral junctions, just lateral to the junctions on the upper surfaces. **Lateral epicondyle:** bilaterally, 2 cm distal to the lateral epicondyles. **Gluteal region:** bilateral upper outer quadrants of the buttocks. **Greater trochanter:** bilaterally, posterior to the greater trochanteric prominence. **Knee:** bilaterally, at the medial fat pad proximal to the joint line. > Digital palpation should be performed using approximately 4 kg/cm^2 of pressure. A tender point is considered "positive" only if the patient reports that palpation is "painful". "Tenderness" alone should not be considered "pain".
***** For classification purposes, patients are classified as having fibromyalgia if both criteria are satisfied. Widespread pain must have been present for at least 3 months. The presence of another clinical disorder does not exclude the diagnosis of fibromyalgia.

Table 1. The 1990 American College of Rheumatology classification criteria for fibromyalgia

In 2010, the ACR introduced new diagnostic criteria based on two multidimensional instruments: the Widespread Pain Index (WPI) and the Symptom Severity Scale (SSS) (22). The WPI assesses pain in 19 body regions (score range 0-19) (see Figure 2). The SSS includes fatigue, non-restorative sleep, and cognitive symptoms (SSS-2a), rated on a 0-3 Likert scale, and a 41-item symptom checklist (SSS-2b), with symptoms grouped into severity categories contributing to a total score ranging from 0 to 12. A diagnosis is established when either WPI ≥7 and SSS ≥5, or WPI 3-6 and SSS ≥9 are present (22).
In 2011, Wolfe et al. revised the 2010 criteria to facilitate their use in epidemiological and community studies, although not specifically for clinical diagnosis (39).
In 2016, the ACR proposed a combined revision of the 2010 and 2011 criteria to improve diagnostic applicability in clinical practice (9) (see Figure 3).
In 2016, the ACR proposed a combined revision of the 2010 and 2011 criteria to improve diagnostic applicability in clinical practice (9) (see Figure 3).

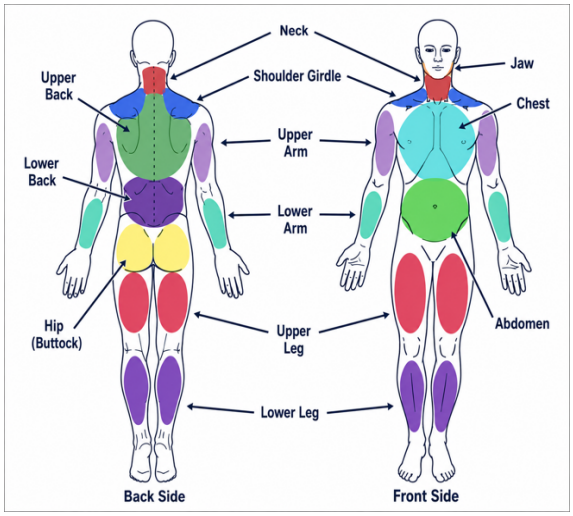

Figure 2. Anatomical regions included in the Widespread Pain Index (WPI) of the 2010 American College of Rheumatology fibromyalgia diagnostic criteria

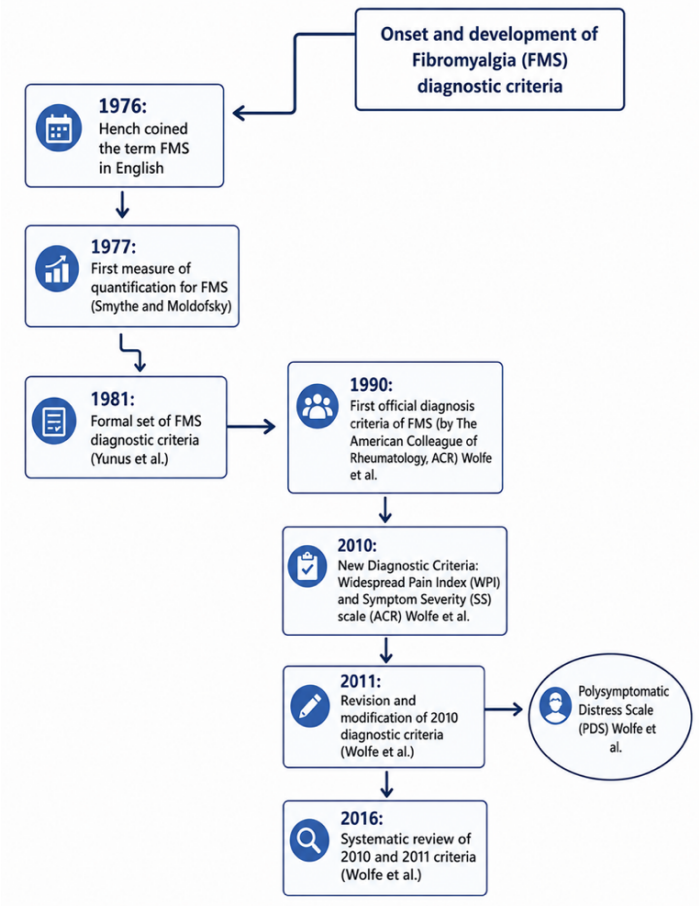

Figure 3. Roadmap illustrating the key milestones in the development of the diagnostic criteria for fibromyalgia syndrome

