Review

Pathogenetic and clinical aspects of fibromyalgia: one year in review 2026

C. Iannuccelli[1], M. Favretti[2], B. Bianchi[3], G. Dolcini[2], C. Cauli[4], V. Ferraro[4], C. Gioia[5], L. Bazzichi[6], F. Atzeni[7], A. Batticciotto[8], F. Galli[9], G. Varrassi[10], J.N. Ablin[11], R. Gualtierotti[12], F. Conti[4], M. Di Franco[1], F. Salaffi[3], P. Sarzi-Puttini[6,13], M. Di Carlo[3], on behalf of the Pain Study Group of the Italian Society of Rheumatology (SIR)

Affiliations: see page 1065.

*Cristina Iannuccelli, MD, PhD**
*Martina Favretti, MD**
Benedetta Bianchi, MD
Giulio Dolcini, MD
Carlo Cauli, MD
Vincenzo Ferraro, MD
Chiara Gioia, MD
Laura Bazzichi, MD
Fabiola Atzeni, MD, PhD
Alberto Batticciotto, MD, PhD
Federica Galli, MD, PsyD
Giustino Varrassi, MD, PhD
Jacob N. Ablin, MD
Roberta Gualtierotti, MD
Fabrizio Conti, MD, PhD
Manuela Di Franco, MD
Fausto Salaffi, MD, PhD
Piercarlo Sarzi-Puttini, MD
Marco Di Carlo, MD

**These authors contributed equally to this work and share first authorship.*

Please address correspondence to:
Alberto Batticciotto
Reumatologia,
Dipartimento di Medicina Interna,
Azienda Socio-Sanitaria Territoriale (ASST) Sette Laghi,
Ospedale di Circolo,
Fondazione Macchi,
21100 Varese, Italy.
E-mail:
alberto.batticciotto@asst-settelaghi.it

Received on May 18, 2026; accepted in revised form on May 28, 2026.

Clin Exp Rheumatol 2026; 44: 1057-1068.

Key words: fibromyalgia, pathogenesis, clinical aspects, central nervous system sensitisation, nociplastic pain

Competing interests: see page 1065.

ABSTRACT

Fibromyalgia (FM) is a complex chronic pain condition with a multifaceted pathogenesis and heterogeneous clinical presentation. This narrative review summarises the most relevant studies published in 2025 on the pathogenetic and clinical aspects of FM. Central sensitisation remains the main neurobiological mechanism, supported by evidence of increased ascending nociceptive signalling, impaired descending inhibition, network reorganisation and autonomic dysfunction. Emerging findings have also explored a possible role for non-classical autoimmune mechanisms, as patient-derived IgG has been shown to induce pain hypersensitivity and bind dorsal root ganglion neurons and satellite glial cells, suggesting potential interactions between immune and metabolic pathways. The gut microbiome is increasingly implicated, showing reduced diversity, distinct signatures, and transferable pain phenotypes. Genetic studies identify a predominantly neuronal architecture involving 26 loci linked to proteins essential for neuronal function. Oxidative stress remains a major hypothesis, supported by elevated biomarkers and preclinical evidence for mitochondrial-targeted strategies. Early-life stress may selectively affect the right amygdala, contributing to long-term vulnerability. Clinically, pain in FM appears heterogeneous and may not be entirely explained by a purely nociplastic paradigm, as some studies have suggested the presence of neuropathic-like features in at least a subset of patients. Likewise, residual pain in inflammatory arthritis remains a multifactorial and incompletely characterised entity, potentially sharing some mechanisms with FM while also encompassing distinct and broader pathophysiological processes. Cognitive dysfunction (fibro-fog) represents a multidimensional clinical construct whose underlying mechanisms remain only partially understood. FM is also associated with high affective burden, systemic symptoms, and reduced muscle performance consistent with dynapenia. Stigma and symptom invisibility continue to negatively affect care, while sex and gender influence disease expression and burden. Digital health and AI offer new opportunities but also raise concerns regarding misinformation. Overall, current evidence supports a multidimensional view of FM and highlights the need for updated diagnostic criteria and more integrated, personalised models of care.

Introduction

Fibromyalgia (FM) is a chronic pain syndrome characterised by widespread musculoskeletal pain, fatigue, non-restorative sleep, cognitive dysfunction and a variety of associated somatic symptoms that substantially affect patients' quality of life. Although considerable progress has been made in understanding FM over recent decades, its pathophysiology remains only partially understood. Current evidence supports a multifactorial model involving central sensitisation, altered pain processing, neuroimmune mechanisms, genetic predisposition and environmental factors; however, the relative contribution and interaction of these mechanisms have yet to be fully clarified.

FM continues to pose significant clinical and scientific challenges owing to its heterogeneous phenotype and the incomplete understanding of the biological processes underlying symptom development and persistence. As a result, important gaps remain in our knowledge of both the pathogenesis and clinical expression of the disease.

Research interest in FM remains substantial, as demonstrated by the publication of more than 1,000 articles in 2025 alone. This growing body of literature has provided novel insights into disease mechanisms and clinical features, while also highlighting areas that warrant further investigation.

The aim of this narrative review is to summarise and critically discuss the most relevant studies on the pathogenesis and clinical aspects of FM published between January and December 2025, with particular emphasis on emerging biological mechanisms, phenotypic heterogeneity and advances in the understanding of disease manifestations.

Pathogenesis

Central sensitisation

Central sensitisation is widely considered a core pathophysiological mechanism in FM, reflecting a sustained imbalance between enhanced nociceptive facilitation and deficient endogenous pain inhibition (Fig. 1).

