Review

Fibromyalgia: one year in review 2025

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ABSTRACT

Fibromyalgia (FM) is a chronic syndrome characterised by widespread pain, high prevalence, and a significant impact on quality of life. Despite extensive research, its pathogenesis and treatment remain only partially understood, driving continued investigation throughout 2024. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system has been linked to chronic stress responses and neuroinflammation, with neuroimaging and preclinical studies confirming altered pain and stress processing. Low-grade inflammation and metabolic disturbances, including cytokine imbalance and increased adipose tissue infiltration, further exacerbate symptoms. Alterations in the gut microbiota contribute to immune and emotional dysregulation. MRI studies continue to reveal brain changes that differentiate FM from other chronic pain disorders. Multi-omics approaches, including transcriptomic and metabolomic analyses, show promise as diagnostic biomarkers. Mitochondrial dysfunction also emerges as a key factor, since impaired energy metabolism seems to correlate with symptom severity. From a clinical perspective, recent studies have explored under-recognised aspects of FM, such as sexual and cognitive dysfunction, the role of gender, environmental exposures, and the disease's impact on relationships and family life. The differential diagnosis of FM and long COVID has ignited discussion about potential shared mechanisms. Conversely, residual pain in inflammatory diseases remains insufficiently addressed. Therapeutically, non-pharmacological strategies, particularly physical activity and psychosocial interventions, remain fundamental. Emerging areas such as non-invasive neuromodulation, psychedelic therapies, and the integration of technologies like virtual reality and artificial intelligence are opening new frontiers in treatment, patient care, and research. These advances underscore the multifactorial nature of FM and the need for personalised, interdisciplinary approaches.

Introduction

Fibromyalgia (FM) is a chronic pain condition characterised by widespread musculoskeletal pain, fatigue, unrefreshed sleep, and cognitive disturbances. While significant progress has been made in understanding FM in recent years, much remains to be explored (1, 2). The aetiopathogenesis of the disease is still not fully understood, and there are numerous unmet needs, both clinical and pathophysiological. International scientific interest in FM remains high, as evidenced by the publication of approximately 1,000 studies in 2024 alone. Despite these advancements, further research is essential to unravel the complexities of FM and improve patient care. This article aims to conduct a narrative review of the literature on FM published from January to December 2024.

Aetiopathogenesis and pathophysiology

Recently, a new integrative model of FM (3) has been proposed, suggesting that this condition results from an imbalance between the threat and soothing systems, which keeps the salience network (SN) in a state of continuous alert. This imbalance appears to be generated and maintained by a complex and not yet fully understood interplay of multiple systems and processes. Recent studies have helped to better

characterise the functional alterations within these interconnected systems, offering a deeper understanding of FM pathophysiology.

Hypothalamic-pituitary-adrenal axis and sympathetic nervous system dysfunction

Since several key symptoms of FM appear to be linked to dysautonomia, the contribution of sympathetic nervous system (SNS) dysfunction and maladaptive responses to chronic stress remains a key area of research in 2024. One group of authors published studies (4, 5) in FM showing that blood pressure regulation relies primarily on increased vascular resistance, a pattern reflecting impaired autonomic flexibility and supporting the involvement of SNS dysfunction. Elevated hair cortisol concentration, a marker of chronic cortisol exposure, has also been associated with increased vascular resistance, pointing to a state of sustained physiological arousal (6). In contrast, longer disease duration correlates with downregulation of the hypothalamic-pituitary-adrenal (HPA), suggesting progressive exhaustion and dysregulation of stress response systems.

Neuroimaging studies have identified disrupted connectivity in FM, particularly between the locus coeruleus, involved in norepinephrine (NE) release and stress regulation, and the parabrachial nucleus and thalamus, suggesting altered processing of stress and sensory information (7).

Preclinical FM-like pain models provide additional support for these mechanisms. In these models, the onset of hyperalgesia has been linked to skeletal muscle loss in rats. Activation of the HPA axis appears to drive hyperalgesia specifically (8), whereas alterations in epinephrine levels affect both pain sensitivity and muscle wasting (9). These findings suggest that adrenergic dysregulation may play a broader role in FM pathophysiology, influencing both sensory and metabolic dimensions of the disease.

In line with these observations, chronic stress has also been shown to induce phenotypic changes in dorsal root ganglia (DRG) neurons, particularly affecting satellite glial cells (SGCs), which play a pivotal role in the maintenance of chronic pain states. Stress-induced activation of SGCs promotes the release of molecules that amplify nociceptive signalling, a process further exacerbated by SNS dysfunction (10). Moreover, chronic stress in FM-like models triggers the activation of specific intracellular pathways that sustain neuroinflammatory responses in both the DRG and spinal cord, further contributing to central sensitisation and persistent pain (11, 12).

