Fibromyalgia as a Disorder of Multi-System Regulation: From Pathogenetic Modeling to Therapeutic Perspectives

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Abstract. *Fibromyalgia (FM) is a multifactorial syndrome characterized by chronic widespread pain and associated symptoms. Despite evidence implicating central nervous system dysfunction and psychoneuroendocrine interactions, its pathogenesis remains unclear, limiting the development of mechanism-based therapies. We discuss FM within the frameworks of Psychoneuroendocrinoimmunology and Dynamical Systems Theory, proposing a pathogenetic model based on interactions between neuroendocrine and thalamocortical regulatory circuits. The model hypothesizes that an imbalance between GABAergic inhibition and glutamatergic excitation, potentially driven by stress and gonadal hormones, may promote a stable state of increased neuronal activity. This framework may help explain the association of FM with stress and its higher prevalence in women. Although not yet experimentally validated, the model is consistent with several literature findings and suggests potential therapeutic targets, including neurosteroids, non-invasive brain stimulation, mind-body therapies and dietary interventions. Overall, this framework may help reconceptualize FM as a disorder of dynamically dysregulated, interconnected systems and guide the development of individualized, mechanism-oriented therapeutic strategies.*

Keywords: *Dynamical Systems Theory, GABA, Glutamate, Neurosteroids, Non-Invasive Brain Stimulation, Diet.*

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Introduction

Fibromyalgia (FM) is a syndrome characterized by chronic widespread musculoskeletal pain, accompanied by a constellation of other symptoms and comorbidities, among which chronic fatigue, sleep disturbances, and cognitive dysfunction (such as difficulties with concentration, memory loss, and mental confusion) represents the core features of the condition (Sarzi-Puttini *et al.*, 2020).

These manifestations, which may be incomplete or fluctuate over time, are assessed using the Widespread Pain Index, which quantifies pain across 19 body regions, and the Symptom Severity Scale, which evaluates the severity of associated symptoms. Together, these indices form the basis for the clinical diagnosis of FM according to the revised American College of Rheumatology criteria (Wolfe *et al.*, 2016).

In the absence of validated specific biomarkers, whether serological or imaging-based, diagnosis often takes several years to be formally established (Demori, Molinari, *et al.*, 2022); (Kulekcioglu, 2022).

Diagnostic challenges also affect prevalence estimates, which are generally reported to range from approximately 1% to 3% of the global population, with considerable variations depending on the characteristics of the populations studied (D'Souza *et al.*, 2026).

Fibromyalgia as a Disorder of Regulatory Systems

The complex clinical picture of FM encompasses additional symptoms and comorbidities, which may be severe in a substantial proportion of patients. These include mood disturbances and depression, metabolic and gastrointestinal disorders, obesity, autonomic dysfunction and balance disturbances, migraine, and sensory hypersensitivity (Wu, 2025).

The complexity of FM also stems from the lack of a well-established pathogenetic model. At present, FM can be conceptualized as a multifactorial disorder that may be triggered by various physical or emotional stimuli, giving rise to different pathophysiological processes and disease phenotypes, associated with a range of symptoms and comorbidities whose prevalence and severity vary from patient to patient. It is important, however, to recognize that all disease manifestations mutually influence one another. For instance, heightened pain perception may negatively affect sleep quality and mood, and vice versa (Iannuccelli *et al.*, 2026); (Pinto *et al.*, 2023).

This perspective also transcends the debate over whether FM should be regarded as a disorder of the mind or the body. Indeed, in keeping with the psychoneu-

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roendocrinoimmunology (PNEI) paradigm, reciprocal etiopathogenetic interactions in FM occur through both bottom-up pathways, primarily involving inflammatory, endocrine, and nociceptive signals, and top-down pathways, predominantly mediated by psychological, cognitive, and emotional signals (Sarzi-Puttini *et al.*, 2020; Pinto *et al.*, 2023).

In FM, communication within the PNEI network appears to be disrupted in multiple ways. The psychoneuroendocrine core of this network is particularly implicated, given the observed association between FM and stress responses. Studies investigating human stress-response systems have consistently demonstrated alterations in the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system in patients with FM (Beiner *et al.*, 2023). A clear association has also been reported between FM and exposure to early-life stressors, including physical and psychological trauma and abuse (Beiner *et al.*, 2025). Such experiences may have programmed the HPA axis towards a dysfunctional and hyperactive state, although paradoxical responses, such as the hypocortisolism observed in a subset of patients, should also be taken into account (Beiner *et al.*, 2023); (Jurado-Priego *et al.*, 2024).