The 2016 criteria aimed to be more easily applicable by non-specialists and useful for longitudinal patient assessment. They rely on the WPI and SSS instead of tender point examination. A diagnosis of fibromyalgia is made when the following criteria are met (see also Table 2) (9):

1. WPI ≥7 and SSS ≥5, or WPI 4-6 and SSS ≥9;
2. generalized pain in at least 4 of 5 body regions (jaw, chest, and abdominal pain are excluded);
3. symptoms present for at least 3 months;
4. the diagnosis is valid regardless of other comorbid conditions, provided they do not fully explain the clinical picture.

This last point is particularly important, as careful differential diagnosis is required with conditions that may present with overlapping symptoms, including infectious diseases (e.g., infectious mononucleosis), neuropsychiatric disorders (e.g., depression), endocrine diseases (e.g., hypothyroidism), rheumatologic diseases (e.g., Sjögren's syndrome, undifferentiated connective tissue disease, Ehlers-Danlos syndrome, osteoarthritis), and environmental or chemical-related syndromes (e.g., silicone implant illness). Importantly, fibromyalgia may also coexist with other conditions (40-43). For example, concomitant fibromyalgia has been reported in patients with systemic lupus erythematosus and Sjögren's syndrome in 6-61% and 18-55% of cases, respectively, depending on the studied population beyond thyroid and inflammatory bowel diseases (44).

2016 revised American College of Rheumatology diagnostic criteria for fibromyalgia

CRITERIA

A patient must satisfy the following conditions:

1. Widespread Pain Index (WPI) ≥ 7 and Symptom Severity Scale (SSS) score ≥ 5, or WPI 4-6 and SSS score ≥ 9.
2. Generalized pain must be present, defined as pain in at least 4 of 5 regions. Pain in the jaw, chest, and abdomen is not included in the definition of generalized pain.
3. Symptoms must have been present for at least 3 months.
4. A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important diseases.

INVESTIGATIONS

1. WPI: record the number of areas in which the patient has experienced pain during the previous week. In how many areas has the patient experienced pain? The score ranges from 0 to 19.

Left upper areas (Region 1)	**Right upper areas (Region 2)**
1. Right jaw	1. Left jaw
2. Right shoulder girdle	2. Left shoulder girdle
3. Right upper arm	3. Left upper arm
4. Right lower arm	4. Left lower arm

Left lower areas (Region 3)

1. Left hip (buttock, greater trochanter)
2. Left thigh
3. Left lower leg

Right lower areas (Region 4)

1. Right hip (buttock, greater trochanter)
2. Right thigh
3. Right lower leg

Axial areas (Region 5)

1. Neck
2. Upper back
3. Lower back
4. Chest
5. Abdomen

2. Symptom Severity Scale (SSS) score:

1. Fatigue
2. Non-restorative sleep
3. Cognitive symptoms

For each of the three symptoms listed above, indicate the severity during the previous week using the following scale:

0 = No problem
1 = Mild or slight problems, generally mild or intermittent
2 = Moderate problems, considerable, frequently present and/or of moderate severity
3 = Severe problems: pervasive, continuous, and interfering with quality of life

The **Symptom Severity Scale (SSS) score** is the sum of the severity scores for the three symptoms (fatigue, waking unrefreshed, and cognitive symptoms) (0-9), plus the total score (0-3) for the following symptoms that have bothered the patient during the preceding 6 months:

1. headache (0-1)
2. lower abdominal cramping pain (0-1)
3. depression (0-1)

> The final Symptom Severity Scale ranges from 0 to 12.
> The Fibromyalgia Severity (FS) score is the sum of WPI and SSS.

Table 2. 2016 revised American College of Rheumatology diagnostic criteria for fibromyalgia

1.7 Management and treatment

Despite fibromyalgia is a highly prevalent condition, its therapeutic management remains a significant challenge. The inherent transparency and subjectivity of pain often represent an obstacle to the quality of care in these patients.

In 2017, the European League Against Rheumatism (EULAR) published a set of recommendations for the management of patients with fibromyalgia (see Table 3) (12). Optimal management requires early diagnosis and a comprehensive assessment of pain, function, and the psychosocial context. General principles recommend a stepwise, multidisciplinary approach tailored to the patient's reported symptoms and based on shared decision-making. A fundamental element is therefore a strong physician-patient relationship and good adherence to the prescribed therapy. Treatment consists of a combination of pharmacological and non-pharmacological approaches.

Initial management should primarily rely on non-pharmacological interventions, including aerobic and strengthening exercise, cognitive-behavioral therapy, combined approaches (e.g., psychotherapy and exercise), physical therapies such as acupuncture and hydrotherapy, meditative and movement-based techniques (e.g., qigong, yoga, tai chi), and stress-reduction strategies such as mindfulness. Patients should be encouraged to maintain normal daily activities, provided they are not excessively demanding, and to engage in physical activity with gradual progression.

