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MANAGEMENT OF FIBROMYALGIA: A COMPREHENSIVE REVIEW OF ESTABLISHED AND EMERGING THERAPEUTIC STRATEGIES AND PATHOPHYSIOLOGICAL MECHANISMS

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ABSTRACT

Our review article summarizes current knowledge on the clinical features, underlying mechanisms, and therapeutic strategies for fibromyalgia. Recent evidence identifies fibromyalgia as a complex neuroimmune and neuroplastic disorder driven primarily by central sensitization, with additional contributions from peripheral nociceptor dysfunction, low-grade inflammation, neuroendocrine alterations, and psychosocial factors. These mechanisms explain the heterogeneous symptom profile, including widespread pain, fatigue, sensory hypersensitivity, cognitive impairment, and mood disturbances, suggesting the existence of distinct phenotypic subgroups. Current pharmacological treatments, such as tricyclic antidepressants, SNRIs, gabapentinoids, and sublingual cyclobenzaprine, offer moderate and variable benefits, while emerging agents targeting novel pathways remain under investigation. Non-pharmacological interventions, including structured exercise, cognitive-behavioral therapy, and selected complementary techniques, demonstrate comparable effectiveness, particularly within multidisciplinary care.

Overall, the literature highlights the need for personalized, holistic management and further biomarker-driven studies to advance precision-medicine approaches in fibromyalgia.

KEYWORDS

Fibromyalgia, Central Sensitization, Neuroinflammation, Chronic Pain, Fatigue

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Methods

This review was conducted through a structured literature search and synthesis. We systematically searched PubMed and Google Scholar for scientific publications published between 2000 and 2025, with particular emphasis on studies published since 2015 to capture the most recent advances in fibromyalgia research. Studies were included if they reported on pathophysiological mechanisms, clinical manifestations, or pharmacological and non-pharmacological interventions. Historical sources were consulted solely to provide context regarding diagnostic criteria and validated assessment tools. We considered clinical trials, observational studies, meta-analyses, and major international guidelines. Due to the heterogeneity of study designs, the evidence was synthesized using a narrative approach rather than a formal meta-analysis. The collected information guided the presentation of diagnostic frameworks and therapeutic strategies in the Results section.

Introduction

Fibromyalgia (FM) is a chronic nociplastic pain disorder characterized by generalized musculoskeletal pain persisting for more than three months, accompanied by fatigue, sleep disturbances, and a spectrum of cognitive and somatic symptoms including headaches, dizziness, paraesthesias, and attentional or memory disturbances often referred to as “fibro fog” [1,2]. These multisystem manifestations, together with marked interindividual variability, make FM a clinically heterogeneous syndrome. The condition most commonly affects adults in midlife, with a higher prevalence in women, although updated diagnostic criteria have narrowed the female-male ratio and indicate that sex-related differences in clinical expression and pathophysiology remain underexplored [1].

Historically, FM evolved from early descriptions of *muscular rheumatism* nearly five centuries ago. The term *fibrositis* appeared in 1904 to describe localized musculoskeletal pain, but the concept of generalized pain defining modern FM was only articulated in 1972 [3]. Over subsequent decades, controlled clinical and

neuroendocrine studies have validated FM as a distinct condition, emphasizing mechanisms of central sensitization and neurohormonal dysregulation [3].

FM frequently overlaps with or coexists alongside other chronic nociplastic and functional pain syndromes - including migraine, irritable bowel syndrome, chronic pelvic pain, temporomandibular disorders, interstitial cystitis, and chronic fatigue syndrome - which share common neurobiological mechanisms and collectively amplify symptom burden [2]. This high rate of comorbidity, combined with the nonspecific and variable clinical presentation of FM, contributes to substantial diagnostic challenges, as symptoms often mimic rheumatologic, neurologic, infectious, or endocrine conditions and require careful clinical evaluation to avoid misclassification [1, 2]. Environmental triggers such as barometric pressure fluctuations, infections, psychological stress, and extreme temperatures may further exacerbate symptoms or influence disease onset [1].

Multiple theories regarding FM pathogenesis - including central sensitization, small-fiber dysfunction, autonomic imbalance, and immune-neural interactions - have been proposed, reflecting the multifactorial nature of this syndrome [1]. This complexity also underpins the therapeutic challenges, as FM management requires multidisciplinary, individualized approaches integrating patient education, physical activity, psychological strategies, and pharmacologic or emerging biologically targeted treatments.

Results

1. Diagnostic Assessment

The diagnosis of fibromyalgia is based on criteria established by the American College of Rheumatology (ACR). Historically, the diagnosis of fibromyalgia was based on the 1990 ACR criteria, which required widespread pain for a minimum three months and tenderness in eleven or more of the eighteen specified tender points [4]. Over the following decades, these criteria were gradually modified to incorporate broader symptom assessments, including fatigue, sleep disturbances, cognitive symptoms, and other somatic complaints, leading to the development of the Widespread Pain Index (WPI) and Symptom Severity Scale (SSS) in the 2010 and 2011 revisions [5, 6]. The 2016 ACR revision refined the diagnostic criteria to include generalized pain in at least four of five body regions, a persisting symptom duration of three months or longer, and the application of the WPI/SSS system to assess disease burden [7]. A formal diagnosis may be issued if a patient reports pain in seven or more of nineteen body regions with an SSS score ranging from five to twelve, or in four to six regions with an SSS score of nine or greater, provided that the symptoms have persisted for at least three months and are widespread across a minimum of four out of five regions. These criteria allow for the diagnosis of FM even in the presence of other coexisting conditions, providing a more comprehensive and clinically practical framework for identifying patients with the syndrome.