Given the immunomodulatory properties of cortisol, alterations in HPA axis function are closely associated with changes in immune activity, particularly an increase in inflammatory tone (Liu *et al.*, 2017). FM is not a classical chronic inflammatory disease; however, a recent meta-analysis supports the presence of low-grade systemic inflammation, which may be particularly associated with disease phenotypes characterized by obesity, dysbiosis, and metabolic disturbances. Nevertheless, identifying a consistent cytokine profile remains challenging due to the substantial methodological heterogeneity across studies (Fernandez-Rodriguez *et al.*, 2026).

A very recent genetic analysis involving more than 2.5 million individuals, including both FM patients and unaffected controls, used a genome-wide association study (GWAS) approach to investigate the genetic basis of FM.

The findings provide strong support for the hypothesis that FM has a predominantly central neurological component, while not excluding possible interactions with other regulatory systems. The meta-analysis identified 26 genetic loci associated with an increased risk of developing FM. The most significant associations involved genes playing important roles in the Central Nervous System (CNS) and, more specifically, in neuronal function. Associations emerged with brain regions, including, among others, the frontal cortex, anterior cingulate cortex, and hippocampus, which are involved in fundamental processes such as sensory information processing, pain processing and modulation, memory, and emotional regulation. Interestingly, the involvement of enteric neurons was also identified, lending sup-

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port to the hypothesis that the gut–brain axis may play a role in FM (Kerrebijn *et al.*, 2026).

Fibromyalgia in the Light of Dynamical Systems Theory

The PNEI paradigm allows FM to be conceptualized as a disorder involving the dysregulation of multiple interconnected systems, providing a theoretical basis for developing a pathogenetic model that more accurately reflects the clinical complexity of the syndrome. However, constructing such a model and using it to identify novel therapeutic targets and, ultimately, more effective treatments also requires the integration of other systemic approaches, including Dynamical Systems Theory and some of its subsequent developments (Jaeger & Monk, 2014).

Dynamical Systems Theory provides a conceptual framework for understanding how interconnected systems evolve over time in response to internal and external perturbations. In living beings, dynamical systems are generally characterized by negative or positive feedback loops (El-Samad, 2021). Negative feedback loops generally contribute to homeostasis by counteracting deviations from a set point and display stable single-point equilibria or cyclic equilibria (limit cycles). By contrast, positive feedback loops amplify changes and may contribute to the emergence of alternative stable equilibrium points, allowing the system to acquire multistability (Blanchini *et al.*, 2014).

As previously proposed by one of the authors (B.B.), if biological systems can exhibit multistable dynamics and diseases involve changes in the functional state of the organism, then pathogenetic processes may be understood in terms of transitions between alternative stable states (Burlando, 2022).

Bifurcation parameters are variables that influence system dynamics. When one or more of these parameters reach critical values, known as bifurcation points, the qualitative behavior of the system may change, potentially triggering a transition from one stable state to another (Freyer *et al.*, 2012). Bifurcation analysis may therefore provide a powerful framework for identifying potential therapeutic targets, particularly those capable of modulating system dynamics and promoting a transition towards a pathological state, as well as its reversal back to a physiological state (Burlando, 2022).

In the case of FM, we have developed a pathogenic model by taking into account the role of the CNS in the syndrome and the distinctive features of FM pain, including hyperalgesia and allodynia, which are thought to involve altered central pain processing and neuroplastic changes within neural networks. The term "nociplastic pain" has been proposed to describe this type of pain, highlighting the involvement of altered nociceptive processing and the plasticity of the central and

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peripheral nervous systems in response to various internal and environmental influences (Kosek, 2024).

A Proposed Pathogenetic Model of Fibromyalgia

We proposed a model based on the identification, within the complex network of central pain-processing circuits, of a thalamocortical loop comprising the ventral posterolateral nucleus of the thalamus (VPL), the somatosensory cortex (SC), and the thalamic reticular nucleus (TRN) (Groh *et al.*, 2018). This loop is characterized by negative feedback mediated by GABAergic projections from the TRN to the VPL, which exert inhibitory control over glutamatergic pathways within the reciprocally excitatory connections among the VPL and SC (Lam & Sherman, 2011). In this system, the bifurcation parameter mostly linked with pathogenesis is the strength of GABAergic inhibition. If this decreases, or if the GABA/glutamate ratio is reduced, positive feedback mechanisms may become dominant, allowing bistability to emerge. As we have demonstrated mathematically, the network may then shift from a physiological configuration, characterized by low firing rates across its neuronal elements, to a new stable configuration characterized by high firing rates. The latter may be associated with the disease state, as it could sustain chronic pain in response to very weak or even absent stimuli (Demori, Giordano, *et al.*, 2022); (Demori *et al.*, 2024).