The pharmacological treatment of fibromyalgia aims to reduce pain, improve sleep quality, alleviate fatigue, and manage associated psychiatric comorbidities such as anxiety and depression. Since no disease-modifying therapy exists, treatment must be individualized and integrated with non-pharmacological strategies (12).

Pharmacological treatments include:

1. Cyclobenzaprine hydrochloride, a centrally acting muscle relaxant structurally related to tricyclic antidepressants. Its mechanism of action involves the reduction of tonic somatic motor neuron activity at the brainstem level through modulation of descending serotonergic and noradrenergic pathways. It also exhibits antagonistic activity at 5-HT_2 serotonin receptors, contributing to central sensitization reduction and improvement of sleep quality (45,46).

Recommendations
General principles 1. Optimal management requires early diagnosis. A comprehensive understanding of fibromyalgia requires a holistic assessment of pain, function, and psychosocial context. Fibromyalgia should be recognized as a complex and heterogeneous condition characterized by abnormal pain processing and associated secondary features. In general, fibromyalgia management should follow a stepwise approach. 2. Management of fibromyalgia should aim to improve health-related quality of life by balancing the risks and benefits of treatment. This often requires a multidisciplinary approach combining pharmacological and non-pharmacological modalities, tailored to pain intensity, functional status, associated features (such as depression), fatigue, sleep disturbances, patient preferences, and comorbidities. Shared decision-making with the patient is essential. Initial management should focus on non-pharmacological therapies.
Specific recommendations
Non-pharmacological management: 1. Aerobic and strengthening exercise 2. Cognitive-behavioral therapy 3. Multicomponent therapies 4. Physical therapies such as acupuncture or hydrotherapy 5. Meditative movement therapies (qigong, yoga, tai chi) and mindfulness-based stress reduction
Pharmacological management: 1. Amitriptyline (low dose) 2. Duloxetine or Milnacipran 3. Tramadol 4. Pregabalin 5. Cyclobenzaprine hydrochloride

Table 3. 2017 European League Against Rheumatism (EULAR) recommendations for the management of patients with fibromyalgia

Clinical studies have shown also partial benefits on pain and sleep, however its use may be limited by anticholinergic side effects and sedation (45).

2. Fluoxetine, a selective serotonin reuptake inhibitor (SSRI). It selectively blocks the serotonin transporter (SERT), increasing synaptic serotonin availability. Enhanced

serotonergic transmission strengthens descending inhibitory pain pathways and improves depressive symptoms commonly associated with fibromyalgia (47). However, due to the lack of noradrenergic activity, its analgesic efficacy is generally lower compared to dual-action antidepressants (SNRI, NDRI), which increase serotonin and noradrenaline levels, and in some cases dopamine.

3. Duloxetine, a serotonin and noradrenaline reuptake inhibitor (SNRI), is one of the most widely recommended drugs in international guidelines for fibromyalgia management. It inhibits both SERT and NET transporters, increasing synaptic availability of serotonin and noradrenaline. This enhances descending antinociceptive pathways originating in the brainstem, reducing central sensitization responsible for chronic widespread pain (48,49). Clinical trials have demonstrated significant improvements in pain intensity, physical function, and quality of life in patients treated with duloxetine (48).

4. Pregabalin, a structural analogue of gamma-aminobutyric acid (GABA), although it does not directly interact with GABA receptors. It binds selectively to the $\alpha_2\delta$ subunit of voltage-gated calcium channels in presynaptic terminals, reducing calcium influx and the release of excitatory neurotransmitters such as glutamate, substance P, and calcitonin gene-related peptide (CGRP). This mechanism reduces neuronal hyperexcitability and central sensitization, improving pain control and sleep quality (50,51). Pregabalin is among the drugs with the strongest evidence of efficacy in fibromyalgia, particularly in patients with prominent sleep disturbances and anxiety symptoms (49).

5. Alprazolam, a benzodiazepine acting as a positive allosteric modulator of the GABA-A receptor. By binding to the receptor complex, it increases chloride channel opening frequency, enhancing GABA-mediated inhibitory effects and producing anxiolytic, sedative, and muscle-relaxant effects (52-54). Although it may transiently improve anxiety and sleep quality, it has no specific analgesic effect in fibromyalgia and is not recommended as routine treatment due to risks of tolerance, dependence, and cognitive impairment (12,52-54).

6. Amitriptyline, a tricyclic antidepressant historically among the most widely used drugs in fibromyalgia, particularly at low doses. It inhibits serotonin and noradrenaline reuptake via SERT and NET blockade, enhancing descending inhibitory pain pathways.

It also antagonizes histaminergic H_1, muscarinic, and α_1-adrenergic receptors, contributing to sedation and adverse effects such as dry mouth, somnolence, and orthostatic hypotension (1,55). Amitriptyline has been shown to improve pain, sleep quality, morning stiffness, and fatigue, and remains a first-line therapeutic option in selected patients (55).