Chronic inflammation

The debate over whether FM is an autoimmune disease remains unresolved, with conflicting evidence from experts (13). While prior studies suggested an immune component in FM, no new data supports FM as an autoimmune disorder. However, an international workshop (14) highlighted growing evidence that immunoglobulin transfer from patient donors can induce chronic pain disorders in mouse models. At the same time, chronic low-grade inflammation seems to be present and associated with metabolic alterations. Subclinical inflammation in FM patients has been linked to increased symptom severity, with elevated IL-6 and IL-8 levels correlating with pain, fatigue, and sleep disturbances, further supporting the role of neuroinflammation in FM pathogenesis (15, 16).

Studies on body composition revealed increased adipose tissue infiltration in muscles and reduced fat-free muscle volume in FM patients, even when body mass index is controlled for. These metabolic changes are associated with systemic low-grade inflammation, with cytokine and chemokine levels correlating with pain intensity. Both pro-inflammatory and anti-inflammatory cytokines are elevated in FM, indicating a complex immune response rather than a traditional autoimmune pathology (17). Research has also identified significantly elevated levels of vaspin, an adipochine involved in metabolic regulation, in FM patients (18). As vaspin is considered a marker of metabolic dysfunction and insulin resistance, but may also be implicated in inflammatory processes, these findings suggest a potential link between metabolic disturbances and inflammation in FM.

Gut-brain axis

Emerging research highlights the critical role of the gut microbiota in FM, linking it to immune activation, metabolic dysregulation, and disruptions in the brain-gut axis. A Mendelian randomisation study (19) found a causal relationship between gut microbiota and FM, identifying Coprococcus2, Eggerthella, and Lactobacillus as potential risk factors. Another study (20) indicate that FM patients have reduced microbial diversity, with an overrepresentation of pro-inflammatory bacteria and a depletion of beneficial species. Altered microbiota composition also correlates with psychological distress and reduced functional connectivity in the SN (21), with increased Phascolarctobacterium linked to depression severity. These microbiota imbalances contribute to gut-brain axis dysfunction, where gut-derived metabolites impact central nervous system (CNS) function, influencing pain sensitivity and emotional regulation. Metabolomic profiling using machine learning reveals disruptions in purine, pyrimidine, and tyrosine pathways in FM, with reduced serotonin (5-HT) production due to tryptophan degradation via the kynurenine pathway. These findings suggest that microbiome alterations and autonomic nervous system dysfunction play a key role in FM pathogenesis (22). Indeed, a clinical study conducted on 45 patients demonstrated that faecal microbiota transplantation significantly improved symptoms in FM patients, alongside increasing 5-HT and GABA levels while reducing glutamate (23). These results suggest that modulating the microbiota could be a promising therapeutic strategy for FM, also through specific dietary interventions.

MRI studies

Several studies in 2024 have advanced our understanding of brain alterations in FM. Activation likelihood estimation analysis identified abnormal activation in the anterior cingulate cortex (ACC) and insula, along with disrupted pain-related network connectivity, indicating

pain pathway imbalances (24). Altered functional connectivity in networks like the default mode network (DMN), SN, and central executive network showed moderate accuracy in distinguishing FM from healthy controls (HC), suggesting that advanced imaging combined with machine learning could aid diagnosis (25). FM patients also exhibited structural brain changes compared to localised pain conditions like temporomandibular disorder (26), including reduced volumes of the right thalamus and thinner cortical areas in the right anterior prefrontal cortex, both of which were correlated with pain intensity. Resting-state neuroimaging studies comparing FM patients with individuals suffering from inflammatory conditions, such as ankylosing spondylitis, highlighted specific brain alterations in FM. Notably, FM patients displayed decreased connectivity between the dorsal DMN and the left caudate nucleus, as well as increased grey matter volume in the left posterior cerebellum, suggesting disruptions in both pain processing and reward-related mechanisms (27).
Finally, a pain modulation study found distinct patterns of thalamus-insula and insula-periaqueductal grey connectivity among patients with low and normal pain threshold, highlighting different pain modulation mechanisms in FM subgroups (28).

Potential biomarker

Recent advances in molecular research have revealed the complexity and heterogeneity of FM, uncovering significant alterations in gene expression, protein, and small non-coding RNA profiles, which may serve as potential biomarkers for diagnosis and personalised treatment. Whole transcriptome analysis has identified distinct subgroups of patients with unique gene expression patterns, such as extracellular matrix dysregulation and immune dysfunction (29). These molecular signatures could guide the development of biomarkers that improve diagnostic accuracy and enable personalised treatment strategies. Additionally, proteomic studies have shown significant dysregulation of proteins related to immune response, oxidative stress, and inflammation, suggesting that these biomarkers could serve both diagnostic and monitoring purposes (30). Research on transfer RNA-derived fragments (tRFs), small non-coding RNAs derived from transfer RNAs, has identified them as functional regulators of gene expression in immune and nervous system pathways. Their modulation in FM indicates their potential as novel biomarkers for diagnosis and disease monitoring (31). Furthermore, amino acid profiling has revealed imbalances in neurotransmitter-related amino acids, such as glutamic acid, which has been strongly associated with pain sensitivity and severity, making it a promising biomarker for FM diagnosis and central sensitisation (CS) (32). Shifting from single-marker studies to multi-omics strategies could offer a more comprehensive approach for biomarker research in FM.