In line with this model, Garcia-Hernandez *et al*. (1) provided psychophysical evidence of disrupted pain modulation in FM. They showed that the slowly repeated evoked pain (SREP) protocol, considered a marker of central sensitisation, elicits stronger pain amplification in patients with FM compared to healthy controls. Conversely, conditioned pain modulation (CPM), a proxy of endogenous descending inhibition, is significantly reduced in FM. Importantly, SREP sensitisation is inversely associated with CPM efficacy, indicating that impaired descending inhibitory control may partly account for enhanced pain facilitation. Both reduced CPM and increased SREP responses correlate with symptom severity, anxiety, and fatigue, and patients lacking effective CPM exhibit more severe clinical manifestations (1).

Neurobiological evidence further reinforces this imbalance between ascending and descending pain processes. A large-scale population-based neuroimaging study by Kelleher *et al*. (2) demonstrated that increasing FM symptom burden is associated with altered structural and functional connectivity within the descending pain modulatory system, particularly across brainstem-limbic circuits involving the periaqueductal grey, amygdala and hypothalamus. These connectivity patterns correlated with core nociplastic features (fatigue, mood disturbance, sleep dysfunction, and widespread pain) independently of pain intensity or neuropathic characteristics, supporting a dimensional brain-based signature of impaired endogenous pain control (2).

Task-based functional magnetic resonance imaging (fMRI) studies conducted by Stroman *et al*. (3) additionally demonstrated a heightened pre-stimulus rise in BOLD activity in patients with FM, consistently observed across imaging runs and associated with greater pain sensitivity, anxiety traits, and autonomic symptom burden. Subsequent analyses localised this effect predominantly to grey matter regions involved in pain processing and modulation (including the insular cortex, anterior and posterior cingulate cortex, thalamus, and periaqueductal grey) supporting the hypothesis of a persistent hyperexcitable neural state (4). Importantly, this anticipatory hyperactivation, accompanied by increased pupil dilation and enhanced pain sensitivity, appears to reflect dysregulated stress responsivity and autonomic imbalance, consistent with a state of sustained hypervigilance that may contribute to central sensitisation.

At the network level, resting-state fMRI studies consistently report increased functional connectivity between the default mode network (DMN) and interoceptive regions, particularly the insula, together with reduced connectivity within descending pain modulatory circuits. A recent meta-analysis confirmed enhanced DMN coupling with self-related regions and diminished connectivity within pain-modulatory networks, with intra-DMN connectivity associated with pain intensity (5).

Structural imaging studies further indicate distributed grey matter alterations in regions involved in pain processing and affective regulation, including the insula, anterior cingulate cortex, and prefrontal areas, suggesting long-term neuroplastic adaptations rather than focal abnormalities (6).

Beyond structural and connectivity findings, altered brain dynamics have also been described. Increased brain entropy, particularly in prefrontal regions, reflects greater temporal variability of neural signals and may indicate inefficient or unstable neural processing in chronic pain conditions, as observed by Del Mauro *et al*. (7).

In parallel, as described by Abenavoli *et al*., (8) molecular imaging studies using positron emission tomography and computed tomography (PET/CT) have revealed alterations in metabolic activity, neurotransmitter systems and neuroinflammatory markers in FM, particularly within the thalamus, insula, anterior cingulate cortex, and limbic regions. Findings include dopaminergic hypofunction, reduced μ-opioid receptor availability, altered GABAergic signalling, and increased TSPO expression consistent with glial activation, although results remain heterogeneous and derived from relatively small cohorts (8). Despite long-standing hypotheses implicating altered neurotransmitter systems, direct contemporary human evidence in FM remains limited, highlighting an important gap in the neurochemical characterisation of central sensitisation.

Finally, recent evidence by Garcia-Hernandez *et al*. (9) supports the systemic dimension of central sensitisation. Higher Central Sensitisation Inventory (CSI) scores have been associated with increased hair cortisol concentrations and a sympathetic predominance in patients with FM, linking symptom burden to neuroendocrine and autonomic dysregulation. Together, these findings suggest that central sensitisation in FM extends beyond altered pain processing to encompass stress-axis and cardiovascular autonomic imbalance.

Collectively, converging psychophysical, neuroimaging, structural, molecular, and neuroendocrine evidence sup-

ports a model of FM as a state of persistent central dysregulation, characterised by amplified ascending nociceptive signalling, deficient descending inhibition, network-level reorganisation, structural remodelling, altered neural dynamics, and systemic stress-axis imbalance.

Autoimmunity

Recent evidence has challenged the traditional view of FM as a purely non-immune condition, suggesting that immune mechanisms may contribute to symptom generation in a subset of patients (Fig. 1). Based on translational and experimental data, Goebel *et al*. (10) proposed that FM may involve a form of non-classical or functional autoimmunity, in which autoantibodies modulate nociceptive signalling without inducing overt inflammatory tissue damage. This concept is supported by studies showing that IgG purified from patients with FM can induce pain hypersensitivity when passively transferred to animal models, in the absence of detectable inflammation.

In a large case-control study, Seefried *et al*. (11) demonstrated IgG binding to dorsal root ganglion (DRG) neurons and satellite glial cells in approximately one third of patients with FM, while no binding was observed in control sera. Distinct DRG binding patterns correlated with clinical features: IgG binding to satellite glial cells was associated with higher pain intensity, whereas binding to TRPV1-expressing neurons was linked to burning pain. These findings suggest a potential functional relationship between specific autoantibody reactivity and pain phenotypes in FM.

More recently, lipidomic analyses have provided additional support for an interaction between metabolic and immune pathways in FM. In a case-control study, patients exhibited alterations in circulating lipid species, particularly within lysophosphatidylcholine, phosphatidylcholine, sphingomyelin and triglyceride classes. Notably, specific lysophosphatidylcholines were positively associated with both pain intensity and levels of IgG antibodies targeting satellite glial cells. Although these findings are exploratory and do not establish causality, they support the hypothesis of a neuro-immune-metabolic interaction contributing to pain generation in FM (12).