Fibromyalgia is considered the prototype of central sensitization syndromes and currently has no gold-standard treatment. Complete remission of symptoms is rare, and only approximately 25% of patients achieve long-term improvement (12,56-59). Regarding combination pharmacotherapy, guidelines from the American Pain Society (APS), EULAR, and the Association of Scientific Medical Societies in Germany (AWMF) do not provide specific recommendations for or against combination therapy (60). Joint guidelines from the Canadian Pain Society (CPS) and the Canadian Rheumatology Association (CRA) state that an ideal pharmacological choice may target multiple symptoms simultaneously and may require drug combinations, in which case attention should be paid to drug-drug interactions (level 5, grade D) (61). At the national level, a panel of experts from the Italian Society of Rheumatology (SIR) has confirmed this multimodal approach (62) (see Table 4). It should also be noted that combined therapeutic strategies may benefit from the integration of pharmacological treatments and nutraceutical approaches.

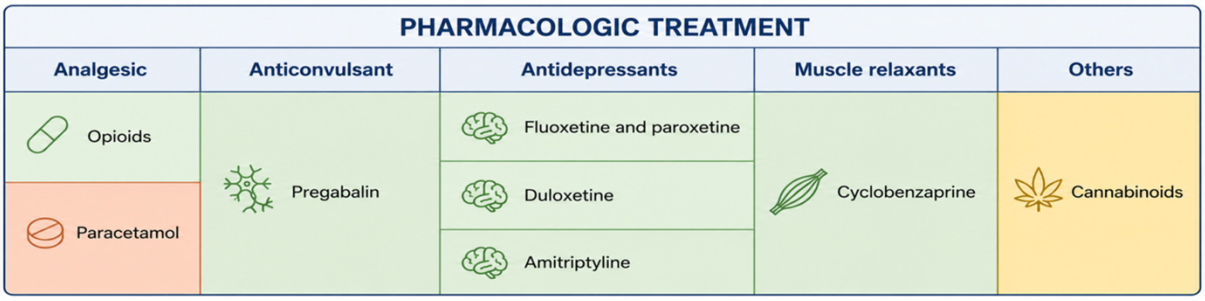

Table 4. The Italian Society of Rheumatology guidelines. Summary of pharmacological treatment options for management of fibromyalgia with respective level of evidence (the green colored squares correspond to Level 1 Grade A; the yellow colored squares correspond to Level 3 Grade C; the orange colored squares correspond to Level 5 Grade D)

Evidence supporting the use of nutraceuticals and dietary supplements in fibromyalgia remains limited and heterogeneous, and none is currently recommended as standard therapy by international guidelines (12). Nevertheless, selected supplements may be considered as adjunctive treatments in carefully selected patients. Vitamin D supplementation has been associated with improvements in pain and quality of life mainly in individuals with documented vitamin D deficiency, whereas routine supplementation in vitamin D-replete patients is not supported by current evidence (63-65). Similarly, coenzyme Q10, acetyl-L-carnitine, magnesium, and melatonin have shown potential benefits in reducing pain, fatigue, and sleep disturbances in small randomized clinical trials; however, the overall quality of evidence remains low because of methodological limitations, small sample sizes, and inconsistent findings across studies (66-71). Palmitoylethanolamide (PEA), owing to its anti-inflammatory and neuromodulatory properties, has also emerged as a promising adjunctive option, although robust confirmatory trials are still lacking (71-75). Finally, nutraceutical containing acmella and boswelia seem promising (see Table 5).

Therefore, nutraceutical supplementation should not replace evidence-based pharmacological and non-pharmacological interventions but may be considered on an individual basis after careful assessment of nutritional deficiencies, symptom profile, and patient preferences.

NUTRACEUTICALS	Proposed Mechanism of Action	Clinical Evidence	Effects on Symptoms	Practical Considerations
Vitamin D	Immunomodulatory and neuromuscular effects	Moderate (in deficient patients)	↓ Pain, ↓ Fatigue	Particularly useful in patients with vitamin D deficiency
Magnesium	NMDA receptor modulation, muscle relaxation	Low-Moderate	↓ Pain, ↓ Muscle cramps	Often combined with malic acid
Coenzyme Q10	Improves mitochondrial function	Moderate	↓ Pain, ↓ Fatigue	Some positive randomized controlled trials (RCTs)
Acetyl-L-carnitine	Neuronal energy metabolism	Moderate	↓ Pain, ↑ Function	Good tolerability
Omega-3 fatty acids	Anti-inflammatory activity	Low	↓ Mild pain	Inconsistent evidence
Melatonin	Regulation of sleep	Moderate	↑ Sleep quality, ↓ Pain	Particularly useful in patients with sleep disturbances
5-HTP	Serotonin precursor	Low	↓ Pain, ↑ Mood	Potential adverse effects
SAMe	Neurotransmitter modulation	Moderate	↓ Pain, ↑ Mood	Fair evidence
Curcumin	Natural anti-inflammatory agent	Low	↓ Pain	Preliminary evidence
Capsaicin (topical)	Nociceptor desensitization	Moderate	↓ Localized pain	Topical administration
Boswellia serrata	5-lipoxygenase inhibition (↓ leukotriene synthesis)	Low	↓ Pain	Indirect evidence (stronger in osteoarthritis)
Acmella oleracea	Analgesic effect (spilanthol acting on nociceptive receptors)	Very low	↓ Localized pain	Limited evidence; mainly topical use
Resveratrol	Antioxidant activity	Very low	Uncertain	Limited studies
B-complex vitamins	Neurological support	Very low	Uncertain	Not routinely recommended

Table 5. Nutraceuticals for fibromyalgia treatment

Chapter 2
Experimental section

Efficacy of add-on pharmacological therapy in patients with primary fibromyalgia.