In clinical practice, several patient-reported outcome measures are used to assess and monitor fibromyalgia. The Fibromyalgia Impact Questionnaire (FIQ) evaluates physical functioning, mood, sleep, pain, stiffness, and fatigue, and is mainly used to measure disease severity and treatment response rather than for diagnosis [8]. Its updated version, the Revised Fibromyalgia Impact Questionnaire (FIQR), adds items related to cognition, sensitivity, and balance, offering a broader assessment of functional impairment and symptom burden [9]. The Brief Pain Inventory (BPI) focuses on pain intensity and how it interferes with daily activities, providing a standardized measure helpful for guiding therapeutic decisions [10].

2. Differential Diagnosis

The differential diagnosis of fibromyalgia encompasses multiple conditions that may present with widespread pain, fatigue, or sleep disturbances [11, 12]. Endocrine disorders such as hypothyroidism, hyperparathyroidism, and growth hormone deficiency, as well as metabolic insufficiencies including vitamin D, B12, folate, and ferritin deficiencies, can mimic fibromyalgia symptoms. Medication-induced myalgias, particularly from statins, should also be considered. Rheumatic and systemic diseases - including polymyalgia rheumatica, rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, and ankylosing spondylitis - may initially present with diffuse pain, but usually demonstrate distinctive clinical or laboratory features suggesting inflammatory character [12]. Neurologic disorders - such as multiple sclerosis, myasthenia gravis, peripheral neuropathies, and nerve entrapment syndromes - must also be considered during diagnosis because of their frequent pain symptoms in patients presented. Infectious diseases - including Lyme disease, hepatitis C, and various parasitic infestations (e.g., fascioliasis, amebiasis, and giardia) - as well as posttraumatic conditions such as whiplash-associated disorders, are less common yet can contribute to widespread pain.

Particularly important is myofascial pain syndrome (MPS), which can present with multiple painful trigger points and diffuse discomfort that may fulfill the ACR criteria for fibromyalgia, leading to potential

misdiagnosis. Unlike fibromyalgia, MPS has identifiable peripheral nociceptive sources in myofascial trigger points, which can maintain central sensitization but are amenable to targeted interventions including physical therapy, trigger point injections, and other local treatments [13, 14]. Recognition of MPS is clinically relevant, as effective localized treatments may relieve symptoms that would otherwise be attributed to fibromyalgia.

Functional pain disorders such as irritable bowel syndrome, interstitial cystitis, vulvodynia, and temporomandibular disorder, as well as neuropsychiatric conditions including depression and anxiety, may overlap with fibromyalgia but require distinct management strategies [12]. A thorough history, focused physical examination, and selective laboratory testing are essential to differentiate fibromyalgia from these alternative or comorbid diagnoses and guide appropriate therapy.

3. Pathophysiological Mechanisms

3.1. Central and Peripheral Sensitization

Fibromyalgia is primarily characterized by central sensitization, a phenomenon of neuronal signal amplification within the central nervous system, resulting in heightened pain perception, allodynia, and hyperalgesia [15]. Functional neuroimaging has demonstrated increased activation of pain-processing areas, including the insula, secondary somatosensory cortices, and the amygdala, correlating with sensory and affective dimensions of pain [16]. Dysregulated neurotransmission is evident, with elevated excitatory neurotransmitters such as glutamate and substance P, alongside reduced serotonin and norepinephrine in descending antinociceptive pathways. Peripheral mechanisms also contribute, including increased excitability of C-fibers, altered acid-sensing ion channel (ASIC3) activity in skeletal muscles, and abnormal nociceptor responses, which sustain nociceptive input and promote central sensitization [16].

3.2. Neuroinflammation and Immune Dysregulation

Neurogenic inflammation is increasingly recognized in FM pathophysiology, with elevated pro-inflammatory cytokines (IL-6, IL-8, TNF-α) in both serum and cerebrospinal fluid, as well as activation of glial and immune cells [16, 17]. These processes are influenced by stress and may exacerbate pain, fatigue, and cognitive dysfunction. Subgroups of FM patients demonstrate autoimmune features, such as ANA positivity, suggesting that low-grade inflammation and autoimmunity may contribute to symptom heterogeneity [16].

3.3. Genetic Susceptibility

Genetic factors appear to modulate FM risk and pain sensitivity. Polymorphisms in serotonin transporter genes (SLC64A4, 5-HTT), catechol-O-methyltransferase (COMT), TRPV2, GRIA4, and genes regulating dopamine availability (TAAR1, RGS4) have been associated with altered nociception, affective processing, and susceptibility to chronic pain [16]. Genome-wide studies also implicate variants in MYT1L and NRXN3, which are implicated in neuronal differentiation and synaptic function, suggesting a role in cognitive and affective symptoms. Despite these findings, FM remains a multifactorial condition, and gene–environment interactions likely influence disease manifestation.

3.4. Neuroendocrine and Hormonal Factors

Alterations in the hypothalamic–pituitary–adrenal axis are reported in FM, including blunted circadian cortisol variation and reduced responsiveness to adrenocorticotropic hormone (ACTH) [16]. Dysregulation of the growth hormone (GH)/insulin-like growth factor 1 (IGF-1) axis has also been observed, particularly in relation to nocturnal GH secretion and sleep disturbances. Although estrogens appear to play a limited role, increased G protein-coupled estrogen receptor (GPER) levels have been reported in female FM patients, potentially serving as a biomarker [16].