Overall, current data do not support FM as a classical systemic autoimmune disease. Rather, they point toward immune-mediated modulation of peripheral nociceptive pathways in a biologically defined subgroup of patients. Further work is needed to clarify antigen specificity, pathogenic mechanisms, and clinical stratification before autoimmunity can be integrated into routine diagnostic or therapeutic frameworks (13).

Microbiome

In recent years, the gut microbiome has emerged as a potential modulator of FM pathophysiology, particularly through the gut-brain-immune axis and its interaction with mechanisms of central sensitisation (Fig. 1). Clinical observational studies consistently report reduced microbial diversity and a distinct taxonomic profile in patients with FM compared with healthy controls, with dysbiosis correlating with pain intensity, fatigue, and gastrointestinal symptoms (14).

A major advance was provided by a recent mechanistic study by Cai *et al*., demonstrating that faecal microbiota transplantation from patients with FM into germ-free mice is sufficient to induce pain hypersensitivity, immune activation and metabolic alterations resembling those observed in FM patients (15). Notably, replacement of the FM-associated microbiota with a healthy microbiota attenuated pain behaviours in mice and was accompanied by symptom improvement in a preliminary open-label human cohort.

Emerging data further suggest that microbiota-derived metabolites, including short-chain fatty acids, together with vitamin D status and pro-inflammatory cytokines, may influence nociceptive processing and disease severity (16). The high prevalence of disorders of gut-brain interaction and their strong association with pain severity and sleep disturbance further underscore the clinical relevance of this axis in FM (17). In addition, Mendelian randomisation analyses have proposed a potential causal contribution of specific microbial taxa and immune mediators to FM susceptibility; however, the biological significance and directionality of these associations remain to be clarified (18). Overall, despite methodological heterogeneity and limited longitudinal data, current evidence supports a contributory, rather than primary, role of the gut microbiome in FM pathogenesis, highlighting the need for well-controlled interventional studies to define therapeutic potential and mechanistic pathways (19).

Mitochondria and oxidative stress

Elevated concentrations of reactive oxygen and nitrogen species, together with mitochondrial dysfunction, mechanisms broadly encompassed within the framework of oxidative stress, are included among the principal pathogenetic hypotheses proposed for FM (Fig. 1). A noteworthy preclinical investigation explored the potential contribution of mitochondrial transplantation, more commonly referred to as artificial mitochondrial transfer (AMT), in an experimental animal model of FM. In this study, mitochondria were isolated from H9C2 cells, a cell line derived from embryonic rat myocardium.

Administration of exogenous mitochondria to the FM model, consisting of rats treated with reserpine, resulted in a significant restoration of dopamine and serotonin levels within cortical tissues of reserpine-exposed animals compared with control groups. At the level of the soleus muscle, mitochondrial infusion further enhanced endogenous antioxidant defences, as demonstrated by increased concentrations of glutathione and catalase. Concomitantly, a reduction in oxidative stress markers was observed, specifically nitric oxide and malondialdehyde.

From a functional and behavioural perspective, mitochondrial administration significantly prolonged thermal hyperalgesia latency in the FM animal model, indicating an attenuation of nociceptive hypersensitivity. Collectively, these findings suggest that mitochondrial-based therapeutic strategies may represent a promising avenue for future preclinical investigations aimed at evaluating mitotherapy as a potential intervention in FM (20).