2.1 Introduction

Fibromyalgia is a chronic disorder characterized by debilitating widespread musculoskeletal pain associated with sleep disturbances, chronic fatigue, neurocognitive impairment, and symptoms such as headache, irritable bowel syndrome, and urinary urgency that do not respond to standard analgesic therapy (1,2,12,76,77).
As no standardized therapy or therapeutic regimen is currently available, complete remission of symptoms is rarely achieved, and only 25% of patients experience long-term clinical improvement (59).
Therefore, the aim of this single-center retrospective study was to evaluate the effectiveness of different pharmacological therapies administered according to an add-on strategy rather than a substitution approach (the latter adopted only in cases of treatment failure or intolerance/adverse reactions to an individual drug), with the objective of identifying the most promising add-on pharmacological therapy in terms of efficacy and long-term clinical improvement in a cohort of 180 patients with primary fibromyalgia, over a 12-month follow-up period. Based on these findings, an attempt was made to identify a standardized add-on pharmacological therapy algorithm, when cyclobenzaprine alone is not enough to control the symptoms.

2.2 Materials and methods

According to revised 2016 American College of Rheumatology criteria for fibromyalgia, a cohort of 180 patients (including 7 men and 173 women), with a mean age of 53±12 years, was enrolled and evaluated at intervals of approximately 3-4 months over a 12-month observation period. During this time, different add-on pharmacological regimens were adopted according to treatment response and the need for therapeutic escalation, following the routine clinical practice of our Clinic.

If adequate symptom control was not achieved during follow-up, pharmacological therapy was intensified according to a predefined add-on strategy by adding a new drug to the pharmacological regimen initiated at baseline (T0), during the 6-month (T6) and/or 12-month (T12) evaluations, with the aim of achieving better control of the clinical condition. Conversely, drug substitution was performed only in cases of intolerance or adverse reactions of the specific medication.

The most commonly used add-on daily regimen in naïve patients at our Clinic is: cyclobenzaprine 5 mg, followed by cyclobenzaprine 10 mg, followed by the addition of fluoxetine 20 mg, then duloxetine 60 mg and/or alprazolam 0.25 mg, and subsequently pregabalin 25-75 mg).

However, the use of different pharmacological regimens in naïve patients allowed the cohort to be stratified according to the different therapeutic strategies adopted during the first two visits (first two drugs employed) into the following groups: Group 1, cyclobenzaprine plus fluoxetine (C/F, 37 patients); Group 2, cyclobenzaprine plus duloxetine (C/D, 48 patients); Group 3, cyclobenzaprine plus other agents (pregabalin, tizanidine hydrochloride, alprazolam, paracetamol, codeine/paracetamol, oxycodone/paracetamol, bromazepam, levacetylcarnitine, tapentadol, buprenorphine, sertraline, medical cannabis, and dietary supplements containing palmitoylethanolamide) (C/O, 34 patients); Group 4, cyclobenzaprine alone (C, 61 patients).

This approach is consistent with the joint guidelines of the Canadian Pain Society and the Canadian Rheumatology Association, which state that “an ideal pharmacological choice may target multiple symptoms simultaneously and may require drug

combinations, in which case attention should be paid to drug-drug interactions" (61). This multimodal approach has also been endorsed in the guidelines proposed by an expert panel of the Italian Society of Rheumatology (62).

In this single-center study, in order to ensure consistency with the majority of contemporary fibromyalgia studies, both the 1990 American College of Rheumatology fibromyalgia classification criteria and the revised 2016 American College of Rheumatology criteria were used in combination as the primary outcome measure to assess disease severity by calculating the Widespread Pain Index (WPI), Symptom Severity Scale (SSS), Polysymptomatic Distress Scale (PDS), and Tender Point (TP) count at each assessment (8-9). In addition, the TP assessment was integrated with a scoring system developed at our Center to evaluate pain intensity on a scale ranging from 0 (absence of pain) to 3 (very severe pain), referred to as the Tender Point Score (TPs).

At each evaluation, beyond the clinical assessment, all patients were asked to complete questionnaires including the WPI and SSS.

At the end of the 12-month observation period, the clinical data and the data obtained from the questionnaires collected at T0, T6, and T12 were used for the statistical analysis, which was performed using non-parametric tests. The *Friedman test* was used to compare related groups of variables, the *Wilcoxon signed-rank test* to compare two paired groups, the *Mann-Whitney U test* to compare independent groups, and the *Spearman rank correlation test* to assess the strength and direction of a monotonic relationship between two variables, along with *Regression analysis* to examine and quantify the relationship between one dependent variable and one or more independent variables. A p-value ≥ 0.05 was considered statistically significant.