3.5. Psychopathology and Sleep Disturbances

Psychiatric comorbidities, including depression and anxiety, are prevalent and exacerbate affective pain processing through limbic system dysregulation [16]. Sleep disturbances, particularly alpha-delta sleep intrusion and reduced sleep spindle activity, not only correlate with symptom severity but may precede FM onset, suggesting a bidirectional relationship between disrupted sleep and pain [15, 16]. Sleep deficits may enhance central sensitization and inflammation, including increased IL-6, thereby perpetuating the clinical manifestations of FM [16].

3.6. Nutritional and Metabolic Factors

Emerging evidence suggests that various vitamin and mineral deficiencies are linked to the presence of widespread or chronic pain [15]. Vitamin D and magnesium deficiencies are associated with musculoskeletal pain and may modulate nociceptive transmission, including serotonin and noradrenergic pathways, as well as inflammation [18]. Vitamin B12 and folate deficiencies may contribute to impaired methylation in immune cells, potentially affecting neuronal and immune functions [15]. Thiamine (vitamin B1) deficiency has been linked to widespread pain, possibly due to intracellular transport dysfunction rather than low serum levels. Furthermore, insufficient levels of antioxidant vitamins (A, C, E) may increase oxidative stress, triggering local tissue inflammation and further contributing to central and peripheral sensitization [15].

4. Pharmacotherapy

Pharmacological management of fibromyalgia encompasses both agents with established clinical efficacy and those considered investigational or adjunctive therapies. The first group includes drugs with well-documented benefits in symptom reduction, such as tricyclic antidepressants (TCAs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and gabapentinoids. Conversely, several other pharmacological classes - including cannabinoids, NMDA receptor antagonists, atypical antipsychotics, serotonin (5-HT_3) receptor antagonists, GABAergic agents, and testosterone - are currently regarded as investigational adjunctive options, with their efficacy and safety profiles still under evaluation. Although multiple evidence-based treatment guidelines exist, until August 2025 only three drugs — pregabalin, duloxetine, and milnacipran — were approved by the U.S. Food and Drug Administration (FDA) for fibromyalgia; since then, a fourth, sublingual cyclobenzaprine (Tonmya™), has received FDA authorization [19, 20].

4.1. Antidepressants

4.1.1. Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

SNRIs represent one of the principal pharmacologic classes investigated for the management of fibromyalgia, offering both analgesic and mood-stabilizing properties. These agents modulate central pain processing by enhancing serotonergic and noradrenergic neurotransmission within descending inhibitory pathways, thereby attenuating the heightened pain sensitivity characteristic of the disorder. Among the available SNRIs, duloxetine and milnacipran have received approval from the U.S. Food and Drug Administration, while venlafaxine, desvenlafaxine, and selective norepinephrine reuptake inhibitors such as esreboxetine and reboxetine have been evaluated in clinical studies with varying outcomes [21]. Evidence from randomized controlled trials indicates that duloxetine and milnacipran are superior to placebo in achieving at least a 50% reduction in pain intensity and in improving overall well-being and health-related quality of life [22]. Duloxetine, typically titrated to a target dose of 60 mg/day, has demonstrated improvement in pain and depressive symptoms, with additional benefit reflected in global functional indices such as the FIQ and mental quality-of-life measures; however, its effects on fatigue and sleep disturbance remain inconsistent. Milnacipran, administered at 100–200 mg/day, has similarly shown efficacy in reducing pain and, to a lesser extent, fatigue, though outcomes for depression and sleep-related symptoms are mixed [15]. Adverse events, including nausea and drowsiness, occur more frequently than with placebo, leading to higher treatment discontinuation rates in some cohorts [22]. Despite these limitations, SNRIs remain among the most effective pharmacologic options currently available.

4.1.2. Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs act by selectively inhibiting the reuptake of serotonin in the synaptic cleft, thereby enhancing serotonergic neurotransmission. Meta-analytic evidence indicates that SSRIs can produce a modest but statistically significant reduction in pain, particularly in female patients over 45 years of age, although effects are generally short-term and monotherapy provides limited symptomatic relief [23]. Among SSRIs evaluated for fibromyalgia, fluoxetine has shown the most consistent efficacy: flexible dosing between 10–80 mg/day improved pain, fatigue, depressive symptoms, and overall severity, whereas a fixed dose of 20 mg/day failed to outperform placebo. The controlled-release formulation of paroxetine yielded benefits in fatigue and overall symptom burden, yet it did not provide significant pain relief.

Evidence for other SSRIs is limited: citalopram (two trials) at standard antidepressant doses showed no meaningful effect on pain or fatigue, sertraline improved pain and sleep disturbances in one comparative trial, and escitalopram did not demonstrate superiority over an active neurofeedback comparator despite modest symptom improvements [24].

Overall, while SSRIs appear to have a favorable safety profile with low rates of treatment discontinuation due to adverse events, their clinical efficacy in fibromyalgia remains limited. Consequently, guidelines differ internationally: EULAR recommendations do not endorse SSRIs for fibromyalgia, whereas both the Canadian and AWMF (German) guidelines support their use in selected cases [25].

4.1.3. Tricyclic Antidepressants (TCAs)

Tricyclic antidepressants, mainly amitriptyline, have been a cornerstone of fibromyalgia treatment due to numerous studies demonstrating their effects on pain relief, sleep quality, and overall patient well-being. TCAs inhibit the reuptake of both serotonin and norepinephrine while also exhibiting antagonistic effects at muscarinic, histaminergic, and α-adrenergic receptors. Their analgesic effects in fibromyalgia are primarily attributed to the enhancement of descending inhibitory pain pathways mediated by serotonin and norepinephrine. Amitriptyline remains the only TCA approved by the FDA for fibromyalgia treatment.

