

REVIEW ARTICLE

Gut–brain axis and fibromyalgia:
Neurobiological mechanisms, microbiome
composition, psychological comorbidities, and
diagnostic approachesVictoria Tischer Sawka¹ and Guilherme Welter Wendt¹Department of Medicine, School of Medicine, Western Paraná State University (UNIOESTE),
Francisco Beltrão, Paraná, Brazil

Abstract

Fibromyalgia is a chronic nociplastic pain syndrome affecting 2–4% of the global population, with marked female predominance, substantial functional impairment, and an incompletely understood pathophysiology. Diagnosis still relies on symptom-based criteria, and treatment options remain limited. Over the past decade, evidence has positioned the gut–brain axis as a key pathway linking intestinal microbiome dysbiosis, altered microbial metabolites, peripheral immune activation, and central nervous system dysfunction. This review synthesizes current findings across four domains: (i) neurobiological mechanisms by which gut-derived signals influence central sensitization, neuroinflammation, neurotransmitter balance, and neuroendocrine function; (ii) microbiome compositional changes and their metabolic consequences, particularly involving short-chain fatty acids and secondary bile acids; (iii) bidirectional relationships between gut dysbiosis and the psychological comorbidities associated with fibromyalgia; and (iv) limitations of current diagnostic criteria and the potential of multimodal biomarker panels. Evidence from translational animal models, human observational studies, and early-phase trials indicates that gut microbiota contribute to pain perception and psychological symptoms through metabolite-mediated immune and neuroendocrine pathways, although the human evidence remains predominantly associative. Fecal microbiota transplantation, synbiotic supplementation, and metabolite-targeted strategies have shown promising therapeutic potential but remain constrained by small sample sizes, methodological heterogeneity, and a lack of placebo-controlled trials. Microbiome signatures, bile acid profiles, and proteomic markers show promise as adjunctive diagnostic tools but require validation in large, diverse cohorts. Although the field presents compelling mechanistic evidence, methodological limitations must be addressed before these findings can be translated into clinical practice. Overall, microbiome-directed therapies and multimodal biomarker panels represent promising strategies for precision management of fibromyalgia but require rigorous clinical validation.

Keywords: Fibromyalgia; Gut–brain axis; Gut microbiota; Nociplastic pain; Bile acids; Short-chain fatty acids; Dysbiosis; Biomarkers

***Corresponding author:**
Guilherme Welter Wendt
(guilherme.wendt@unioeste.br)

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1. Introduction

Fibromyalgia (FM) is a chronic nociplastic pain syndrome characterized by widespread musculoskeletal pain, persistent fatigue, sleep disturbances, cognitive impairment, and a set of somatic complaints that meaningfully reduce quality of life.¹ Global prevalence is estimated at 2–4%, with a female predominance that varies by diagnostic criteria: the 1990 American College of Rheumatology (ACR) criteria, which are based on tender-point examination, typically yield female-to-male ratios of 7–9:1, whereas the symptom-based 2010 and 2016 ACR criteria, when applied to unselected community samples, yield ratios closer to 2:1, reflecting selection rather than biological sex differences alone.² Decades of investigation have not produced a definitive laboratory or imaging marker, and diagnosis still depends on symptom-based clinical criteria.³

Traditional accounts of FM emphasized central nervous system (CNS) dysfunction, particularly central sensitization, a state of heightened excitability of nociceptive pathways that amplifies pain perception.¹ Evidence accumulated over the past decade, however, indicates that peripheral mechanisms such as immune activation, neuroendocrine dysregulation, and metabolic disturbances also contribute to disease pathogenesis.⁴ Within this broader peripheral picture, the gut microbiome has emerged as a meaningful modulator of pain, mood, and systemic inflammation through bidirectional gut–brain axis crosstalk.^{5,6}

The gut–brain axis links the gastrointestinal tract and the CNS through neural pathways (vagal and spinal afferents), endocrine pathways (including the hypothalamic–pituitary–adrenal axis), immune signaling (cytokines and chemokines), and microbial metabolites.⁷ Dysbiosis—understood as a shift in the composition, diversity, or functional capacity of the gut microbiota—has been implicated in several neurological and psychiatric conditions, including depression, anxiety, autism spectrum disorders, and chronic pain syndromes.^{4,7} In FM, multiple lines of evidence now suggest a relevant role for the gut microbiota in modulating pain sensitivity, neuroinflammation, and psychological symptoms, though causality in humans remains to be fully established.