All patients gave written informed consent to enter the study and to anonymously manage their clinical data.

2.3 Results

During the follow-up, an overall statistically significant progressive improvement was observed in all clinical and clinimetric parameters ($p < 0.0001$), with the greatest improvements occurring in the C/F and C groups (see Table 6 and Table 7 for further statistical data).

Comparing the different treatment groups, the better response observed in the C group (progressive improvement with sustained clinical stability throughout the study period) was related to a less aggressive disease at baseline and a good answer to cyclobenzaprine alone treatment that did not require further add-on pharmacological therapy.

Conversely, patients in the C/O group showed an initial statistically significant improvement of their clinical condition from T0 to T6, followed by worsening of several clinical parameters at T12.

Non optimal 25-OH-Vitamin D serum levels (<30 ng/mL) were observed at baseline in 69% of patients. After supplementation, a progressive statistically significant increase of vitamin D values was observed during follow-up ($p = 0.0013$) (Table 6). However, any statistically significant correlation was observed between serum vitamin D levels and clinimetric parameters at all time.

Body mass index (BMI) was also assessed in the present study. BMI was normal (18.5-24.9) in 44% of patients, overweight (25-29.9) in 38% of patients, and obesity (>30) in 17% of patients. However, any statistically significant correlation was observed between BMI and clinical parameter values at any time.

Adverse events were one of the leading causes of pharmacological treatment discontinuation and are reported in Table 8. The most frequent adverse events observed during Cyclobenzaprine treatment were somnolence/sedation representing the predominant reason, followed by cardiovascular adverse events and asthenia. The retention rate was better administrating the drug early evening at low initial dose. Duloxetine was associated with a high discontinuation rate due to adverse events, mainly related to somnolence, gastrointestinal disorders, and cognitive impairment. Also tizanidine showed a high discontinuation rate mainly due to asthenia and somnolence. Adverse events leading to pregabalin discontinuation were predominantly

characterized by cognitive disturbances and somnolence. In contrast, discontinuations of fluoxetine and alprazolam were less frequent.

When possible the adverse event was managed by reducing the daily dose, otherwise the drug was discontinued.

	T0	T6	T12	p T0 vs T6vs T12	p T0 vs T6	p T0 vs T12
Overall cohort (n=180)						
WPI (mean ± SD)	13.16±3.5	12.15±3.8	11.34±3.8	<0.0001	<0.0001	<0.0001
SSS (mean ± SD)	8.75±2.3	7.72±2.5	7.51±2.5	<0.0001	<0.0001	<0.0001
PDS (mean ± SD)	21.89±4.6	19.89±5.4	18.94±5.1	<0.0001	<0.0001	<0.0001
TP number (mean ± SD)	15.44±4.2	13.38±5.7	13.21±5.6	<0.0001	<0.0001	<0.0001
TP score (mean ± SD)	2.26±0.8	1.94±0.9	1.93±0.9	<0.0001	<0.0001	<0.0001
25-OH-Vitamin D	25.32±12.4	30.38±16.1	38.49±19.0	0.001	<0.0001	<0.0001
BMI	26.20±5.0	-	-	-	-	-
Group 1, C/F (n=37)						
WPI (mean ± SD)	13.41±3.9	12.7±3.5	10.91±3.6	<0.0001	0.02	0.0003
SSS (mean ± SD)	8.81±2.5	7.51±2.6	6.87±2.7	<0.0001	<0.0001	0.0001
PDS (mean ± SD)	22.22±5.0	20.44±5.2	17.81±5.2	<0.0001	0.0009	<0.0001
TP number (mean ± SD)	15.41±5.1	15.03±4.9	13.81±4.9	0.05	0.05	0.05
TP score (mean ± SD)	2.32±0.9	2.14±0.8	2.06±0.9	0.05	0.05	0.05
Group 2, C/D (n=48)						
WPI (mean ± SD)	13.73±3.5	13.26±3.9	12.11±3.9	<0.0001	0.003	0.0007
SSS (mean ± SD)	9.42±2.2	8.44±2.3	7.75±2.3	<0.0001	0.0003	0.0001
PDS (mean ± SD)	23.06±4.4	21.73±5.0	20.06±5.1	<0.0001	0.0007	<0.0001
TP number (mean ± SD)	16.67±2.5	14.33±4.9	13.58±6.1	0.0004	0.001	0.002
TP score (mean ± SD)	2.44±0.7	2.09±0.9	1.89±1.0	0.0004	0.005	0.0006
Group 3, C/O (n=34)						
WPI (mean ± SD)	13.74±3.6	12.52±3.5	12.30±3.7	0.02	0.006	0.003
SSS (mean ± SD)	9.21±2.0	8.0±2.4	8.52±2.3	n.s.	0.02	0.05
PDS (mean ± SD)	22.94±4.8	20.56±5.3	20.74±4.9	0.003	0.001	0.003
TP number (mean ± SD)	15.38±4.1	13.35±6.0	15.04±4.7	n.s.	0.02	n.s.
TP score (mean ± SD)	2.29±0.7	1.85±0.9	2.26±0.8	n.s.	0.01	n.s.
Group 4, C (n=61)						
WPI (mean ± SD)	12.23±3.2	10.48±3.8	10.42±3.8	<0.0001	<0.0001	<0.0001
SSS (mean ± SD)	7.93±2.3	7.02±2.6	7.14±2.4	<0.0001	<0.0001	<0.0001
PDS (mean ± SD)	20.17±4.1	17.28±5.1	17.69±4.8	<0.0001	<0.0001	<0.0001
TP number (mean ± SD)	14.54±4.6	11.19±6.3	11.26±5.7	<0.0001	<0.0001	0.0003
TP score (mean ± SD)	2.07±0.8	1.69±1.0	1.67±0.9	0.02	0.003	0.006