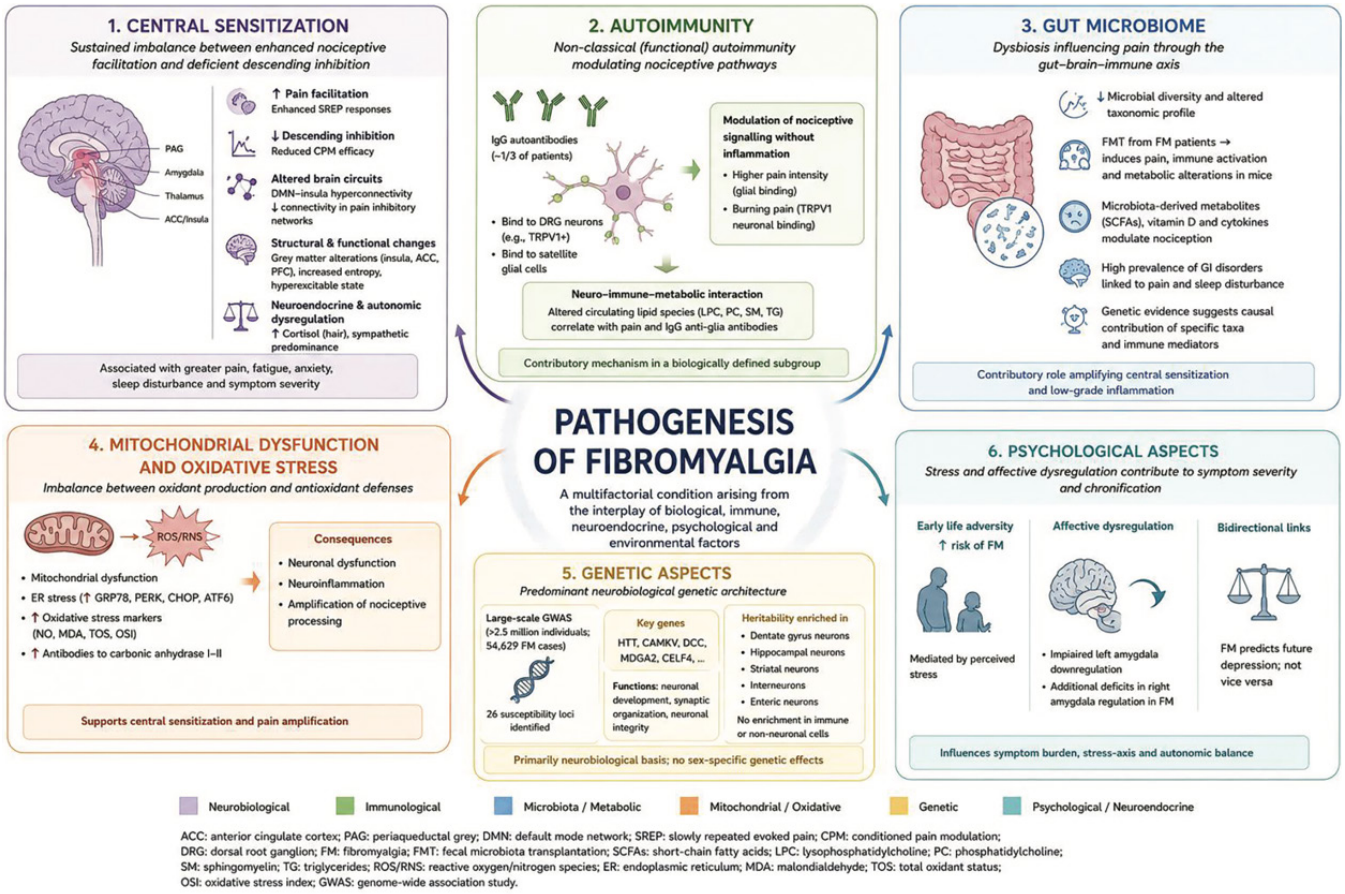

Fig. 1. Proposed pathogenesis of fibromyalgia.
The figure has been created using ChatGPT Edu provided by the Università Politecnica delle Marche, Italy.

A further original investigation conducted by Turkish researchers examined oxidative stress in patients with FM, focusing on biomarkers derived from a cellular organelle distinct from mitochondria, namely the endoplasmic reticulum. The authors quantified serum concentrations of established endoplasmic reticulum stress markers (specifically GRP78, PERK, CHOP, and ATF6) and identified significantly higher levels in individuals diagnosed with FM compared with healthy control subjects. These findings provide additional evidence supporting the involvement of oxidative stress-related pathways in the mechanisms underlying pain centralisation and the amplification of nociceptive processing in FM (21).

However, although individuals with FM consistently exhibit higher levels of oxidative stress compared with healthy controls (a finding corroborated by an additional cohort study that assessed total antioxidant status, total oxidant status, malondialdehyde, and the oxidative stress index) these biochemical alterations do not appear to correlate with established clinical measures of disease severity, such as the Fibromyalgia Impact Questionnaire (FIQ), nor with validated scales evaluating depressive and anxiety symptoms (22).

An additional investigation reported that patients with FM exhibit significantly higher circulating levels of antibodies directed against carbonic anhydrase I and II compared with healthy control subjects. These enzymes play a pivotal role in the regulation of acid-base homeostasis and have been hypothesised to participate in neuroinflammatory pathways.

Moreover, increased titres of anti-carbonic anhydrase antibodies in affected individuals were accompanied by elevated serum concentrations of malondialdehyde, total oxidant status, and oxidative stress index when compared with controls, whereas total antioxidant status did not differ significantly between the two groups (23).

Therefore, despite the growing body of evidence documenting redox imbalance in FM, the potential diagnostic value and clinical applicability of laboratory-based oxidative stress parameters remain uncertain. Further well-designed investigations are required to clarify their pathophysiological relevance, determine their relationship with symptom burden, and establish whether these biomarkers can meaningfully contribute to routine clinical assessment or therapeutic stratification before they can be considered for widespread implementation.

Genetic aspects

With regard to genetic markers, an important preprint study published in 2025 investigated the genetic architecture of FM in an exceptionally large cohort comprising more than 2.5 million individuals, including 54,629 patients diagnosed with FM (24). The primary objective was to explore genome-wide associations in order to identify novel

susceptibility loci, prioritise putative causal genes, and clarify the underlying biological mechanisms, including the specific tissues implicated in disease pathogenesis. The study also examined shared genetic liability with other disorders and assessed potential sex-specific differences in genetic architecture.

The dataset was derived from 11 European and North American cohorts, providing substantial statistical power for discovery analyses. This large-scale Genome-Wide Association Study (GWAS) identified 26 loci significantly associated with FM. Among the most notable genes were HTT, CAMKV, DCC, MDGA2, and CELF4, all of which encode proteins involved in neuronal development, synaptic organisation, and neuronal functional integrity.

Heritability analyses demonstrated that the genetic signal was predominantly enriched in neuronal cell populations, including dentate gyrus neurons, hippocampal neurons, striatal neurons, interneurons, and enteric neurons. In contrast, no significant enrichment was observed in non-neuronal tissues or immune cell populations, suggesting a primarily neurobiological genetic basis for FM.

Of particular interest was the association involving HTT and its regulatory partner GPR52. The HTT gene encodes huntingtin, a protein whose pathogenic mutations are responsible for Huntington's disease. Notably, GPR52 is currently under investigation as a pharmacological target in therapeutic development programs for Huntington's disease, highlighting a potentially relevant molecular pathway shared between neurodevelopmental and chronic pain mechanisms.

Finally, despite the marked predominance of women in the study population (87.7%), the analysis did not reveal sex-specific differences in the overall genetic architecture of FM (24).