A recent translational study by Cai *et al.*² showed that fecal microbiota transplantation (FMT) from women with FM into germ-free mice reproduced key features of the human disease, including mechanical hypersensitivity, peripheral immune activation, and metabolomic changes. Conversely, replacing the FM-associated microbiota with healthy donor communities reversed these phenotypes in mice and reduced pain in an open-label human

pilot.^{2,8} These findings argue that the gut microbiota is not only a correlate but a mechanistic contributor to FM pathophysiology.

Parallel work in metabolomics has identified microbial metabolites, particularly bile acids and short-chain fatty acids (SCFAs), that are altered in FM and correlate with symptom severity.^{9–11} These metabolites can modulate immune cell function, blood–brain barrier integrity, microglial activation, and neurotransmitter synthesis, offering plausible molecular links between gut dysbiosis and CNS dysfunction.¹¹ Psychological comorbidities such as depression and anxiety—present in up to 70% of patients with FM—are also associated with specific microbiome signatures and may respond to microbiome-targeted interventions.^{5,12,13}

Nevertheless, several important challenges remain. Microbiome studies in FM differ widely in design, sequencing methods, sample size, and control of confounders such as diet, medications, and comorbidities.^{6,11,14} Diagnostic criteria have evolved over time, and the absence of objective biomarkers complicates both clinical care and research cohort definition.³ The translation of microbiome findings into therapy requires large, well-controlled trials with standardized protocols.¹⁵

This review synthesizes current evidence on the gut–brain axis in FM across four connected domains: (i) neurobiological mechanisms linking gut-derived signals to CNS dysfunction; (ii) microbiome compositional changes and their functional consequences; (iii) bidirectional relationships between psychological comorbidities and gut dysbiosis; and (iv) the limitations of current diagnostic criteria and the potential of emerging biomarker approaches. Evidence from animal models, observational human studies, interventional trials, and systematic reviews is integrated to identify gaps and priorities for future research and clinical translation.

2. Literature search strategy

This review is narrative in design and was not conducted according to a formal systematic review protocol. A literature search was conducted in PubMed, Scopus, and Web of Science databases, using combinations of the following search terms: “fibromyalgia,” “gut microbiome,” “gut microbiota,” “gut–brain axis,” “dysbiosis,” “short-chain fatty acids,” “bile acids,” “fecal microbiota transplantation,” “probiotics,” “synbiotics,” “nociplastic pain,” “neuroinflammation,” “central sensitization,” “psychological comorbidities,” and “biomarkers.”

The search covered publications from January 2018 through June 2026. No language restriction was applied

during the database search; however, only English-language full-text articles were ultimately included. References of retrieved articles were also manually screened to identify additional relevant sources. Inclusion criteria were: (i) peer-reviewed original research articles, systematic reviews, and meta-analyses addressing the gut–brain axis, gut microbiome composition, microbial metabolites, or microbiome-targeted interventions in FM; (ii) studies published between January 2018 and June 2026; and (iii) articles available in full text. Animal studies were included when they provided mechanistic evidence directly relevant to FM pathophysiology.

Exclusion criteria were: conference abstracts, case reports, and articles that did not specifically address FM or the gut–brain axis. Because no formal Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol or predefined study selection algorithm was applied, this review is subject to the selection biases inherent in narrative reviews, and findings should be interpreted accordingly.

Study quality was not formally assessed using standardized tools such as AMSTAR-2, RoB 2, or GRADE; the strength of evidence is therefore evaluated narratively, based on study design, sample size, control conditions, and methodological transparency, as discussed throughout the text.