Table 6. Clinical and clinimetric parameters of enrolled patients at baseline and during follow-up

C/F = cyclobenzaprine/fluoxetine, C/D = cyclobenzaprine/duloxetine, C/O = cyclobenzaprine/other drugs, C = cyclobenzaprine alone, WPI = Widespread Pain Index, SSS = Symptom Severity Scale, PDS = Polysymptomatic Distress Scale, TP = tender points.

	WPI T0	SSS T0	PDS T0	TP number T0	TP score T0
C/F	13.41±3.92	8.81±2.51	22.22±4.96	15.41±5.12	2.32±0.85
C/D	13.73±3.46	9.42±2.20	23.06±4.42	16.67±2.49	2.44±0.68
C/O	13.74±3.56	9.21±2.01	22.94±4.80	15.38±4.13	2.29±0.72
C	12.23±3.15	7.93±2.27	20.17±4.06	14.54±4.63	2.07±0.79
p C/F vs C/D	n.s.	n.s.	n.s.	n.s.	n.s.
p C/F vs C/O	n.s.	n.s.	n.s.	n.s.	n.s.
p C/F vs C	n.s.	0.05	0.02	n.s.	0.05
p C/D vs C/O	n.s.	n.s.	n.s.	n.s.	n.s.
p C/D vs C	0.02	0.001	0.0009	0.02	0.01
p C/O vs C	0.05	0.008	0.009	n.s	n.s
	WPI T6	**SSS T6**	**PDS T6**	**TP number T6**	**TP score T6**
C/F	12.7±3.53	7.51±2.56	20.44±5.15	15.03±4.89	2.14±0.79
C/D	13.26±3.87	8.44±2.31	21.73±4.97	14.33±4.90	2.09±0.87
C/O	12.52±3.51	8±2.37	20.56±5.27	13.35±6.02	1.85±0.86
C	10.48±3.75	7.02±2.55	17.28±5.06	11.19±6.33	1.69±0.96
p C/F vs C/D	n.s.	0.05	n.s.	n.s.	n.s.
p C/F vs C/O	n.s.	n.s.	n.s.	n.s.	n.s.
p C/F vs C	0.01	0.01	0.01	0.002	0.03
p C/D vs C/O	n.s.	n.s.	n.s.	n.s.	n.s.
p C/D vs C	0.0008	0.009	<0.0001	0.01	0.05
p C/O vs C	0.03	0.09	0.009	n.s.	n.s.
	WPI T12	**SSS T12**	**PDS T12**	**TP number T12**	**TP score T12**
C/F	10.91±3.58	6.87±2.66	17.81±5.23	13.81±4.93	2.06±0.93
C/D	12.11±3.85	7.75±2.32	20.06±5.14	13.58±6.09	1.89±0.96
C/O	12.30±3.66	8.52±2.26	20.74±4.86	15.04±4.65	2.26±0.76
C	10.42±3.78	7.14±2.35	17.69±4.81	11.26±5.73	1.67±0.90
p C/F vs C/D	n.s.	n.s.	0.05	n.s.	n.s.
p C/F vs C/O	n.s.	0.02	0.04	n.s.	n.s.
p C/F vs C	n.s.	n.s.	n.s.	0.05	0.05
p C/D vs C/O	n.s.	n.s.	n.s.	n.s.	0.05
p C/D vs C	0.05	n.s.	0.04	0.05	n.s.
p C/O vs C	0.05	0.01	0.02	0.006	0.008

Table 7. Clinical and clinimetric parameters during follow-up in different groups of treatment

C/F = cyclobenzaprine/fluoxetine, C/D = cyclobenzaprine/duloxetine, C/O = cyclobenzaprine/other drugs, C = cyclobenzaprine alone, WPI = Widespread Pain Index, SSS = Symptom Severity Scale, PDS = Polysymptomatic Distress Scale, TP = tender points.