The role of mitochondria

2024 saw increasing interest in the pathophysiological role of mitochondrial dysfunction in FM. A narrative review explored the relationship between muscle hypoxia and FM, emphasising the complex pathophysiology of the condition (33). Disrupted muscle oxygen saturation is identified as a key factor in chronic pain and fatigue, with mitochondrial dysfunction playing a central role by impairing ATP production and inducing oxidative stress, which exacerbates muscle problems. Murine studies confirmed that FM is linked to impaired mitochondrial function in both skeletal muscle (34) and CNS (35), showing reduced mitochondrial content, compromised oxidative phosphorylation, and lower expression of biogenesis markers. A pilot study on FM patients found significant mitochondrial morphological changes, including cristae loss, which correlated with clinical pain severity (36). Additionally, impaired mitochondrial function in FM patients, measured using the Bioenergetic Health Index and mitochondrial coupling efficiency, was linked to chronic pain and fatigue (37). These findings position mitochondrial dysfunction as both a potential biomarker and therapeutic target for FM, shedding light on the disease's pathophysiology and offering directions for future treatment strategies.

Take home messages

- SNS dysfunction and maladaptive stress responses play a key role in FM pathogenesis, contributing to chronic pain (8, 9). Chronic stress, through the activation of neuroinflammatory mechanisms, exacerbates nociceptive hypersensitivity and the overall disease burden (11, 12).
- Chronic low-grade inflammation (15, 16), metabolic dysfunction (17, 18), and neuroinflammation interact in a complex manner in the pathogenesis of FM, suggesting a multifactorial origin rather than a solely autoimmune disease.
- Emerging evidence suggests gut-brain axis alterations in FM, with dysbiosis disrupting metabolite production and influencing pain and emotion (20, 21, 23).
- Studies support unique brain alterations in FM, including abnormal activation in pain-related networks (24, 25), and structural changes, differentiating it from other chronic pain conditions (26, 27).
- Advanced techniques like transcriptomics (29), proteomics (30), and RNA profiling (31) provide a more integrated approach to identifying reliable biomarkers for FM. Shifting from single-marker studies to multi-omics strategies could enhance patient stratification.
- Mitochondrial dysfunction, muscle hypoxia, and oxidative stress seems to play crucial roles in the pathophysiology of FM, suggesting that targeting mitochondrial health could offer potential avenues for both diagnosis and treatment strategies (36, 37).

Clinical aspects and diagnosis

This year, there has been growing interest in understanding the roles of gender, environmental influences, and the patient journey in shaping FM.

Role of gender

FM is still considered a prevalent female condition. Even after the new diagnostic criteria resized the female:male ratio from 9:1 to 3:1, almost every FM research published in 2024 was conducted on a female-only cohorts. For this reason, gender differences in aeti-

opathogenesis, clinical presentation and treatment are still mostly unexplored. One study (38) revealed significant differences in pain presentation between male and female patients, both in severity (women reported greater pain severity) and localisation (men more frequently experienced chest and hip pain, while woman referred more pain in upper back and shoulder girdle). Additionally, pain quality was different with women describing more numbness and men reporting more shooting pain.
Also, comparison of small fibre neuropathy revealed notable differences, with a higher denervation prevalence in men (50% *vs*. 15% in women) and distinct patterns: proximal denervation was rarely observed in men but was common in women (39).

Role of the environment
Environment defined as the surroundings or conditions in which a person, animal, or plant lives or operates (40-42) influences the development and the course of FM (43). Barometric pressure fluctuations enhance pain, frigid climates increase stiffness and pain, and hot temperatures raise fatigue levels. Infections such as Lyme disease, HIV, HCV, mycoplasma, HBV, HTLV-I, and parvovirus B19 are linked to a higher incidence of FM. Additionally, exposure to electromagnetic fields can trigger or worsen symptoms. Physical and psychological traumatic stress is more common in FM patients. Air pollution, metal hypersensitivity, and exposure to xenobiotic are also contributing factors. The role of intestinal microenvironment is covered in the previous gut-brain section of this review.
FM can also negatively impact orthopaedic surgery outcomes: patients with FM who undergo spine surgery or shoulder arthroplasty consume more opioids postoperatively, experience more complications, and report less favourable patient-reported outcome measures (44, 45). Conversely, procedures like knee replacement have also been identified as potential triggers for the onset of FM (46).