In a meta-analysis of ten AMT trials involving 612 patients, AMT was superior to placebo in reducing pain, sleep disturbances, and fatigue, although improvements in health-related quality of life (HRQOL) were small [26]. Adjusted indirect comparisons indicated that AMT was more effective than duloxetine (DLX) and milnacipran (MLN) in reducing pain, sleep disturbances, fatigue, and limitations of HRQOL [26].

Systematic reviews from more recent studies indicate that the quality of evidence varies by symptom: low-quality evidence supports pain reduction, moderate-quality evidence supports sleep and fatigue improvements, and high-quality evidence supports HRQOL benefits [27]. Safety and tolerability are generally acceptable, with no significant differences in dropout rates compared to other antidepressants [27].

Recent evidence indicates that low-dose AMT (typically 25 mg daily) is associated with the highest response rate for ≥50% pain reduction (R50%) compared to other pharmacological options - pregabalin and duloxetine - highlighting its efficacy in severe pain [28]. Despite methodological limitations in earlier trials, AMT remains a first-line treatment option in fibromyalgia, particularly for patients with prominent pain and sleep disturbances.

4.1.4. Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs), particularly the reversible MAO-A inhibitors pirlindole and moclobemide, have been studied in fibromyalgia with distinct symptom-specific effects. MAOIs inhibit the enzyme monoamine oxidase responsible for the degradation of serotonin, norepinephrine, and dopamine, thereby increasing their synaptic availability. Pirlindole (75 mg b.i.d.) has demonstrated statistically significant reductions in pain and tender point counts compared with placebo, though it showed minimal impact on psychological symptoms, fatigue, or sleep disturbances, with nausea and vomiting being the most frequently reported adverse events [29]. In contrast, moclobemide (150 mg b.i.d.) significantly improved depression, sleep quality, and fatigue relative to placebo, but did not exert meaningful analgesic effects [24]. These findings indicate that while MAOIs may confer benefits for selected fibromyalgia symptoms, their therapeutic utility remains limited, and their use is infrequent and recommended only under specific guidelines, such as those of EULAR.

4.1.5. Other Antidepressants

Mirtazapine

Mirtazapine, a noradrenergic and specific serotonergic antidepressant, has shown mixed efficacy in fibromyalgia. Some studies report no significant advantage over placebo for major pain reduction or functional improvement, with only modest benefits for mild pain and sleep disturbances and frequent adverse effects such as somnolence and weight gain [30]. Other evidence suggests improvements in pain, sleep, and quality of life, including findings that 12-week treatment with mirtazapine (30 mg/day) effectively reduced fibromyalgia pain in non-depressed adults [31, 32].

Reboxetine

Esreboxetine, reboxetine's active enantiomer, is a selective noradrenaline reuptake inhibitor that enhances descending inhibitory pain pathways. Clinical studies demonstrate that esreboxetine is generally well tolerated and can reduce pain and fatigue in fibromyalgia patients, with evidence suggesting that a 4 mg/day dose provides therapeutic benefit with minimal risk [33]. Open-label trials further indicate that reboxetine may alleviate pain and associated symptoms comparably to tricyclic antidepressants, though larger, placebo-controlled studies are necessary to confirm these findings [34].

Trazodone

Trazodone is a multifunctional drug with dose-dependent pharmacologic effects: at higher doses, it acts as an antagonist of 5-HT2A and 5-HT2C serotonin receptors and inhibits serotonin reuptake, whereas at lower doses, through blockade of 5-HT2A receptors, H1 histamine receptors, and α1 adrenergic receptors, it exerts hypnotic effects [35].

In an open-label, 12-week study, trazodone (50–300 mg/day) markedly improved sleep quality, mood, and functional outcomes in patients with fibromyalgia, with tachycardia being reported as the most frequent adverse effect [36]. In a subsequent 24-week open-label study, combination therapy with trazodone and pregabalin further enhanced improvements in fibromyalgia severity, depression, and pain interference, while also reducing bodily pain, demonstrating synergistic benefits and good tolerability [37].

4.2. Antiepileptic Drugs

Gabapentinoids, a subclass of antiepileptic drugs, bind to the $\alpha_2\delta$ subunit of voltage-gated calcium channels, reducing calcium influx and subsequent release of excitatory neurotransmitters such as glutamate and substance P. This action decreases neuronal hyperexcitability and central sensitization, which are key features in fibromyalgia pathophysiology. Pregabalin became the first FDA-approved drug for fibromyalgia in 2007. Randomized, placebo-controlled trials and meta-analyses demonstrate that pregabalin reduces pain intensity and improves sleep quality, with additional benefits for fatigue, anxiety, and depression in some patients, while the most common adverse effects are dizziness and somnolence [38]. A 2024 prospective cohort study comparing pregabalin, duloxetine, and milnacipran found that, although duloxetine provided superior improvements in overall quality of life, pregabalin remained particularly effective for pain reduction and sleep management [39]. Regarding gabapentin, available evidence remains limited and inconsistent, with one clinical trial demonstrating modest, low-quality analgesic effects compared to placebo [40], while another reported that extended-release formulations significantly improved pain, sleep quality, and overall functioning in fibromyalgia patients [41].