3. Historical evolution of fibromyalgia conceptualization

Recognition of FM as a distinct clinical entity has evolved over the past century. Early descriptions of widespread musculoskeletal pain date to the 19th century, when terms such as “muscular rheumatism” and “fibrositis” were used to label conditions of chronic pain and tender points in the absence of inflammatory or structural pathology.¹ The label “fibromyalgia” was introduced in the 1970s to reflect the absence of demonstrable tissue inflammation, shifting the focus from peripheral tissue pathology to CNS pain processing abnormalities.¹

Publication of the ACR 1990 classification criteria was an important milestone, defining FM as widespread pain plus at least 11 of 18 tender points on physical examination.³ These criteria standardized research and clinical recognition but were criticized for relying on a subjective tender-point examination and for failing to capture the non-pain symptoms, including fatigue, cognitive dysfunction, and sleep disturbances, that patients consistently report.³

The ACR 2010 and 2016 revisions removed the tender-point examination and introduced the Widespread Pain

Index (WPI) and Symptom Severity Scale (SSS), which assess pain distribution and associated symptoms in a more patient-centered manner.³ These changes improved diagnostic sensitivity and specificity while reducing examiner-dependent variability.³

Advances in neuroimaging, neurophysiology, and molecular biology reshaped the conceptual basis of the disorder. Functional magnetic resonance imaging (fMRI) studies have shown altered pain processing in patients with FM, with stronger activation of pain-related brain regions in response to both noxious and non-noxious stimuli, consistent with central sensitization.¹ Quantitative sensory testing has confirmed reduced pain thresholds and impaired descending pain modulation.¹ These findings led the International Association for the Study of Pain to classify FM as a “nociceptive pain” condition, that is, pain arising from altered nociceptive processing without tissue damage or inflammation.¹⁶

Recognition of peripheral and systemic factors in FM pathogenesis is more recent. Studies of immune activation, cytokine dysregulation, and neuroendocrine abnormalities have challenged purely CNS-centric models.^{4,11} The identification of gut microbiome alterations in FM represents the most recent shift, integrating peripheral immune and metabolic mechanisms with CNS dysfunction through the gut–brain axis.^{2,5,6} This view places FM within the broader frame of gut–brain–immune axis disorders.⁷

4. Neurobiological mechanisms of the gut–brain axis in fibromyalgia

4.1. Central sensitization and nociceptive pain

Central sensitization, defined as hyperexcitability of central nociceptive neurons that amplifies pain perception, is widely considered a core neurophysiological mechanism in FM.¹ It is characterized by reduced pain thresholds, exaggerated responses to noxious stimuli (hyperalgesia), and pain triggered by normally innocuous stimuli (allodynia).¹ fMRI studies have consistently shown stronger activation of pain-processing regions, including the insula, anterior cingulate cortex, and somatosensory cortex, in patients with FM compared with healthy controls.^{1,5}

Several pathways allow the gut microbiome to influence central sensitization. Microbial metabolites, especially SCFAs such as acetate, propionate, and butyrate, can cross the blood–brain barrier and influence neuronal excitability and synaptic plasticity.^{4,7} Bacterial fermentation products, bile acids modified by gut microbes, and microbial cell-wall components can also signal through the vagus nerve and the systemic circulation to modify central pain processing.

^{4,7}

4.2. Neuroinflammation and microglial activation

Neuroinflammation, particularly microglial activation in the spinal cord and brain, contributes to chronic pain states, including FM.¹ As the resident immune cells of the CNS, microglia can adopt pro-inflammatory phenotypes in response to peripheral immune signals, releasing cytokines, chemokines, and reactive oxygen species that enhance neuronal excitability and synaptic transmission in pain pathways.¹

4.3. Immune activation and peripheral-to-central signaling

The translational study by Cai *et al.*² provided compelling experimental evidence implicating gut microbiota in FM pathogenesis through immune-mediated mechanisms, primarily in germ-free murine models. Fecal microbiota from patients with FM was transplanted into germ-free mice, which developed mechanical hypersensitivity and thermal hyperalgesia comparable to the human phenotype. These mice also showed peripheral immune activation, with elevated serum interleukin (IL)-6 and tumor necrosis factor α and altered immune cell profiles, alongside metabolomic changes that paralleled those observed in patients. Replacing the FM-associated microbiota with healthy donor microbiota in mice reversed pain behaviors and normalized immune profiles. These findings indicate that gut microbiota are capable of driving pain through immune activation in animal models and suggest that peripheral immune signals, mediated by microbial metabolites, lipopolysaccharide (LPS), or other bacterial products, communicate with the CNS to modulate nociceptive processing. The precise molecular routes remain under investigation but likely include cytokine signaling, vagal afferent activation, and blood–brain barrier modulation.^{7,11}