According to this model, factors that reduce the GABA/glutamate ratio play a role in reshaping the system's behavior, potentially driving it towards the pathological equilibrium state. In this regard, we extended the model to incorporate the association between FM and stress, as well as the role of the hypothalamic-pituitary-gonadal (HPG) axis and sex hormones. In fact, another distinctive feature of FM is its markedly higher prevalence in women, with a global average female-to-male ratio of approximately 3:1, although ratios as high as 10:1 have been reported in some populations (D'Souza *et al.*, 2026); (Arout *et al.*, 2018). From puberty to menopause, the female reproductive lifespan is characterized by significant neuroendocrine changes that may contribute to FM pathogenesis (Mucci *et al.*, 2023). Fluctuations in gonadal hormone levels throughout the menstrual cycle and across the different stages of the female reproductive lifespan may influence pain sensitivity and the manifestation of various FM-related symptoms. In particular, both estrogens and progesterone also exert neuroprotective effects against glutamate-induced excitotoxicity (Aloisi & Sorda, 2011); (Wise, 2002). Women with FM report worsening pain during the luteal and menstrual phases of the cycle (Alonso *et al.*, 2004); (Alonso *et al.*, 2004). Similarly, pregnancy-related hormonal fluctuations may affect FM symptoms, with worsening reported during the third trimester and

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postpartum period (Ostensen *et al.*, 1997); (Genc *et al.*, 2017). Finally, the menopausal transition may also be associated with changes in pain perception, sleep quality, and mood. In some women, this period may coincide with the onset or worsening of FM symptoms (Vidal-Neira *et al.*, 2024).

The Role of Stress and Sex Hormones

Our pathogenetic model was extended by incorporating a neuroendocrine loop involving the HPA and HPG axes alongside the above thalamocortical loop (Demori *et al.*, 2024). We showed that GABAergic transmission is positively associated with neurosteroids derived from gonadal hormones, particularly allopregnanolone (Allo), whereas glutamatergic transmission correlates positively with stress hormones, especially cortisol. We then developed a dynamical model of the HPG and HPA axes, represented as a mutually inhibitory regulatory loop capable of exhibiting multistability. The model predicts the existence of a high-HPA/low-HPG stable state, which may be favored in women by the effects of premenstrual or postpartum reductions in brain Allo levels combined with stress. This endocrine configuration may, in turn, promote the transition of the thalamocortical circuit towards a stable high-firing-rate state, providing a possible link between endocrine dysregulation and altered neural activity in FM pathogenesis (Demori *et al.*, 2024).

Consistency of the Proposed Model

The model has not yet been validated through direct experimental testing, either in preclinical studies or in clinical trials. Nevertheless, it is grounded in the available literature and is therefore consistent with several observations reported in studies on FM. First, it aligns with the concept of nociplastic pain, in which central and peripheral PNEI signaling and genetic predisposition may contribute to structural and functional plasticity in pain-processing circuits (Kosek, 2024). Second, it is consistent with evidence of altered GABAergic and glutamatergic signaling in FM, including reports of reduced glutamic acid decarboxylase levels (Foerster *et al.*, 2012); (Fitzgerald & Carter, 2011). Third, it is compatible with the generally limited efficacy of current FM pharmacotherapies, as well as the comparatively greater efficacy reported for gabapentinoids (Tzadok & Ablin, 2020). Fourth, the model offers a potential explanation for both the higher prevalence of FM in women and its association with stress.

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Therapeutic Targets Suggested by the Model

Neurosteroids

The limited understanding of FM pathogenesis constrains the development of mechanism-based treatments, favoring symptomatic approaches that may not target the underlying pathogenetic processes.

The proposed model suggests that therapeutic strategies should focus on modulating GABA–glutamate signaling and/or the PNEI factors, including the HPA and HPG axes, which may contribute to neurotransmitter dysregulation. The most direct therapeutic implication concerns the potential use of Allo and related neurosteroids. Allo is a positive allosteric modulator of both synaptic and extrasynaptic GABA-A receptors, enhancing phasic and tonic GABA-mediated inhibitory transmission. Within the framework of our model, this action could modulate the strength of GABAergic inhibition—the proposed bifurcation parameter—and thereby shift the dynamics of the system towards a more physiological state. Assessing the therapeutic effects of Allo or related compounds could thus provide an initial experimental test of the model's predictions (Burlando & Demori, 2024).