4.3. Muscle Relaxants

Cyclobenzaprine, recently approved by the FDA as the fourth drug for the treatment of fibromyalgia, is a tricyclic amine salt structurally related to tricyclic antidepressants, acting centrally as a skeletal muscle relaxant that reduces muscle hyperactivity. [42].

In a phase 3, double-blind, placebo-controlled trial, patients received nightly sublingual cyclobenzaprine (TNX-102 SL) beginning with 2.8 mg nightly for two weeks, followed by 5.6 mg nightly for twelve weeks [20]. This dosing regimen produced a substantially greater reduction in mean daily pain intensity at week 14 compared with placebo. Moreover, TNX-102 SL achieved superiority across all six secondary outcomes, including global patient-reported improvement, functional measures from the Revised Fibromyalgia Impact Questionnaire, and indices of sleep disturbance and fatigue, indicating multidimensional therapeutic benefit extending beyond analgesia. Regarding safety, systemic adverse effects were generally infrequent, with somnolence and headache being the most commonly reported [20]. Local administration-site reactions - particularly transient oral hypoesthesia, dysgeusia, and oral paresthesia - were substantially more common but self-limited, supporting an overall favorable tolerability profile.

Tizanidine, a centrally acting α2-adrenergic agonist, may provide analgesic effects by inhibiting glutamate release at spinal synapses, and limited evidence suggests potential improvements in tender points and fatigue, particularly in patients with pronounced myofascial pain [43].

4.4. Cannabis and Cannabinoids

Cannabinoid-based interventions, including THC- and CBD-containing formulations as well as pharmaceutical-grade cannabinoids such as nabilone and dronabinol, have been explored for symptom management in fibromyalgia [44]. Preclinical studies suggest that cannabinoids may exert analgesic, anxiolytic, and immunomodulatory effects, potentially via FAAH inhibition, serotonergic modulation, TRPV1 desensitization, and GPR55 antagonism [44].

Clinically, a review of nine studies, including four randomized controlled trials with 564 participants, indicates low-quality but generally positive evidence for short-term pain reduction, with only one trial showing no advantage over placebo [45]. Legalization trends have expanded access to cannabis and cannabinoid products, increasing both their real-world use and the accumulation of clinical data, yet regulatory variability continues to influence study quality and patient selection. Importantly, potential risks - particularly with THC-

containing formulations - include psychosis, schizophrenia, other psychiatric comorbidities, and cognitive or memory impairment, which are especially concerning in younger populations and warrant cautious, medically supervised use [46].

Despite these limitations, patient surveys and retrospective studies suggest a potential benefit of cannabinoids as adjunctive therapy, especially when combined with physical activity and psychosocial support [46].

4.5. Opioids

Opioids exert their analgesic effects by binding to μ-opioid receptors in the central and peripheral nervous systems, inhibiting the transmission of nociceptive signals. However, their use in fibromyalgia remains controversial due to limited efficacy in chronic centralized pain and risk of dependence. Recent data suggest that long-term opioid therapy in fibromyalgia may increase the risk of depression, sleep disturbances, and suicidal ideation [47]. Despite guideline recommendations, opioids such as hydrocodone, oxycodone, tramadol, codeine, and fentanyl continue to be prescribed to a significant subset of patients. Altered endogenous opioid activity in fibromyalgia may explain the reduced analgesic efficacy of exogenous opioids. Tramadol, a weak opioid with serotonin-norepinephrine reuptake inhibitor properties, shows some efficacy in treatment-resistant cases but is associated with adverse effects including dizziness, constipation, nausea, and serotonin syndrome [48]. Low-dose naltrexone has emerged as a potential off-label therapy, acting as a glial modulator and transient opioid receptor antagonist, enhancing endogenous opioid signaling and improving pain and fatigue with a favorable safety profile [49]. Overall, current evidence supports restricting opioid use to refractory cases while emphasizing safer alternatives.

4.6. Antipsychotic Drugs

Second-generation antipsychotics act primarily through antagonism of dopamine D_2 and serotonin 5-HT_2A receptors, with variable affinity for other serotonergic (5-HT_1A, 5-HT_2C), adrenergic (α_1, α_2), histaminergic (H_1), and muscarinic receptors, depending on the specific drug. Neural circuits associated with affective dysregulation and central sensitization may be stabilized by atypical antipsychotics through reducing dopaminergic overactivity and increasing serotonergic tone, both of which are implicated in fibromyalgia. Olanzapine, quetiapine, risperidone, aripiprazole, and ziprasidone are the only AAs with published studies in pain management [50]. Among these, olanzapine has shown preliminary and consistent efficacy in fibromyalgia and headache/migraine, although only one study was a randomized controlled trial with level I evidence of efficacy [50].

According to a Cochrane systematic review, quetiapine, used at bedtime doses ranging from 50 to 300 mg/day, showed very limited analgesic efficacy in fibromyalgia: it did not outperform placebo in achieving ≥50% pain reduction, though a small increase in ≥30% pain improvement and modest benefits in sleep, anxiety, and depressive symptoms were observed [51]. Tolerability was comparable to placebo except for notable weight gain. In another study, the XR formulation of quetiapine at similar doses demonstrated significant antidepressant and analgesic effects in patients with comorbid major depressive disorder and fibromyalgia [52].