Psychological aspects

Exposure to adverse events during early life is a well-recognised risk factor for the subsequent development of chronic pain conditions, although the biological and psychophysiological mechanisms underlying this association remain not completely understood (Fig. 1). One study investigated both acute and chronic stress in individuals reporting childhood adversity, employing clinimetric assessments alongside biochemical measurements of salivary cortisol and hair cortisol concentrations in patients diagnosed with FM and in healthy control subjects.

Compared with controls, patients more frequently reported exposure to early-life stressors, and the severity of FM symptoms appeared to be mediated by perceived stress levels. However, no significant differences emerged between groups with respect to the hormonal parameters evaluated (25).

Another important study published in 2025 highlighted differences in affective dysregulation among patients with FM, major depressive disorder, and healthy controls. Compared with healthy individuals, both FM and major depressive disorder groups exhibited comparable psychopathological profiles and patterns of affective dysregulation, including impaired regulation of left amygdala activity following neurofeedback. In addition, patients with FM also demonstrated deficits in right amygdala regulation, suggesting distinctive alterations in emotional regulation that may be specific to FM (26).

However, the relationship between FM and affective disorders remains complex. Longitudinal data support bidirectional associations between functional disorders and internalising conditions, although an asymmetrical pattern has been observed for FM and major depressive disorder, with FM predicting subsequent depression but not vice versa, suggesting a role for chronic symptom burden in the development of affective disturbances (27).

Take home messages

- Central sensitisation represents a core neurobiological mechanism in FM. Converging psychophysical, neuroimaging, structural, molecular, and neuroendocrine evidence demonstrate enhanced ascending nociceptive signalling and deficient descending inhibition, as reflected by augmented slowly repeated evoked pain (SREP) (1), impaired conditioned pain modulation (2), heightened pre-stimulus BOLD activity on functional MRI (3), network-level reorganisation (5), and autonomic imbalance with sympathetic predominance (9).
- FM may involve a form of non-classical or functional autoimmunity. IgG purified from patients has been shown to induce pain hypersensitivity when passively transferred to animal models in the absence of overt inflammation; moreover, a large case-control study demonstrated that patient-derived IgG binds to dorsal root ganglion neurons and satellite glial cells in approximately one third of cases, a finding not observed in healthy controls (11). Emerging evidences also suggest a potential interaction between immune mechanisms and metabolic pathways, as specific lipid alterations have been associated with both symptom severity and autoantibody levels (12).
- The gut microbiome is increasingly recognised as a key contributor to FM pathophysiology. Patients display reduced microbial diversity and a distinct taxonomic signature compared with healthy controls (14); microbiota-derived metabolites have been linked to nociceptive processing and symptom severity, and faecal microbiota transplantation from patients into germ-free mice is sufficient to induce pain hypersensitivity (15).
- Large-scale genetic studies indicate that the principal heritable traits of FM are predominantly localised at the neuronal level. The genetic architecture of FM is characterised by distinct features mapped to 26 loci encoding proteins crucial for neuronal function, including huntingtin (24).
- Oxidative stress remains one of the leading pathogenetic hypotheses underlying the development of FM. Compared with healthy controls, patients exhibit higher serum levels of oxidative stress-related biomarkers (22). In animal models of FM, mitochondrial transplantation has been shown to ameliorate oxidative stress and pain-related symptoms (20).
- Early-life stressful events appear to