Patient journey
Patients affected by FM regularly face many challenges in both family, social and work settings. A new diagnosis of FM can disrupt family roles (47), deeply affect couple's life, and strain family finances. In women (48), difficulties in fulfilling maternal roles and persistent sexual discomfort are particularly burdensome. Male patients also face unique challenges beyond chronic pain (49), including societal pressures related to traditional gender roles. The inability to meet these expectations can lead to negative emotions such as worthlessness, depression, sadness, and even suicidal thoughts.
Additionally, partners (50, 51) play a crucial role in managing FM: affectionate engagement within the couple has a protective effect on quality of life (QoL), and evidence shows that FM affects the mental health of both partners. These findings support the use of dyadic mental health interventions.
In healthcare settings, FM patients often feel misunderstood, even by the clinicians meant to support them (52). It has been shown (53) that FM severity is linked to the time taken for diagnosis, particularly if diagnosed within one year. Perhaps, a new set of diagnostic criteria that will take into account biological, psychological and social variables are needed (54) to replace the current biomedical model, as recommended by the World Health Organisation, in order to guarantee a steadfast diagnosis.

Take home messages
- Gender differences in FM remain significantly understudied. However, considering these differences is essential for effectively managing all patient populations (38, 39, 49, 55).
- FM is influenced by a wide range of environmental factors, including climatic and weather conditions, pollution, psychophysical stress and trauma (40-42), including orthopaedic surgical procedures (44-46).
- FM significantly affects family and couple dynamics. Partner involvement in supporting and understanding the patient greatly enhances the overall quality of life for both partners (47, 48, 50, 51).
- Within the healthcare system, delayed diagnosis further complicates the journey of FM patient (52-54).

Overlooked symptoms
While many clinical manifestations of FM have been extensively studied in recent years, certain aspects, such as cognitive and sexual dysfunction, remain underexplored and often overlooked in clinical practice.

- Cognitive dysfunction
Patients with FM tend to report deficits in cognitive functions, but there is still no clear consensus on the specific cognitive domains affected. A study on 130 FM woman (56) found significant impairments in selective attention, long-term visual memory, processing speed, and mental inhibition compared to HC. Notably, these cognitive deficits were not linked to anxiety, depression, or sleep quality. These findings have been partially replicated (57), further suggesting that, beyond executive dysfunction, attentional and inhibitory control mechanisms are also compromised in FM.
A network analysis (58) performed on 130 women with FM revealed that attention variables were highly interconnected within the neurocognitive network in both patients and controls. However, psychological variables had the strongest influence on the overall network only in the patient group. Notably, subjective cognitive complaints did not correlate significantly with objective cognitive deficits. However, these complaints were significantly associated with slower information processing speed, which more accurately reflects the "brain fog" commonly reported by FM patients (59).
Cognitive function studies showed hippocampal subregion atrophy in FM patients with mild cognitive impairment (MCI), linked to executive function and attention deficits, while FM patients without MCI had hippocampal volumes comparable to HC, suggesting compensatory mechanisms (60) before cognitive decline occurs. There is also evidence (61) that plasma levels of neurofilament light chains, a marker of axonal deterioration, are elevated in FM patients, in association with a slight reduction in working memory performance, a phenomenon that does not correlate with the severity and duration of disease.

- Sexual dysfunction

Despite its significant influence on patients' overall QoL, one aspect that remains underexplored is the impact of FM on sexuality, also due to the physicians' difficulty in addressing the topic. A recent systematic review (62) evaluated sexual function in 2,450 women with FM, revealing a marked decrease in sexual desire and satisfaction, diminished arousal, reduced lubrication, and a significant decline in both orgasm frequency and overall sexual fulfilment. These issues were also linked to significantly higher levels of sexual pain during intimate encounters. Comparative research (63) on women with various nociplastic pain conditions highlighted that FM patients more frequently experience constant, steady pain localised in the vaginal introitus and deeper parts of the vagina. In addition, lower sexual satisfaction in FM patients correlated with higher levels of CS. However, comparing evidence on sexual dysfunction in FM remains challenging due to the variety of assessment tools used across studies. To address this, the Qualisex questionnaire, a reliable tool consisting of 10 gender-neutral questions, was recently validated to facilitate the evaluation of sexuality in FM patients (64).

Difficult and controversial differential diagnosis

The emergence of new chronic pain conditions like Long Covid and residual inflammatory pain has sparked debate over the challenging differential diagnosis of FM.

- Long Covid

After the 2020 Covid-19 pandemic, clinicians worldwide observed the emergence of a new chronic condition known as Long Covid, which shares many clinical characteristics with FM. This similarity has sparked a stimulating debate among experts (65-69) about whether Long Covid should be considered synonymous with FM. Many researchers agree that both FM and Long Covid involve CS and present with similar symptoms, including fatigue, widespread pain, sleep disturbances, cognitive issues, and brain fog. However, some experts argue that the pathogenesis of Long Covid may involve multiple non-FM-specific mechanisms, such as viral persistence, reactivation of latent viruses, autoimmune inflammation, and dysbiosis. According to this perspective, FM might be better understood as a co-diagnosis rather than the sole condition present in Long Covid patients. Moreover, some studies (70, 71) highlighted that a history of Covid-19 infection can precede the onset of FM and may negatively influence the response of FM patients to non-pharmacologic treatments.