4.7. NMDA Receptor Antagonists

FM is linked to elevated activity of the N-methyl-D-aspartate receptor (NMDAR), indicating that NMDAR modulation could have therapeutic benefits [53]. Evidence indicates that ketamine, a non-competitive NMDAR antagonist delivered by intravenous injection, produces short-term analgesic effects through inhibition of NMDAR-mediated central sensitization, with longer or repeated infusions potentially extending pain relief [54]. Other NMDAR modulators, including oral memantine and oral ketamine, have demonstrated modest but clinically meaningful improvements in pain, with oral ketamine showing >50% pain reduction in some patients over several weeks of treatment; nevertheless, the overall efficacy of current NMDAR antagonists are generally limited, and careful monitoring is essential due to the potential for psychomimetic, gastrointestinal, and cardiovascular adverse effects [53, 43].

4.8. GABAergic Drugs

Sodium oxybate (SXB), the sodium salt of gamma-hydroxybutyrate, acts as a GABA-B receptor agonist enhancing slow-wave restorative sleep, thereby addressing the non-restorative sleep abnormalities central to fibromyalgia pathophysiology [55]. Clinical studies indicate that nightly SXB significantly improves pain, sleep quality, fatigue, and overall functional outcomes in fibromyalgia patients, while similar GABA-B receptor agonists such as baclofen may exert comparable sleep-promoting effects through slow-wave sleep modulation, although data remain limited [56, 57]. Common adverse events with SXB include nausea, dizziness, somnolence, and headache, and despite demonstrated efficacy, the drug remains unapproved for this indication due to concerns regarding misuse and safety [56].

4.9. Serotonin (5-HT3) Receptor Antagonists

Serotonin (5-HT_3) receptor antagonists exert analgesic effects in fibromyalgia by blocking 5-HT_3-mediated excitatory neurotransmission in peripheral and central nociceptive pathways, inhibiting the release of pro-nociceptive neuropeptides such as substance P and calcitonin gene-related peptide from sensory afferents, and modulating central pain processing in brain regions where 5-HT_3 receptors are overexpressed, thereby reducing neurogenic inflammation, peripheral sensitization, and maladaptive central sensitization [58]. During the 1990s and early 2000s, several studies investigated the therapeutic potential of 5-HT_3 antagonists - most notably tropisetron - in fibromyalgia, but research on this drug class has since declined, with attention shifting toward newer agents such as ramosetron. Contemporary evidence from a double-blind, placebo-controlled trial demonstrates that short-term intravenous ramosetron significantly reduces pain intensity and improves depressive symptoms in fibromyalgia patients, although these effects were not fully sustained beyond the treatment period, and gastrointestinal adverse events such as constipation were the most common [59].

4.10. Testosterone

In fibromyalgia, longitudinal monitoring has shown that daily fluctuations in serum testosterone - as well as progesterone - are inversely correlated with pain severity, suggesting that higher testosterone concentrations may exert a protective, analgesic effect, potentially by modulating central nociceptive processing [60]. A clinical feasibility study suggests that low baseline testosterone may predispose to heightened nociceptive sensitivity, and that supplementation via transdermal testosterone gel could serve as a safe, targeted intervention to mitigate chronic pain [61]. A subsequent pilot trial confirmed that daily application of transdermal testosterone gel over 28 days effectively raised serum free testosterone levels to mid/high-normal ranges and improved core fibromyalgia symptoms, including muscle pain, stiffness and fatigue [62]. In summary, transdermal testosterone is an innovative but still insufficiently validated therapeutic option for fibromyalgia, warranting further investigation.

5. Non-Pharmacological Treatment

A broad spectrum of non-pharmacological interventions, including structured physical activity programs, psychological and behavioral approaches, and diverse complementary and alternative therapeutic methods, contributes to the comprehensive management of fibromyalgia symptoms. Speaking of non-pharmacological therapies, it is also necessary to emphasize the inclusion of patient education as a crucial component of multidisciplinary treatment, rather than relying solely on usual care in the context of inpatient rehabilitation. Given the chronic nature of the condition and the consequently recurrent problems with maintaining long-term treatment adherence, the implementation of an advanced self-management patient education program should be considered especially warranted.

5.1. Exercise

Physical exercise constitutes a foundation of non-pharmacological management strategies of fibromyalgia, despite patients' frequent intolerance to physical activity and tendency toward sedentary behavior, which may exacerbate comorbidities [63]. According to EULAR, exercise is strongly recommended owing to its positive effects on pain, physical function, and well-being, as well as its safety, affordability, and accessibility [64].

Among various modalities, aerobic training has consistent evidence of improving quality of life, pain, stiffness, and function, although effects on fatigue remain inconclusive. Reported benefits also include reductions in anxiety among adults with fibromyalgia [63]. Aerobic activities such as walking are generally well tolerated and may be incorporated into treatment plans as accessible and low-cost options.

Moderate and moderate-to-high intensity resistance training has been found to improve muscle function, pain sensitivity, and strength in women with fibromyalgia. Resistance training may support functional mobility, reduce the risk of falls, and promote an active lifestyle, particularly in postmenopausal women [65].

Aquatic exercise is another valuable non-pharmacological approach. The buoyancy and warmth of water reduce joint stress while providing resistance that promotes muscle activity, making it suitable for individuals with chronic pain [66]. The beneficial effects of hydrotherapy are linked to mechanisms such as vasodilation, endorphin release, enhanced oxygen uptake, and improved microcirculation, all contributing to reduced pain and stiffness [67]. Typically performed in water heated to around 32–33°C, aquatic physiotherapy facilitates relaxation and modulates pain through sensory competition, where thermal and tactile stimuli help disrupt the pain cycle [68]. Data indicate that aquatic exercise produces measurable benefits across several key outcomes in fibromyalgia, with participants reporting improved overall well-being (+6 units), physical functioning (+4 units), reduced pain (+7 units), and substantially decreased stiffness (+18 units) compared with non-exercising controls [66]. Additionally, aquatic training was associated with a 37% greater increase in muscle strength and a 37-meter improvement in six-minute walk performance, underscoring its relevance as an effective therapeutic modality [66].