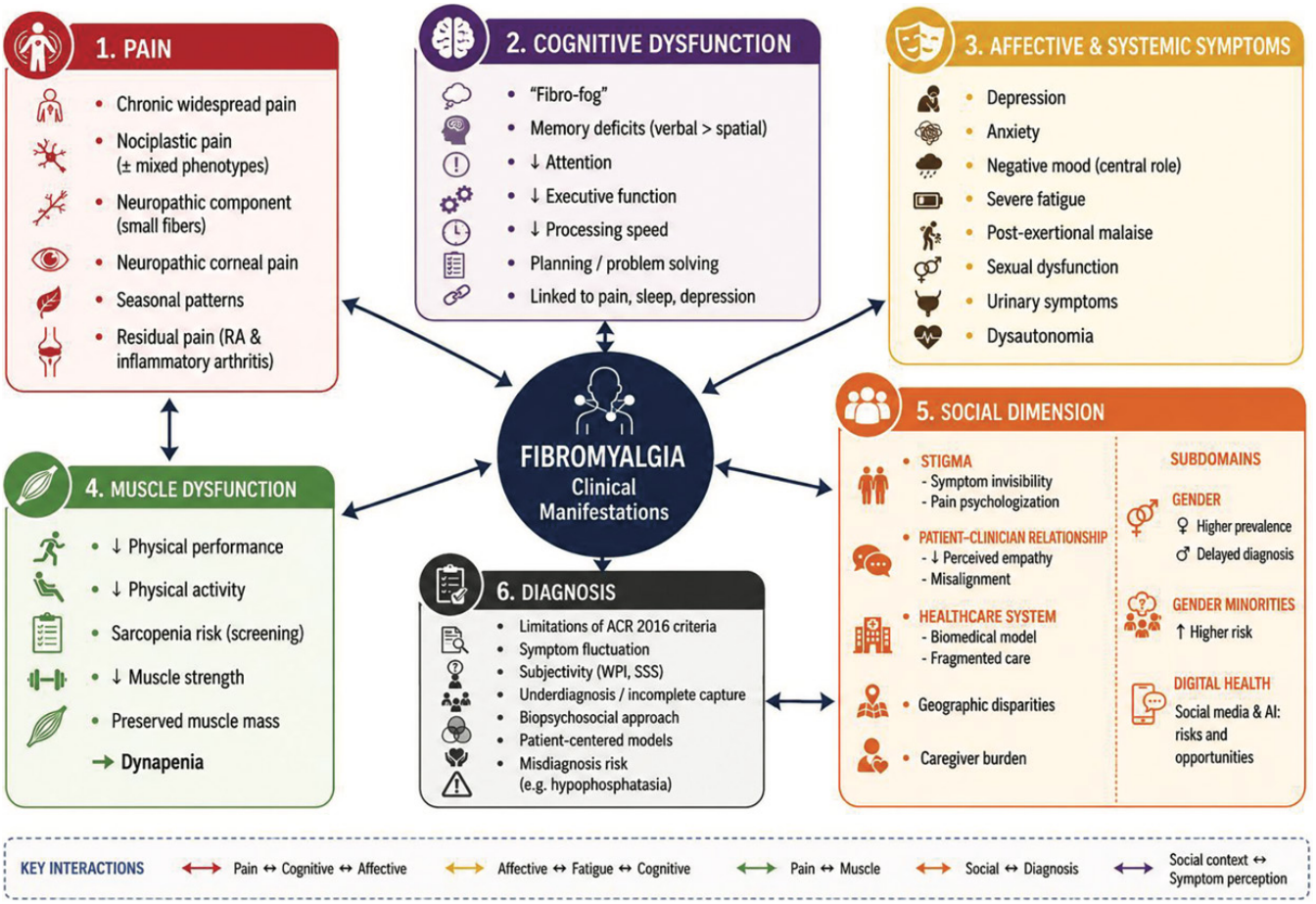

Fig. 2. Clinical manifestations of fibromyalgia.
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exert a significant impact on the right amygdala in patients with FM. This feature is distinctive when compared with both healthy controls and individuals with major depressive disorder (25).

Clinical manifestations

Chronic pain

Chronic widespread pain is the main clinical feature of FM (Fig. 2), and the pain experienced in this condition is widely considered the prototype of nociplastic pain (28-29). However, recent literature suggests that, despite its theoretical relevance, the nociplastic pain descriptor has limited clinical applicability, given the lack of validated tools for routine use (30). To date, only limited evidence is available on its practical implementation: in a single study applying the nociplastic pain grading system (31) not all FM patients were classified as having 'probable nociplastic pain' (32). Recent recommendations further suggest that FM may not be fully captured by a purely nociplastic framework, and that mixed pain phenotypes should also be considered (33). Within this framework, a possible neuropathic contribution has been recognised in a subset of FM patients, potentially related to small fibre pathology. This subgroup appears to be characterised by more severe pain and a higher burden of associated symptoms, together with signs of small fibre dysfunction (34). In addition, neuropathic corneal pain has been described as another relevant manifestation, presenting with burning and irritation symptoms disproportionate to clinical findings, and associated with both functional and morphological nerve alterations (35).

Beyond underlying pain mechanisms, seasonal patterns have also emerged as potential modulators of pain expression (36), with worsening reported in autumn but not observed for other symptom domains, underscoring the influence of environmental factors to symptom variability (37).

Residual pain

A further clinically relevant issue concerns residual pain in inflammatory arthritis, particularly rheumatoid arthritis (RA), and whether this reflects comorbid FM or a distinct pain phenotype (Fig. 2). An Italian study indicated that in RA, residual pain may not be fully explained by central sensitisation or psychiatric factors, while also showing a limited association with residual synovitis, suggesting a more heterogeneous and incompletely understood set of mechanisms (38). At the same time, evidence from early inflammatory arthritis indicates that centrally mediated pain components may already be present at disease onset in a subset of patients, even in the presence of active inflammation, supporting the hypothesis that central pain mechanisms may emerge early and contribute to the later

persistence of symptoms (39). Overall, the issue remains open: although residual pain may share features with FM, it may also reflect a broader and heterogeneous spectrum of mechanisms not fully captured by the diagnostic construct of FM.

Nonetheless, FM comorbidity is frequently observed across other rheumatological diseases where it is associated with higher symptom burden, greater discordance with disease activity, and more complex treatment patterns (40-42).

Cognitive dysfunction

Recent literature suggests that chronic widespread pain is associated with an increased risk of mild cognitive impairment (HR 2.55, 95% CI 1.31-4.97) (43). In this context, cognitive dysfunction represents a relevant clinical dimension of FM, often referred to as "fibro-fog" and characterised by impaired mental clarity and subjective memory complaints (Fig. 2).

Recent evidence supports the presence of working memory deficits in FM, particularly affecting the verbal domain, while spatial working memory appears relatively preserved (44). In line with broader cognitive involvement, global screening with the Montreal Cognitive Assessment has also shown reduced performance in FM patients, particularly in attention, executive function, and processing speed, with more pronounced impairment in untreated individuals and an inverse correlation with disease severity and depressive symptoms (45).

Neuropsychological investigations further indicate that cognitive dysfunction extends beyond working memory, involving executive and higher-order processes such as planning, problem solving, and cognitive flexibility (46). Complementary, a cognitive profiling study reported small but stable deficits in both verbal memory and executive domains, while also identifying pain severity and sleep disturbances as key determinants of cognitive performance (47).

Overall, these findings suggest that cognitive symptoms in FM reflect a multidimensional impairment interconnected with affective and somatic symptom burden, although cognitive alterations may persist independently, indicating that these domains only partially account for dyscognition in FM.

Affective and systemic symptoms burden

Across nociplastic pain conditions, distinct psychological profiles have been identified, with FM more frequently clustering within groups characterised by higher levels of dysfunction and distress (48), confirming its prominent affective burden (Fig. 2). A meta-analysis further highlights the high prevalence of affective disorders in chronic pain, with the greatest burden observed in nociplastic conditions: in FM, over half of patients report clinically significant symptoms of depression and anxiety, while major depressive disorder and generalised anxiety disorder are diagnosed in 38.3% (95% CI 27.9–49.9%) and 33.3% (95% CI 15.4–57.9%) of cases, respectively (49).