Drug	Side effects	%
Cyclobenzaprine (180 pts)	Somnolence	5%
	Asthenia/Sedation	1.7%
	Cardiovascular disorders (tachycardia, palpitations, arrhythmia, pounding heart, and chest tightness)	2.2%
	Neurological disorders (dizziness, paresthesia)	1.1%
	Musculoskeletal disorders (muscle contracture)	0.6%
	Gastrointestinal disorders (constipation)	1.1%
	Total	11.7%
Duloxetine (74 pts)	Somnolence	5.4%
	Gastrointestinal disorders (nausea)	2.7%
	Cognitive disorders (mental confusion)	2.7%
	Arterial hypertension	1.4%
	Liver abnormalities (elevated AST/ALT)	1.4%
	Tension-type headache	1.4%
	Weight gain	1.4%
	Total	16.2%
Pregabalin (45 pts)	Cognitive disturbances (fibrofog/confusion)	4.4%
	Somnolence	2.2%
	Headache	2.2%
	Asthenia/Sedation	2.2%
	Gastrointestinal disorders (gastralgia)	2.2%
	Total	13.3%
Fluoxetine (69 pts)	Neurological disorders (dizziness)	1.5%
	Intolerance (general malaise)	2.9%
	headache	1.5%
	Asthenia/Sedation	1.5%
	Xerostomia	1.5%
	Total	8.7%
Tizanidine (17 pts)	Somnolence	11.8%
	Asthenia/Sedation	5.9%
	Total	17.7%
Alprazolam (27 pts)	Somnolence	7.4%
	Asthenia/Sedation	3.7%
	Total	11.1%

Table 8. Main side effects reported in our cohort un patients

2.4 Discussion

To the best of our knowledge, this is the first retrospective single-center study comparing the effectiveness of different pharmacological therapeutic regimens based on an add-on strategy in a cohort of 180 patients with primary fibromyalgia.

Based on reports collected during clinical assessments performed at variable intervals of 3-4 months over the 12-month observation period, an overall statistically significant positive response to the different pharmacological add-on therapeutic regimens was observed, with a clinically meaningful reduction of symptoms.

It is important to emphasize that, according to our clinical experience, better symptom control was achieved when treatment was initiated with cyclobenzaprine 5 mg daily (to reduce the risk of acute side effects followed by drug discontinuation) strictly administered at 8 p.m. in order the medicine finished its effect by the next morning. If well tolerated, the dose was increased to one tablet daily after 2 weeks. Whenever further symptom control was required, an additional drug was added according to an add-on therapeutic strategy to optimize clinical outcomes, whereas treatment was switched in cases of intolerance. Fluoxetine (20 mg at 1 p.m.) and duloxetine (30 mg for the first two weeks and then 60 mg at 10 a.m.) were the most commonly drug added to cyclobenzaprine. When the clinical situation required further treatment in addition to fluoxetine, either duloxetine or alprazolam 0.25 mg (administered at 22 p.m.) were added, eventually followed by pregabalin 25-75 mg in difficult cases.

The most promising results were achieved in the C/F group where the initial employed drug were cyclobenzaprine followed by fluoxetine. Patients treated according to the C/F group regimen showed an excellent clinical response that was maintained throughout the 12-month follow-up.

Patients in the C group (cyclobenzaprine alone, 61 out of 180 patients = 34%) exhibited progressive clinical improvement with sustained clinical stability throughout the study period and did not require any pharmacological add-on therapy. On the other hand, cyclobenzaprine is one of the oldest and effective drugs employed in the treatment of fibromyalgia (46,78-80).

This study has several limitations. First, it is a retrospective study with the chance to collect only several clinical parameters. Furthermore, the relatively small sample size, together with its subsequent subdivision into four groups according to the pharmacological add-on therapeutic strategy, limited the statistical evaluation to assess treatment efficacy. Issues related to patient compliance and adherence to the prescribed pharmacological therapy were not always reported and not assessed.

To date, a systematic review of the literature conducted using the major scientific databases (PubMed and Google Scholar) indicates a lack of robust evidence supporting standardized combinations of pharmacological and non-pharmacological treatments in routine clinical practice (81,82).

Consequently, based on our clinical experience in the management of fibromyalgia, further high-quality, well-designed, controlled studies are needed, ideally involving collaboration among multiple centers, to study combination treatments in fibromyalgia patients. Such studies should aim to identify pharmacological combinations providing additional clinical benefit, as well as those associated with poor efficacy or adverse outcomes, including intolerance and adverse drug reactions. Future investigations should also evaluate the emotional dimension of the disease and actively involve caregivers, who are frequently directly affected by both the family and occupational/economic consequences of fibromyalgia (1,2,12,13,77).

As a future objective, cooperation among different centers to standardize the use of clinimetric assessment tools and combined pharmacological treatment strategies may represent a promising approach toward developing a standardized therapeutic algorithm for fibromyalgia management. Given the current lack of robust evidence, such collaborative efforts may help identify the most effective pharmacological add-on therapeutic strategy.

2.5 Conclusions

In conclusion, the results of this investigation demonstrate the effectiveness of an add-on pharmacological therapeutic approach in patients with primary fibromyalgia, when cyclobenzaprine alone is not enough to control the symptoms.

Consistent with our results, cyclobenzaprine monotherapy was effective in more than one-third of patients, whereas the initial therapeutic regimen consisting of cyclobenzaprine plus fluoxetine during the first months of treatment appeared to be the most effective strategy.

These findings highlight the pivotal role of combination treatments in addressing multiple symptoms simultaneously.

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