- Residual pain in inflammatory conditions

Despite controlling inflammation, individuals with inflammatory arthritis may continue to experience ongoing pain due to multiple factors, including pain sensitisation (72). The debate on this topic is still open: is this residual pain an associated/secondary FM or a different type of nociplastic pain? Unfortunately, recent literature on this subject remains limited.

The mechanisms underlying non-inflammatory pain chronicity are primarily nociplastic in nature, sharing many similarities with FM, as highlighted in recent reviews (73-75). These mechanisms include CS, a decrease in intraepidermal nerve density, and neuroinflammation and become the dominant driver of the patient's pain and carries significant implications for treatment.

A recent study (76) involving 158 patients with rheumatoid arthritis (RA) showed that 27% of the patients, despite having high levels of DAS28 scores in the absence of ultrasound signs of inflammation, did not met the criteria for FM. This subset of patients likely experienced peripheral-only residual pain, a phenomenon not commonly recognised in current rheumatology practice. More studies are needed to better characterise nociplastic pain in inflammatory rheumatic diseases.

Take home messages

- Cognitive dysfunction in FM patients primarily affects selective attention, long-term visual memory, processing speed, and mental inhibition; however, subjective cognitive complaints do not significantly correlate with objective cognitive deficits (56-59).
- Sexual dysfunction in female FM patients includes reduced desire, satisfaction, and arousal, as well as pain during intimate encounters; this dysfunction is also associated with CS (62-64).
- The distinction between Long Covid and FM remains under discussion, as they share many similarities in pathogenesis and clinical presentation, but differ in aetiology (65-71).
- Nociplastic pain in inflammatory conditions has symptoms similarities to FM and can significantly impact patient management. The debate on this topic is still open: is this residual pain an associated/secondary FM or a different type of nociplastic pain? (73-76).

Management

As known, the best treatment outcomes arise from a personalised, integrated approach, tailoring interventions to individual patient needs and symptom severity. FM requires a multidisciplinary treatment approach, combining psychological, physical, and pharmacological therapies for optimal patient outcomes.

Non-pharmacological therapy

- Exercise therapy and optimal dosage

Physical activity is a cornerstone in managing FM, with aerobic and resistance exercises demonstrating significant improvements in pain, physical function, and sleep quality. Regular movement helps modulate pain pathways, reduce inflammation, improve autonomic nervous system control, and stimulate endorphin release, contributing to long-term symptom relief. However, maintaining an exercise routine can be challenging for individuals with severe fatigue or mobility issues. Supervised exercise programmes tend to have higher adherence rates and are more effective in improving symptoms than self-directed activity (77, 78).

Determining the appropriate exercise dosage is critical to maximising benefits while minimising symptom exacerbation. A meta-analysis (79) highlighted that moderate-intensity,

structured exercise programmes are the most effective for symptom improvement. Exercise programmes need to be prescribed, being customised according to the patient's clinical condition, clinical goal to be reached, FM severity, fitness level, and personal preferences. A successful prescription defines the modality (type), intensity (effort), duration (how long), frequency (how many times weekly) and progression (how to titrate exercise dose up to the desired one) to gradually increase the exercise dose as tolerated by the patient.

According to the World Health Organisation 2020 guidelines (80), to promote and maintain health, all healthy adults need to reach a weekly target range of 150–300 min of aerobic exercise at moderate-intensity, and perform activities that maintain or increase muscular strength and for a minimum of two days weekly. For FM patients, especially those with high disease severity, following these guidelines can be challenging due to barriers like fatigue, pain, mood disorders, and often economic and time constraints, therefore, these recommendations should serve as long-term goals rather than immediate starting points. Exercise prescription needs to be tailored to patient's clinical status and needs, starting with modalities and doses that can be sustained by the patient (81).

A 'start low, go slow' approach ensures that exercise remains sustainable over time.

Endurance and strength exercises are fundamental, nevertheless, flexibility and multicomponent activities like yoga and Tai-Chi might also be incorporated. These disciplines, which blend movement and mindfulness, have confirmed their relevance. A systematic review (82-84) highlighted that Tai Chi is particularly effective in reducing pain and fatigue, while also improving balance and overall well-being. These exercises offer a gentler alternative to conventional aerobic workouts for FM patients characterised by high disease severity, who may not sustain traditional aerobic exercises.

It is fundamental to remember that exercise represents a strategy not simply to treat FM but actually to improve the health of an individual who is also affected by FM, as well as managing other clinical conditions and fostering overall well-being.