4.4. Neurotransmitter dysregulation

Dysregulation of key neurotransmitter systems, including serotonin, γ -aminobutyric acid (GABA), and glutamate, has been implicated in FM pathophysiology.^{1,4} Serotonin plays critical roles in pain modulation, mood regulation, and sleep; GABA is the primary inhibitory neurotransmitter in the CNS; and glutamate is the major excitatory neurotransmitter.¹ Imbalances—namely reduced serotonergic and GABAergic inhibition coupled with enhanced glutamatergic excitation—contribute to central sensitization, pain amplification, and neuropsychiatric symptoms.¹

The gut microbiome is a major producer of neurotransmitter precursors and neuroactive compounds. Approximately 90% of the body's serotonin is synthesized

in the gastrointestinal tract by enterochromaffin cells in a process influenced by gut microbiota.⁷ Several bacterial species directly synthesize GABA, while others modulate glutamate metabolism.⁷ In a human FMT trial, transplantation of healthy donor microbiota into patients with FM was associated with significant increases in serum serotonin and GABA and a decrease in glutamate, alongside reductions in pain intensity and improvements in quality of life.⁸ These findings suggest that microbiome-targeted interventions may restore neurotransmitter balance and alleviate FM symptoms through gut–brain signaling.⁸

4.5. Neuroendocrine and autonomic dysfunction

Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis and autonomic nervous system is well documented in FM and contributes to stress sensitivity, fatigue, and pain amplification.^{1,4,17} Patients with FM often show diminished cortisol responses to stress, altered diurnal cortisol rhythms, and autonomic imbalance characterized by reduced heart rate variability and sympathetic predominance.¹

The gut microbiome can modulate HPA axis function through vagal afferent signaling, immune-mediated cytokine release, and direct effects of microbial metabolites on neuroendocrine cells.⁷ In a randomized controlled trial of synbiotic supplementation (combined probiotics and prebiotics) in patients with FM, treatment was associated with normalization of cortisol dynamics, reduced C-reactive protein and IL-6 levels, and improvements in perceived stress, anxiety, and depression.¹⁸ These results suggest that microbiome-targeted interventions can act on multiple pathophysiological domains in FM simultaneously.¹⁸

These mechanisms together describe a multi-level gut–brain–immune circuit in which microbial composition and metabolites shape immune signaling and central excitability in ways that map onto pain, mood, and neuroendocrine features of FM. Convergent findings across animal models, human observational studies, and early-phase interventional work position the gut microbiome upstream of several of these signaling pathways, rather than as a passive correlate of FM symptoms.

5. Microbiome composition and dysbiosis in fibromyalgia

5.1. Taxonomic alterations

Multiple case–control studies have documented significant alterations in gut microbiome composition in patients with FM compared with healthy controls, although specific taxonomic findings vary across cohorts.^{5,6,11,12} A consistent pattern is reduced abundance of beneficial commensal

bacteria alongside increased abundance of potentially pro-inflammatory taxa.^{5,6}

In a well-characterized case–control study combining 16S ribosomal RNA (rRNA) gene sequencing with fMRI and psychological assessments, Nhu *et al.*⁵ identified several key taxonomic differences. Patients with FM showed decreased abundance of *Faecalibacterium*, a genus known for anti-inflammatory properties and production of butyrate, an SCFA that maintains intestinal barrier integrity and modulates immune function.⁵ They also showed increased abundance of *Phascolarctobacterium* and *Lachnoclostridium*, with *Phascolarctobacterium* abundance positively correlated with depressive symptom scores and with altered resting-state functional connectivity in brain salience networks.⁵ These findings suggest that specific microbial taxa may influence both pain processing and psychological comorbidities through gut–brain signaling.⁵

Systematic reviews of human microbiome studies in FM note that dysbiosis is a consistent finding even when the specific taxa implicated vary across studies, reflecting differences in sequencing methods, geographic populations, dietary patterns, and medication use.^{6,11,12}

5.2. Bile acid metabolism and secondary bile acids

Bile acids are steroid molecules synthesized in the liver from cholesterol and extensively modified by gut bacteria, and they have emerged as key mediators of gut–brain axis crosstalk in FM.^{9,19} Primary bile acids (e.g., cholic acid and chenodeoxycholic acid) are conjugated and secreted into the intestine, where gut bacteria deconjugate and convert them into secondary bile acids (e.g., deoxycholic acid and lithocholic acid).¹⁹ As signaling molecules, bile acids activate nuclear receptors (e.g., farnesoid X receptor [FXR]) and G-protein-coupled receptors (e.g., Takeda G protein-coupled receptor 5), modulating immune function, metabolism, and neuroinflammation.¹⁹