Nevertheless, important limitations must be acknowledged. Neurosteroids, particularly Allo, may cause substantial sedation and other adverse effects. These concerns have also been discussed in the context of the FDA approval of Allo formulations for postpartum depression, underscoring the need to carefully evaluate the safety, tolerability, and therapeutic applicability of this approach in FM (Maguire & Mennerick, 2024).

Non-Invasive Brain Stimulation

Non-invasive brain stimulation (NIBS), including transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS), represents another potential strategy for enhancing GABAergic activity. Sex-related neurobiological differences and gonadal hormone fluctuations may influence responses to neuromodulation; women have been reported to exhibit more pronounced responses to NIBS than men (Chaieb *et al.*, 2008). TMS and tDCS have also been investigated during pregnancy, with preliminary findings suggesting favorable tolerability and no clear maternal or fetal safety signals (Angeline *et al.*, 2025); (Laurin *et al.*, 2022).

In FM, a recent meta-analysis report potential benefits of NIBS, particularly for pain reduction, although protocol heterogeneity and limited sample sizes preclude definitive conclusions (Ahmed *et al.*, 2025). These findings, together with our model, provide a rationale for further investigating tDCS also in pregnant women with

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FM, as a non-invasive approach to modulating GABAergic function. However, its safety and efficacy in this specific population remain to be established (Mucci *et al.*, 2023).

Mind–Body Therapies

The EULAR recommendations state that the primary goal of FM management should be to improve health-related quality of life through a multidisciplinary approach that balances the benefits and risks of available treatments and adopts a gradual strategy, beginning with non-pharmacological interventions (Macfarlane *et al.*, 2017). Several non-pharmacological mind–body interventions, particularly physical exercise, mindfulness, and cognitive behavioral therapy, exert well-established neuromodulatory effects and may influence the functional connectivity of brain networks in FM (Iannuccelli *et al.*, 2025).

In an observational study based on an online survey of 344 patients, we found that the self-reported effectiveness of these and other non-pharmacological interventions was higher than that of pharmacological treatments. However, pain characteristics and psychological traits were also found to influence perceived treatment effectiveness, highlighting the importance of individualized therapeutic approaches (Demori, Molinari, *et al.*, 2022).

Notably, dietary interventions were associated with the highest levels of patient-reported satisfaction. We therefore conducted a further questionnaire-based observational study focusing specifically on Mediterranean diet (MedDiet) adherence in FM patients (Proietti *et al.*, 2024). The main findings showed that greater adherence was associated with lower pain intensity and reduced disease severity, as assessed using the pain intensity Numerical Rating Scale (NRS) and the Revised Fibromyalgia Impact Questionnaire (FIQR), a validated instrument widely used to assess the impact and severity of FM (Salaffi *et al.*, 2021).

Diet and the Microbiota-Gut-Brain Axis

Our findings underscore the importance of providing FM patients with tailored nutritional education and dietary interventions, taking into account the presence or absence of comorbid obesity, gastrointestinal disturbances, and micronutrient deficiencies.

Diet is indeed a major modifiable factor influencing the microbiota-gut-brain axis (MGBA) and, consequently, neurotransmission. Dysbiosis has been associated with several disorders involving the CNS, including altered nociception and FM (Ustianowska *et al.*, 2022).

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Therefore, high-quality intervention studies are needed to evaluate the therapeutic potential of different dietary patterns and supplementation in FM.

The literature provides substantial evidence supporting the beneficial effects of the MedDiet on outcomes that are also relevant to FM, including pain, fatigue and mood disorders, although studies specifically addressing this condition remain limited (Miller *et al.*, 2025). Some of the beneficial effects of the MedDiet may be attributable to its high fiber content, which can modulate the gut microbiota and, consequently, influence MGBA signaling (Dalile *et al.*, 2019). In FM, alterations in the gut microbiota may contribute to symptom modulation through changes in microbial metabolism and signaling along the MGBA. In particular, changes have been reported in the composition of bacterial communities involved in the production of short-chain fatty acids (SCFAs), including butyrate, a metabolite with potential immunomodulatory properties and a role in regulating intestinal homeostasis (Minerbi *et al.*, 2019). In parallel, some evidence points to alterations in microbial glutamate metabolism and in pathways involved in GABA synthesis (Clos-Garcia *et al.*, 2019). These changes may indirectly affect neurotransmission and pain-modulatory mechanisms, supporting the rationale for investigating the potential benefits of supplementing the MedDiet with selected GABA- and/or butyrate-producing probiotic strains.