- Mind-body interventions and brain connectivity in fibromyalgia

Recent research has explored how functional connectivity influences the effectiveness of mind-body treatments in FM patients (85). The interaction between the SN and the somatosensory network (SMN) appears to play a key role in determining treatment response. Studies have shown that Mindfulness-Based Stress Reduction (MBSR) and psychoeducational programmes like Fibro-QoL help reduce pain catastrophising, a psychological factor that amplifies pain perception. Functional MRI scans have demonstrated that patients with lower initial SN-SMN connectivity respond better to mindfulness-based interventions, whereas those with higher connectivity benefit more from psychoeducation. These findings suggest that brain imaging could be used to tailor mind-body treatments, enhancing their effectiveness and ensuring a more personalised approach to FM management.

- Acupuncture

Acupuncture has long been used to relieve chronic pain conditions. Clinical studies suggest that acupuncture can help alleviate pain and fatigue in FM patients, likely through mechanisms involving endorphin release, modulation of pain pathways, and anti-inflammatory effects (86). Recently, electroacupuncture (EA) has been investigated for its potential in reducing FM pain via neuroimmune modulation. Two preclinical studies in FM-pain models have provided insight into how EA might work at a molecular level. One study (87) found that EA reduces pain by inhibiting microglial activation and downregulating the Toll-like receptor (TLR)-4 pathway, a key mediator of neuroinflammation. Another study (88) demonstrated that EA suppresses TRPV1 signalling and IL-17 production, both of which are associated with heightened pain sensitivity. These findings suggest that EA exerts anti-inflammatory and neuroprotective effects, potentially offering a non-pharmacological pain relief strategy for FM patients.

- Complementary and alternative medicine

Meanwhile, balneotherapy, or hydrotherapy, has shown promise in reducing pain and improving mobility for up to six months' post-treatment (89). The therapeutic effects are thought to be mediated through thermal and circulatory changes that promote relaxation and muscle recovery.

- Psychological therapies

Psychological approaches, such as cgnitive behavioural therapy (CBT), have long been recognised as valuable tools in managing FM, reframing maladaptive thoughts about pain, leading to improved coping mechanisms and reducing emotional distress. Studies have demonstrated that CBT significantly reduces pain intensity, depression, and anxiety (90). Acceptance and commitment therapy (ACT), a more recent psychological intervention, shifts the focus from controlling pain to accepting and living meaningfully despite it. Trials (91) suggest that ACT enhances psychological flexibility. Moreover, eye movement desensitisation and reprocessing (EMDR) has demonstrated potential, especially in individuals with a history of trauma, in alleviating pain, depressive symptoms, and post-traumatic stress features (92).

- Nutraceuticals and dietary interventions

A growing body of research suggests that dietary interventions and nutraceuticals can play a supportive role in FM management. The Mediterranean diet, rich in anti-inflammatory foods like olive oil, nuts, fatty fish, and fresh vegetables, has been associated with reduced oxidative stress and improved QoL (93). Similarly, the Low-FODMAP diet, originally developed for irritable bowel syndrome, has demonstrated benefits in reducing gastrointestinal symptoms in FM patients, highlighting the role of the gut-brain axis (94). Emerging evidence also points to ketogenic and oloproteic diets as potential strategies to enhance

mitochondrial function and reduce fatigue, although long-term data are still limited (95). Additionally, supplementation with Coenzyme Q10 (CoQ10), probiotics (96), and micronutrients (97) might help reduce symptoms and systemic inflammation. In this context, the integration of pharmaceuticals and nutraceuticals, such as palmitoylethanolamide (PEA) and acetyl-L-carnitine (ALC), has shown promise (98-100). PEA has been investigated for its analgesic and anti-inflammatory properties in FM, functioning as an endogenous modulator of inflammation and nociception. ALC, uniquely, exhibits analgesic effects mediated through an epigenetic mechanism involving the acetylation of p65/RelA, a key transcription factor in the NFkB pathway (101).

- Neuromodulation therapy

Like last year, several studies (102-109) reaffirmed the efficacy of transcranial direct current stimulation and transcranial magnetic stimulation as innovative non-pharmacologic treatments for FM.

This year non-invasive or minimally invasive vagus nerve stimulation (nVNS) has gained attention. VNS techniques have shown effectiveness not only in addressing underlying pain mechanisms but also in managing comorbid conditions such as mood disorders and substance use disorders.

A recent editorial (110) suggests that auricular percutaneous electric nerve field stimulation is a viable option for treating pain associated with disorders of gut-brain interaction (111). Additionally, nVNS has been shown to alleviate symptoms of primary headache and to reduce pain in high-risk patients with opioid use disorders.