Minerbi *et al.*¹⁹ showed in a metabolomics study that patients with FM exhibit significantly altered serum bile acid profiles, with elevated levels of secondary bile acids and depletion of α -muricholic acid. The severity of bile acid alterations correlated quantitatively with symptom severity, pain intensity, and fatigue.¹⁹ Machine learning algorithms trained on bile acid profiles discriminated patients with FM from controls with high accuracy, indicating their potential as diagnostic biomarkers.¹⁹ Specific bile acid signatures were also associated with distinct gut bacterial taxa, suggesting that microbial dysbiosis drives altered bile acid metabolism in FM.¹⁹

Jakobsson *et al.*⁹ extended these findings by showing that elevated microbially produced secondary bile acids in patients with FM were associated with increased IgG

autoantibody levels (anti-satellite glial cell IgG) and poorer mental well-being. This work implicates bile acid–immune interactions in the pathogenesis of both somatic and psychological symptoms.⁹ The pathways linking altered bile acids to FM pathophysiology likely involve modulation of immune cell function, blood–brain barrier permeability, and neuroinflammation, but mechanistic details remain to be fully defined.¹⁹

5.3. Short-chain fatty acids and metabolite profiles

Short-chain fatty acids, primarily acetate, propionate, and butyrate, are major metabolic products of bacterial fermentation of dietary fibers and resistant starches.^{4,7} SCFAs influence intestinal barrier integrity, immune cell differentiation and function, energy metabolism, and CNS function through histone deacetylase inhibition and G-protein-coupled receptor activation (e.g., GPR43, GPR41, and GPR109A).^{4,7}

Reports of altered SCFA production in FM are inconsistent across studies, with some studies describing reduced butyrate-producing taxa and others finding no significant differences.^{11,12} A reduction in anti-inflammatory SCFA production due to gut dysbiosis is a plausible mechanism by which the microbiome could contribute to neuroinflammation and pain amplification in FM, but direct human evidence remains limited.^{11,12}

Beyond SCFAs and bile acids, broader metabolomic profiling has revealed alterations in amino acid metabolism, lipid profiles, and other microbial metabolites in patients with FM.^{2,11} The FMT study by Cai *et al.*² showed that germ-free mice receiving microbiota from patients with FM exhibited metabolomic changes paralleling those in human patients, including alterations in tryptophan metabolism, lipid signaling, and energy metabolism. These perturbations were associated with immune activation and pain behaviors, suggesting that multiple classes of microbial metabolites may act through interconnected immune and neuroendocrine pathways.²

Table 1 summarizes key metabolite studies in FM.

5.4. Intestinal permeability and barrier function

Increased intestinal permeability, often termed “leaky gut,” has been implicated in FM and may connect gut dysbiosis to systemic inflammation and CNS dysfunction.^{3,11,12} The intestinal epithelial barrier, maintained by tight junction proteins and a protective mucus layer, typically prevents translocation of bacteria, bacterial products such as LPS, and dietary antigens into the systemic circulation.¹¹ Disruption of this barrier can lead to low-grade systemic inflammation, immune activation, and increased blood–brain barrier permeability, allowing peripheral inflammatory signals to reach the CNS.¹¹

Table 1. Summary of key metabolite studies in fibromyalgia

Study (year)	Metabolite focus	Key findings	Limitations
Minerbi <i>et al.</i> ¹⁹ (2023)	Serum bile acids	Elevated secondary bile acids; depleted α -muricholic acid; machine-learning classifier discriminated FM from healthy controls with high accuracy; correlated with symptom severity	Single geographically restricted cohort; no external validation
Jakobsson <i>et al.</i> ⁹ (2026)	Bile acids + SCFAs + IgG autoantibodies	Elevated microbially produced secondary bile acids; associated with increased anti-satellite glial cell IgG and poorer mental well-being scores	Cross-sectional; causality cannot be established
Cai <i>et al.</i> ² (2025)	Broad metabolomics (e.g., tryptophan, lipids)	FM microbiota transplant to mice reproduced metabolomic changes seen in patients; reversed by healthy donor microbiota	Animal model; mechanistic relevance to humans unclear
Various (reviewed in Minerbi <i>et al.</i> ¹¹ [2024])	SCFAs (e.g., butyrate, propionate)	Reduced butyrate-producing taxa (<i>Faecalibacterium</i>) in FM; inconsistent SCFA findings across studies; plausible link to neuroinflammation	Indirect evidence; few direct SCFA measurements in FM cohorts

Abbreviations: FM: Fibromyalgia; SCFA: Short-chain fatty acid.