From a clinical perspective, negative mood and memory difficulties appear to play a central bridging role in the FM-depression interplay across pain, cognitive, and psychological domains, with pain itself not emerging as the primary driver of this comorbidity (50). In parallel, depressive symptoms profiles characterised by anhedonia, weight gain, or greater overall severity are more strongly associated with FM, underscoring the importance of symptom heterogeneity in psychiatric assessment (51).

Beyond affective features, FM is characterised by a broad systemic symptom burden. Fatigue is among the most disabling manifestations, encompassing both physical and cognitive components and showing a pattern closely resembling post-COVID condition, being more intense, less responsive to rest, and more prone to post-exertional worsening than in multiple sclerosis (52). Accordingly, post-exertional malaise emerges as a relevant feature, reflecting a disproportionate exacerbation of symptoms following minimal effort (53). Additional domains, including sexual dysfunction (54-56) and lower urinary tract symptoms (57), further contribute to disease burden and appear influenced by pain severity, psychological factors and comorbid conditions. Finally, autonomic symptoms are frequently reported, supporting a role for dysautonomia in overall symptom expression (58), although its pathophysiological significance remains to be fully clarified (59).

Muscle dysfunction

FM is characterised by reduced physical performance and lower levels of physical activity, conditions that are well recognised in affected patients and possible drivers of muscle dysfunction (Fig. 2). During the past year, increasing attention has been paid to the assessment of this domain, with screening using the SARC-F questionnaire identifying more than half of FM patients as being at risk of sarcopenia, a finding that correlates with disease impact and psychological factors, including depression (60).

However, studies suggest a dissociation between muscle strength and muscle mass. While FM patients consistently show reduced muscle strength compared with healthy controls, no significant differences have been observed in objective measures of muscle mass, such as anterior thigh muscle thickness, when compared to control populations (61, 62). These findings suggest that FM patients may be at increased risk of dynapenia in the absence of a corresponding increase in true sarcopenia.

Social dimension

- Healthcare system and patient-clinician interaction

The theme of stigma emerged this year as a relevant issue for FM patients (Fig. 2). Patients frequently struggle to be believed in both social and healthcare contexts, with stigma rooted in the invisibility of symptoms and the tendency to psychologise pain (63). Experience of stigmatising clinical encounters may even resemble forms of retraumatisation, reinforcing avoidance behaviours and anticipatory anxiety toward healthcare (64).

Closely linked to these dynamics, empathy has been identified as a key modulator of the patient-clinician relationship. A misalignment between patients and

healthcare professionals has been reported, with patients defining empathy in terms of emotional validation and its impact on well-being (65). FM patients may also be more prone than other chronic pain populations to interpret ambiguous clinical interactions negatively, potentially amplifying perceptions of low empathy and contributing to strained therapeutic relationships (66).

These findings reinforce the importance of a biopsychosocial approach, in which validation, communication, and support play a central role in fostering patient engagement and self-management (67, 68).

However, studies (69, 70) have highlighted how these challenges are embedded within healthcare systems that remain predominantly biomedical and are often insufficiently equipped to address conditions such as FM, resulting in fragmented care, limited support and patient disempowerment. Consistently, Italian registry data show significant geographic disparities in FM severity, with worse outcomes in Southern regions, plausibly reflecting inequalities in socioeconomic conditions and healthcare access (71).

Finally, an additional dimension concerns the impact of FM on caregivers. A Turkish study (72) showed that caring for individuals with FM may negatively affect caregivers' work productivity and quality of life, with burden correlating with patients' disease severity.

Gender-related aspects

Sex- and gender-related differences represent an increasingly explored dimension in FM (Fig. 2). Evidence from a meta-analysis on chronic pain in mid-life indicates that women have a consistently higher risk of chronic pain compared to men, with a modest overall increase but a more pronounced difference for widespread pain conditions, including FM (73).

At the same time, FM in men should not be overlooked, with emerging evidence suggesting that male patients may exhibit distinct clinical features. Available data indicate that men tend to be older at diagnosis, suggesting possible diagnostic delay, and display a different comorbidity profile, including lower rates of obesity but higher prevalence of obstructive sleep apnoea (74). Beyond the binary framework of sex, emerging evidence also highlights a high burden of chronic widespread pain and FM in gender minority populations, with prevalence estimates exceeding those observed in the general population (75).

Digital health

Patients have increasingly turned to digital health sources for information and symptom interpretation, including AI-based chatbots and social media platforms (Fig. 2). While these tools may improve access to health-related content and patient engagement, current evidence highlights important limitations, particularly regarding the accuracy and clinical usability of AI-generated responses (76). Social media platforms, where contents related to chronic and 'invisible' conditions is widely disseminated, may also shape patient experience in a bidirectional manner. Although they can facilitate peer support and increase disease awareness, studies suggest that limited understanding of FM and frequent experiences of invalidation may be reinforced in online discourse, potentially contributing to illness-centred identities and a more complex transition to recovery (77, 78).

Within this digital ecosystem, machine learning and natural language processing approaches are emerging as structured tools with potential clinical applications. Recently, large language model-driven sentiment analysis has been explored in FM, suggesting a potential contribution of AI to diagnostic recognition through the analysis of patient narratives and free-text data (79). In parallel, AI-based pipelines applied to general practitioner referral letters and patient-generated free-text descriptions have subsequently shown the ability to identify and prioritise patients with rheumatologic diseases, thereby supporting earlier triage and clinical decision-making (80, 81).