With the growing need to clarify the role of VNS in FM management, a new PRISMA-compliant protocol has been developed to outline the rationale, feasibility, and methodology for conducting a systematic review and meta-analysis of the existing evidence on VNS use in FM treatment (112). Using this framework, a recent review (113) assessed the efficacy of transcutaneous auricular VNS across various pain conditions, including FM. This review identified several research gaps, including the need to determine optimal dosage for different pain conditions, incorporate measures for intervention fidelity, investigate long-term outcomes, and explore co-occurring symptoms and outcomes across different sociodemographic variables. A recent study suggests the clinical benefits of the EXOPULSE Mollii Suit (a multisite transcutaneous electrical nerve stimulation device) in alleviating pain and FM-related fatigue, emotional symptoms, and disease impact (114).

Take home messages

- Exercise therapy is fundamental in FM management (78, 79). Exercise programmes need to be prescribed being customised according to the patient's clinical condition and clinical goal to be reached, starting with modalities and doses that can be sustained by the patient (81). They may consider endurance aerobic and strength exercise, such as multicomponent activities such as Tai Chi and Qigong, which may enhance psychological well-being by incorporating mindfulness elements (82-84).
- Mind-body interventions, including MBSR, have been shown to influence brain connectivity and may help reduce pain catastrophising (85).
- Acupuncture provides moderate but meaningful symptom relief, likely through modulation of pain pathways and anti-inflammatory effects (86).
- Psychological therapies, such as CBT and ACT (90, 91), and EMDR (92) offer structured approaches to reframing pain perception, reducing stress, and improving coping mechanisms.
- Diet and nutraceuticals can play a supportive role in FM management. The Mediterranean diet has been linked to reduced inflammation and oxidative stress (93), while Low-FODMAP diets may alleviate gastrointestinal symptoms (94). Supplements such as CoQ10, probiotics, palmitoylethanolamide (PEA) and acetyl-L-carnitine (ALC), and micronutrients promote symptoms reduction and gut health (96-101).
- VNS and multisite transcutaneous electrical nerve stimulation represents new therapeutic options for FM, but future studies need to fill various research gaps (110-114).

Pharmacological therapy

- Antidepressants

Serotonin-norepinephrine re-uptake inhibitors (SNRIs), like duloxetine and milnacipran, and tricyclic antidepressant, like amitriptyline, are widely used to manage FM symptoms, particularly pain and fatigue (115). However, side effects such as nausea, drowsiness, weight gain and sedation can limit adherence. Both amitriptyline and duloxetine enhance pain inhibition by increasing 5-HT and NE levels at superficial dorsal horn neurons, supporting their role in modulating descending pain inhibitory pathways. Evidence from murine models suggests that they may also exert analgesic effects through additional mechanisms that are not yet fully understood (116). Furthermore, chronobiological variables (*i.e.* eveningness, poor sleep quality) (117) and psychopathological factors (*i.e.* anxiety, anhedonia) (118) have been identified as predictors of poor response to SNRI treatment in FM.

- Gabapentinoids

Pregabalin and gabapentin are often prescribed for neuropathic pain relief by modulating calcium channels. However, recent studies (119) indicate a potential increased risk of cardiovascular events, necessitating cautious use. Additionally, findings from murine models suggest that pregabalin's effects on muscle pain may differ between sexes, with pain relief observed only in male rats. These results underscore the need to consider sex differences in pain management strategies (55).

- Low-dose naltrexone

Low-dose naltrexone (LDN) is an emerging therapy for FM. Unlike traditional opioid treatments, LDN works as an opioid antagonist, temporarily blocking opioid receptors, which then leads to an increase in endogenous opioid production and a subsequent reduction in pain sensitivity. Studies (120) have demonstrated that LDN reduces inflammation by modulating microglial

activation, potentially decreasing CS. Additionally, patients report fewer side effects compared to other pharmacological treatments.

- *Opioids*

Despite being discouraged in clinical guidelines, opioids continue to be prescribed to a subset of FM patients (121). Moreover, prolonged opioid use is associated with higher risks of depression, sleep disorders, and suicidal ideation (122).

- *Cannabinoids*

Cannabis-derived compounds are gaining attention for their analgesic, anti-inflammatory, and neuroprotective properties and clinical practice guidelines are now available (123). Studies (124, 125) suggest that THC-rich formulations provide stronger pain relief, while CBD-dominant products offer anti-inflammatory benefits with fewer cognitive side effects.

- *Muscle relaxants*

Skeletal muscle relaxants provide mild short-term pain relief, but long-term effectiveness is limited. Sedation and dizziness are common side effects (126).

- *Psychedelics*

Psychedelics are a class of psychoactive drugs that primarily cause a perceived "expansion of consciousness" and alterations in perception, thought, and emotion.

Ketamine, a NMDA receptor antagonist, has been investigated for its rapid-acting analgesic effects in chronic pain conditions, including FM. Its mechanism of action involves blocking excitatory glutamate pathways, which are often hyperactive in FM patients, leading to improved pain processing and neuroplasticity. Clinical trials (127) suggest that ketamine provides significant short-term pain relief, with some patients experiencing improvement lasting for several weeks. However, its long-term use remains controversial due to potential cognitive side effects, dissociation, and dependency concerns. Further research is needed to determine optimal dosing regimens and safety for sustained use.