Another dietary approach of potential interest in FM is the ketogenic diet (KD). Of particular relevance to our model, this dietary intervention has been associated with changes in cerebral neurotransmitter metabolism, with potential effects on the balance between excitatory and inhibitory neurotransmission. In particular, ketone bodies may influence glutamate metabolism and increase GABA availability, thereby contributing to the modulation of neuronal excitability (Qiao *et al.*, 2024). With regard to FM, a pilot study has reported encouraging effects across several disease domains in patients with obesity and FM (Ciaffi *et al.*, 2023). These preliminary findings warrant further investigation through larger, well-designed clinical trials to establish the efficacy, safety, and potential therapeutic role of KD interventions in FM.

Conclusions

FM can be conceptualized as a dysfunction of interconnected and dynamically regulated systems. By establishing a framework linking stress, sex hormones, neurosteroids, GABA/glutamate signalling, and the dynamics of pain-related neural networks, our model conceptualizes the disease not simply as an alteration in physiological parameters, but as a qualitative shift in system dynamics towards a self-sustaining dysfunctional state. The most promising emerging therapeutic ap-

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proaches are therefore those aimed at modulating the dynamics of this system, including neurosteroid-based interventions, neuromodulation, and nutritional and MGBA-targeted strategies (Figure 1).

However, it is important to emphasize that integrating these and other therapeutic approaches does not mean indiscriminately combining multiple treatments. Rather, it requires an individualized approach based on the patient's symptom phenotype and other individual characteristics, with the ultimate goal of achieving synergistic effects in modulating system dynamics in each individual patient.

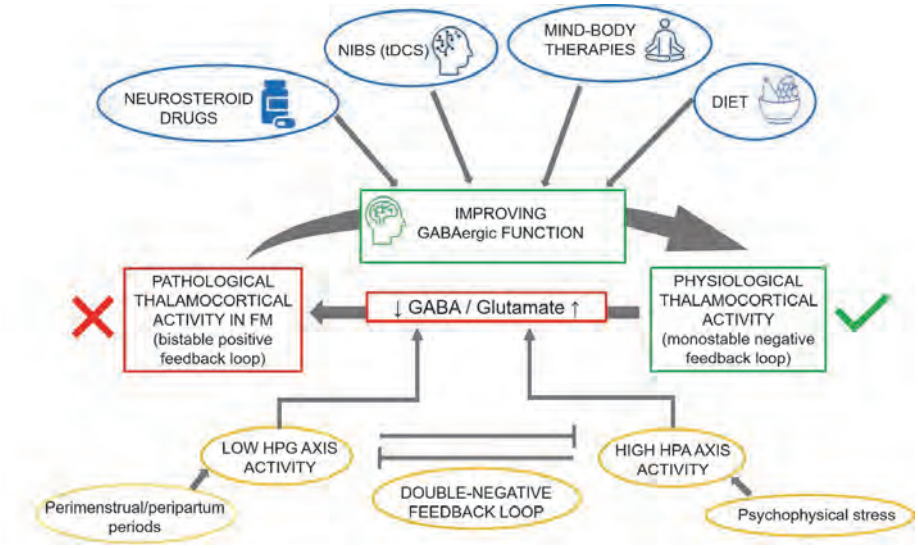


Fig. 1. ***Schematic representation of the proposed pathogenetic model of FM, conceptualized as a dysfunction of interconnected and dynamically regulated systems. According to our model, reduced GABAergic and enhanced glutamatergic transmission may drive the thalamocortical activity from a monostable to a bistable state, thereby disrupting central pain processing. This imbalance in GABA/glutamate signaling may be associated with reciprocal inhibitory interactions between the HPG and HPA axes, potentially leading to a stable state characterized by reduced HPG axis activity and increased HPA axis activity. The model suggests several potential therapeutic approaches aimed at modulating these regulatory mechanisms, including neurosteroids, NIBS, mind-body therapies, and dietary interventions. Neurosteroids may enhance phasic and tonic GABAergic inhibition by acting as positive allosteric modulators of synaptic and extrasynaptic GABA-A receptors, respectively, potentially shifting thalamocortical dynamics towards a physiological state. NIBS, mind–body therapies, and dietary interventions may also influence the interconnected neural, endocrine, and metabolic pathways implicated in the proposed model. Arrowheads indicate activation, T-shaped endings denote inhibition.***

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