5.2. Massage Therapy

A systematic review of ten clinical trials reported that myofascial release significantly reduces pain, anxiety, and depression, with sustained effects in the medium term, while also improving fatigue, stiffness, and quality of life [69]. Other massage modalities, such as connective tissue massage, Shiatsu, and manual lymphatic drainage, demonstrated additional benefits. Manual lymphatic drainage appears to be more effective than connective tissue massage in reducing stiffness, depression, and quality-of-life impairment [69]. Another randomized controlled trial confirmed that manual therapy protocols improve pain intensity, widespread pressure sensitivity, and sleep quality, with potential sex-related differences in treatment response. Women showed a greater reduction in pain and impact of FMS symptoms than men, whereas men reported a higher decrease in depressive symptoms and pressure hypersensitivity [70].

5.3. Electrotherapy

Electrotherapy encompasses a variety of non-pharmacological interventions that utilize electrical or electromagnetic stimulation to modulate pain and improve function in patients with fibromyalgia.

Among the most studied modalities are transcutaneous electrical nerve stimulation (TENS), repetitive transcranial magnetic stimulation (rTMS), and transcranial direct current stimulation (tDCS), each targeting different mechanisms involved in pain processing and central sensitization. Evidence indicates that rTMS applied to the dorsolateral prefrontal cortex can reduce pain intensity and improve overall quality of life, although its effects on depression, anxiety, and fatigue remain inconclusive [71]. TENS has been shown to decrease pain effectively, both as a standalone intervention and when combined with therapeutic exercise, but current data do not confirm consistent improvements in other clinical outcomes such as fatigue, range of motion, or quality of life [72]. Similarly, tDCS, particularly when applied at 2 mA to the left primary motor cortex (M1), demonstrates significant reduction in pain intensity in FM patients, suggesting modulation of cortical excitability as a key mechanism [73]. Across these modalities, treatment protocols, including stimulation parameters and target sites, vary considerably, highlighting the need for standardized guidelines. Overall, electrotherapy represents a promising adjunctive strategy for pain management in fibromyalgia, though further high-quality, large-scale randomized controlled trials are required to optimize parameters and assess long-term efficacy [71–73].

5.4. Laser Therapy and Phototherapy

Phototherapy, including low-level laser therapy (LLLT) and light-emitting diode (LED) interventions, represents a non-invasive, adjunctive approach in the management of fibromyalgia. Evidence indicates that LLLT can significantly decrease pain severity, reduce the number of tender points, and improve fatigue, stiffness, anxiety, and depression in FM patients, with effects being comparable or sometimes superior to placebo or standard exercise therapy [74]. Combined interventions of phototherapy with exercise may provide additional benefits, particularly in terms of pain reduction and functional improvement, although results on depressive symptoms remain less consistent [75]. High-intensity laser therapy (HILT) has also been explored, with preliminary reports suggesting that intermediate to high power levels can produce substantial short-term relief of musculoskeletal pain, improve sleep quality, and increase physical activity in patients resistant to conventional treatments [76]. Phototherapy is generally well tolerated, non-invasive, and safe, making it a promising complementary modality in the multidisciplinary management of FM [74, 76].

5.5. Thermal Therapy

Thermal therapies constitute a diverse set of interventions for fibromyalgia, encompassing both heat-based modalities such as spa therapy and balneotherapy, and cold-based approaches such as whole-body cryotherapy (WBC). These interventions aim to alleviate pain, improve function, and enhance overall quality of life in patients with fibromyalgia.

Evidence from multiple European and Asian centers conducting randomized controlled studies indicates that spa therapy - including balneotherapy, mud-bath treatments, and thalassotherapy - can reduce core fibromyalgia symptoms such as pain, stiffness, fatigue, and anxiety, demonstrating improvements in functional capacity and quality of life [77]. The therapeutic properties are thought to derive from the combined effects of heat, buoyancy, and mineral content, which may modulate musculoskeletal pain and improve relaxation.

Although these benefits are generally well-documented, they tend to be predominantly short-term, with most studies reporting symptomatic relief lasting only weeks to a few months [77].

In an observational study of 100 patients with fibromyalgia who continued standard pharmacological treatment, whole-body cryotherapy (WBC) was associated with markedly greater improvements in pain, fatigue, and health-related quality of life than the control group [78]. Mechanistically, WBC is believed to modulate neurotransmitter levels and the balance of peripheral pro- and anti-inflammatory mediators, contributing to analgesic effects [78]. A separate randomized crossover trial demonstrated that sessions in WBC chambers significantly decreased pain scores (VAS), Fibromyalgia Impact Questionnaire (FIQ) scores, and Combined Index of Severity of Fibromyalgia (ICAF) scores compared with control conditions [79].

5.6. Hyperbaric Treatment

Hyperbaric oxygen therapy (HBOT) involves the administration of 100% oxygen at pressures higher than atmospheric levels, which enhances tissue oxygenation and modulates neuroinflammation and oxidative stress pathways relevant to fibromyalgia pathophysiology [80].