Diagnosis

Over the last year, a debate has emerged regarding the performance of the diagnostic criteria for FM proposed by the American College of Rheumatology (ACR) in 2016 (82) (Fig. 2). Challenges in their clinical application have been highlighted, including symptom fluctuation over time, ambiguity in the interpretation of pain distribution, and the inherent subjectivity of key components such as the Widespread Pain Index (WPI) and Symptom Severity Scale (SSS), which may overlap with coexisting pain and affective conditions (83). A population-based study has further shown that, despite high screening specificity, a substantial proportion of patients does not fully meet diagnostic thresholds. Simplified diagnostic approaches have been explored, yielding only marginal improvements in accuracy (84).

In parallel, attention has been given to the biopsychosocial perspective, emphasising the need to incorporate not only biological and psychological domains but also the social impact of the disease within diagnostic frameworks (85). Patient-centred approaches supported by large language models have also been proposed to translate clinical knowledge into accessible tools, highlighting the relevance of patients' own symptom descriptions in supporting early identification and clinical understanding (86).

Finally, this diagnostic uncertainty also raises the issue of potential misdiagnosis. Evidence suggests that a small but clinically relevant proportion of patients labelled as FM may have alternative conditions, including rare metabolic disorders such as hypophosphatasia (87). These findings underscore the importance of careful evaluation of atypical features or poor response to standard management and support the use of targeted investigations when clinically indicated (88).

Take home messages

- Pain in FM is heterogeneous and may be not fully explained by the nociplastic model (31, 32), with possible neuropathic contributions highlighting complex pain phenotype (33, 34).
- Residual pain in inflammatory arthritis is multifactorial and incompletely understood, potentially overlapping with FM (40-42) but also including distinct and heterogeneous mechanisms (38, 39).

- "Fibro-fog" reflects a multidimensional cognitive impairment involving working memory, attention, and executive function (45-47), only partially explained by pain, mood, and sleep disturbances.
- FM is characterised by a high affective burden and widespread systemic symptoms, including depression, anxiety (49), fatigue (52) and autonomic dysfunction (59), with interconnected domains that amplify overall disease impact and contribute substantially to disability.
- FM is associated with reduced muscle strength and impaired physical performance (60), in the absence of consistent evidence of substantial muscle mass reduction, suggesting a pattern more indicative of dynapenia than sarcopenia (61, 62).
- Stigma, symptom invisibility, and lack of validation (63-66) negatively affect patient experiences and healthcare engagement, highlighting the need for empathetic communication and a biopsychosocial, patient-centred approach (67) within often inadequate healthcare systems (69, 70).
- Sex and gender influence FM risk and clinical presentation, with higher prevalence in women (73), potential diagnostic delays and distinct comorbidities in men (74), and an increased burden of disease in gender minority populations (75).
- Digital health resources improve access and engagement but raise concerns about accuracy and misinformation (76-78), while structured AI approaches show promise in identifying clinically relevant patterns and supporting earlier diagnosis and patient stratification (79, 80).
- According to the most recent literature, current diagnostic criteria require updating (84) and should be complemented by incorporating social assessment (85, 86).

Conclusions

Recent literature on FM reflects a progressively expanding and multidimensional evidence base. Advances in neurobiological research further support central sensitisation as a key mechanism, involving altered nociceptive processing, impaired descending modulation, and large-scale brain network reorganisation. In parallel, emerging data suggest potential contributory roles of immune, microbiome, metabolic, and genetic factors, underscoring the complexity of disease pathophysiology. Clinically, increasing attention has been given to the heterogeneous expression of cognitive, affective, and multisystem symptoms. Overall, current evidence supports a multidimensional model of FM encompassing biological, psychological, and social domains, while highlighting persistent gaps in the understanding of underlying disease mechanisms.

Affiliations

[1]Chronic Musculoskeletal Pain and Fibromyalgia Unit, AOU Policlinico Umberto I, Sapienza University of Rome, Italy; [2]Dept. of Molecular Medicine, Sapienza University of Rome, Italy; [3]Rheumatology Unit, Università Politecnica delle Marche, Carlo Urbani Hospital, Jesi, Italy; [4]Rheumatology Unit, Dept. of Medical and Cardiovascular Sciences, Sapienza University of Rome, Italy; [5]Internal Medicine and Atherosclerosis Prevention, Dept. of Internal Medicine and Medical Specialties, AOU Policlinico Umberto I - Sapienza, Rome, Italy; [6]Rheumatology Unit, IRCCS Galeazzi-Sant'Ambrogio Hospital, Milan; Dept. of Biomedical and Clinical Sciences, University of Milan, Italy; [7]Rheumatology Unit, Dept. of Internal and Experimental Medicine, University of Messina, Italy; [8]Rheumatology Unit, Dept. of Internal Medicine, Azienda Socio-Sanitaria Territoriale (ASST) Sette Laghi, Ospedale di Circolo, Fondazione Macchi, Varese, Italy; [9]Dept. of Dynamic and Clinical Psychology and Health Studies, Sapienza University of Rome, Italy; [10]Fondazione Paolo Procacci, Rome, Italy; [11]Internal Medicine H, Tel Aviv Sourasky Medical Center; and Gray Faculty of Medical and Health Sciences Tel Aviv University, Israel; [12]Dept. of Pathophysiology and Transplantation, Università Degli Studi di Milano; and Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, S.C. Medicina - Emostasi e Trombosi, Milan, Italy; [13]Fondazione Ermete, Milan, Italy.

Competing interests

R. Gualtierotti has received honoraria for educational meetings or speaker's bureau from Bayer, Biomarin, Roche, Sanofi, SOBI and Pfizer, and has been part of the advisory board of Roche, Sobi and Novo Nordisk.

The other authors have declared no competing interests.

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