Other psychedelics, including LSD, psilocybin, and mescaline, are currently being researched for potential therapeutic uses, particularly in mental health treatment and chronic pain conditions (128).

Recently a protocol for a mechanistic study investigating the effects of psychedelic-assisted-therapy in a FM population has been published (129).

Take home messages

- SNRIs and gabapentinoids remain key treatment options for FM but should be tailored to individual patient needs, considering predictors of SNRI response (117, 118) and potential cardiovascular risks (119) and sex-specific effects (55) associated with pregabalin.
- LDN has shown promise in reducing pain and inflammation with a favourable safety profile (120).
- Opioids should be avoided whenever possible due to their high risks and limited long-term benefits in FM (122).
- Cannabinoids offer a potential therapeutic role, with THC providing stronger pain relief and CBD showing anti-inflammatory effects with fewer cognitive side effects (124).
- Muscle relaxants may provide short-term symptom relief, but their effectiveness declines over time, and sedation remains a common drawback (126).
- Ketamine provides rapid pain relief in some patients, but concerns about cognitive side effects and dependency limit its long-term use (127). Other psychedelics are currently under investigation for mental health and chronic pain treatment (129).

New technologies

In recent years, the development of new technologies like artificial intelligence (AI), social media, virtual reality (VR), and machine learning are quickly unlocking new opportunities for the medical world (130). The use of AI in research, as discussed in previous chapters, offers valuable opportunities to deepen our understanding of FM pathophysiology and clinical aspects, while also advancing therapeutic approaches.

Application for treatment purposes

A recent review (131) demonstrated that VR can be an effective and safe treatment option for chronic musculoskeletal pain syndromes. Although several aspects remain unclear, findings primarily indicate short-term pain relief with VR, as well as potential benefits for anxiety, kinesiophobia, and alexithymia. Additionally, evidence suggests that combining VR with other technologies or techniques, such as biofeedback, hypnosis, or VNS, may enhance its effectiveness, positioning VR as a promising non-pharmacological addition for pain management in the near future.

Application for management purposes

The potential of AI-powered platforms like ChatGPT was recently evaluated in a study comparing the accuracy and readability of AI-generated responses about FM to expert responses (132). The study found that ChatGPT's answers were accurate, wordier, but similarly readable to those provided by experts.

A recent study (133) explored the use of smartphone-based manikins as a reliable and valid method for pain self-reporting. The findings suggested that these tools could effectively differentiate FM and osteoarthritis from RA. However, they did not detect changes in pain scores over time.

Moreover, another study (134) analysed FM patients' perceptions of various information and communication technologies (ICT). Although patients report using mostly instant messaging apps, phone consultations with healthcare professionals, specialised online resources for pain management, satisfaction levels remained low. Factors such as age-related digital divide and lower education levels may negatively impact ICT usage and satisfaction, highlighting the need for tailored digital health strategies.

Social media (135) has proven to be a powerful tool for raising awareness and disseminating information about rheumatic diseases, particularly in the context of celebrity-related events. Among various platforms, YouTube is frequently used by FM patients seeking information about their condition and treatment options. However, a recent study (136)

assessing the quality and reliability of exercise videos for FM on YouTube found that most patient-targeted videos were created by non-physician users and lacked quality and credibility. Similar concerns were identified on other social media platforms, like TikTok (137).

Take home messages

- VR represent a safe non-pharmacological new possibility for the management of pain, anxiety, kinesiophobia or alexithymia, and can be combined with biofeedback of hypnosis (59).
- Many ICT are currently used by FM patients for the management of their illness, but quality and patient satisfaction are frequently low (61-63).
- AI is a powerful tool capable of achieving a good accuracy when questioned about FM (60).
- Social media, like YouTube, TikTok or Google could be used to provide awareness and information on FM to the general public (135-137).

Conclusions

In 2024, nearly 1,000 articles on FM were published. These numbers confirm the strong attention the scientific community is paying to this topic. This body of research has contributed to expanding our understanding of the role of HPA axis and SNS dysfunction, chronic inflammation, and the gut-brain axis in the pathogenesis of the disease. Additionally, interesting findings have emerged regarding the potential of a multi-omics approach and the role of mitochondria as diagnostic and therapeutic biomarkers.

There has also been an increased focus on some clinical aspects that are often underrecognised by physicians, such as sexual dysfunction, cognitive disorders, and the influence of gender and environment. Emphasis has also been placed on the importance of differential diagnosis with other chronic pain syndromes (long COVID and nociplastic pain).

From a therapeutic perspective, the multidisciplinary approach remains the most appropriate strategy. New potential approaches include psychedelics, neuromodulation, and the use of emerging technologies.

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