Evidence from systematic reviews and clinical trials supports a beneficial impact of HBOT on several core symptoms of fibromyalgia. Meta-analytic findings indicate that HBOT significantly reduces pain intensity, tender points, fatigue, and sleep disturbances, while also improving multidimensional function and patient global assessment, with generally mild and reversible side effects [81]. Improvements in quality of life and functional capacity, as measured by the Fibromyalgia Impact Questionnaire and Tender Point Count, have been consistently demonstrated across randomized controlled trials [82].

Neuroimaging and mechanistic studies further suggest that HBOT may normalize aberrant brain activity in pain-processing regions, thereby contributing to reduced pain perception and enhanced well-being [80]. Although side effects such as ear discomfort and mild barotrauma have been reported, serious complications are rare, particularly when lower pressure protocols (<2.0 ATA) are used [81].

5.7. Acupuncture

Evidence from randomized controlled trials and meta-analyses indicates that acupuncture is both **effective and safe** in reducing pain intensity and enhancing quality of life among fibromyalgia patients [83, 84]. Clinical findings consistently show significant short- and long-term benefits over sham acupuncture or conventional medication, with improvements observed in pain thresholds, sleep quality, fatigue, stiffness, and psychological well-being [84-86]. Mechanistic studies further suggest that acupuncture exerts its therapeutic effects by **regulating central pain processing and descending inhibitory pathways**, modulating molecular targets such as ASIC3, Nav1.7, Nav1.8, and TRPV1, and influencing autonomic and inflammatory balance [83]. While some heterogeneity exists regarding the magnitude of effects on fatigue and physical function, the overall body of evidence supports acupuncture as a safe, well-tolerated, and evidence-based adjunctive therapy for managing fibromyalgia symptoms [84, 86].

5.8. Cognitive Behavioral Therapy

Neuroimaging studies reveal that cognitive behavioral therapy (CBT) enhances activation within prefrontal cortical regions implicated in executive control and emotional regulation, supporting the hypothesis of a cortical control mechanism that enables cognitive reappraisal of pain signals [87]. Moreover, CBT reduces hyperalgesia and pain-related catastrophizing, effects that correlate with decreased functional connectivity between the primary somatosensory cortex and the insula - key regions in pain perception and affective processing [88]. Complementary findings demonstrate that CBT attenuates abnormal connectivity between the default mode network and somatomotor as well as salience-processing areas, indicating neurofunctional

normalization associated with symptom improvement [89]. Collectively, these results suggest that CBT exerts its therapeutic effects in fibromyalgia by restoring adaptive pain processing through cognitive-emotional modulation and reorganization of pain-relevant brain networks.

Discussion and Conclusions

Fibromyalgia is a complex and heterogeneous syndrome in which diverse biological, psychological, and environmental factors converge to produce chronic widespread pain and multisystemic symptom burden. In recent years, the mechanisms underlying the disorder have become increasingly well-defined, with accumulating evidence supporting a dominant role of central sensitization, accompanied by peripheral nociceptor dysfunction, neuroinflammation, neuroendocrine abnormalities, and a range of metabolic and psychosocial contributors. Functional neuroimaging and neurochemical studies consistently demonstrate augmented central pain processing, alterations in excitatory and inhibitory neurotransmission, and dysregulation of limbic circuits, offering a mechanistic explanation for the characteristic combination of heightened pain sensitivity, affective symptoms, cognitive dysfunction, and sleep disturbances. The presence of peripheral abnormalities, such as C-fiber hyperexcitability, altered ion channel function, low-grade cytokine elevations, and potential autoimmune features, reinforces the concept of fibromyalgia as a disorder of multisystem dysregulation rather than a purely central phenomenon.

Clinical manifestations mirror this pathophysiological complexity, with patients experiencing not only chronic generalized pain and fatigue but also autonomic dysfunction, regional pain syndromes, sensory hypersensitivity, cognitive difficulties, and psychiatric symptoms. Symptom variability also suggests the existence of potential phenotypic subgroups, such as individuals with predominant immune dysregulation, endocrine alterations, or psychological comorbidities, which may guide more personalized management strategies in the future.

Current therapeutic options reflect both the progress and limitations of our understanding. Pharmacologic therapy remains an important component of FM management, although no single agent has been shown to provide universal or sustained benefit. Tricyclic antidepressants, SNRIs, and gabapentinoids remain the most consistently effective agents, with pregabalin, duloxetine, milnacipran, and the recently approved sublingual cyclobenzaprine (Tonmya™) representing the few treatments with regulatory authorization. However, their effect sizes are modest, and their response rates vary considerably. Investigational therapies, including cannabinoids, NMDA receptor antagonists, 5-HT_3 antagonists, atypical antipsychotics, and GABAergic agents, highlight ongoing efforts to target additional neurobiological pathways, although robust, long-term data remain lacking.

Non-pharmacological treatment consistently shows effectiveness equal to that of medications, particularly when these are integrated into multidisciplinary treatment plans. Structured physical activity, cognitive-behavioral therapy, and various complementary modalities, including electrotherapy, photobiomodulation, and acupuncture, provide additional symptom relief, although many offer short-term improvements and require ongoing engagement to maintain benefit. Given the chronic nature of fibromyalgia, the fluctuating course of symptoms, and the risk of treatment discontinuation, integrating patient education into interdisciplinary care is essential to improve adherence and maintain therapeutic gains.

Overall, FM is best managed through holistic, individualized approaches that address biological, psychological, and social dimensions. The growing recognition of FM as a neuroimmune and neuroplastic disorder points to novel therapies, though high-quality randomized controlled trials are still needed, particularly those integrating mechanistic biomarkers, precision-medicine frameworks, and long-term follow-up.

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