Several studies have reported elevated serum levels of LPS-binding protein and zonulin—biomarkers of intestinal permeability—in patients with FM.^{11,12} Gut dysbiosis, particularly reduced abundance of butyrate-producing bacteria such as *Faecalibacterium*, may compromise barrier function, given that butyrate is a critical energy source for colonocytes and promotes tight junction integrity.^{5,11} Systematic reviews have noted associations between intestinal dysbiosis, increased gut permeability, and psychological distress in FM, although the directionality and causality of these relationships are not yet established.¹²

5.5. Methodological considerations and heterogeneity

Despite the consistency of dysbiosis as a finding in FM, substantial heterogeneity exists across studies in specific taxonomic findings, effect sizes, and functional interpretation. This heterogeneity arises from several sources. Many studies have been limited by small sample sizes ($n < 50$), which reduces power to detect taxonomic differences and increases susceptibility to false positives. Variability in DNA extraction protocols, sequencing platforms (16S rRNA gene sequencing versus shotgun metagenomics), bioinformatics pipelines, and taxonomic databases produces inconsistent results across studies. Diet, medications (especially antibiotics, proton pump inhibitors, and opioids), comorbid conditions (e.g., irritable bowel syndrome, obesity, and psychiatric disorders), and lifestyle factors (e.g., physical activity and sleep quality) all shape gut microbiome composition but are often inadequately controlled or reported. Gut

microbiome composition also varies substantially across geographic regions, ethnicities, and dietary patterns, complicating cross-study comparisons. Most studies are cross-sectional, which precludes assessment of temporal dynamics, causality, and microbiome stability over time.

Critical reviews and systematic syntheses have emphasized these limitations and called for large, well-controlled, longitudinal studies with standardized protocols, detailed metadata, and functional validation of taxonomic findings.^{6,11,12,14} Despite these gaps, the convergence of evidence from independent cohorts, animal models, and interventional trials supports a putative association between gut dysbiosis and FM pathophysiology.^{2,5,6}

Table 2 presents the summary of key human microbiome studies in FM.

6. Psychological comorbidities: Anxiety, depression, and gut–brain interactions

6.1. Prevalence and clinical impact

Psychological comorbidities, particularly depression and anxiety, are highly prevalent in FM and influence disease severity, functional outcomes, and quality of life.^{5,12,13} Epidemiological studies report that 40–70% of patients with FM experience clinically significant depressive symptoms, with higher rates in tertiary care settings.¹³ Anxiety disorders are similarly common, affecting roughly 30–50% of patients.¹²

Consistent with the upper end of this range, a treatment–outcome study of 411 patients with FM enrolled

Table 2. Summary of key human microbiome studies in fibromyalgia

Study (year)	Design; n	Key microbiome findings	Limitations
Nhu <i>et al.</i> ⁵ (2024)	Case–control with fMRI; n = 57	Increased <i>Phascolarctobacterium</i> (correlated with depression) and <i>Lachnospirillum</i> ; decreased <i>Faecalibacterium</i> ; linked to brain network changes	Small sample size; cross-sectional; confounders not fully controlled
Cai <i>et al.</i> ² (2025)	FMT germ-free mice + human pilot; n = 31 FM donors	FM microbiota induces mechanical hypersensitivity, peripheral immune activation, metabolomic changes in mice; reversed by healthy microbiota	Mouse model; germ-free conditions differ from clinical FM; human pilot uncontrolled
Palma-Ordóñez <i>et al.</i> ⁶ (2024)	Systematic review (10 studies)	Consistent dysbiosis across cohorts; reduced alpha-diversity; altered Firmicutes/Bacteroidetes; variability in specific taxa	Heterogeneity of included studies; different sequencing methods; confounders variable
Waterman <i>et al.</i> ²¹ (2025)	Narrative review	Reports <i>Helicobacter pylori</i> as a potential biomarker; microbiome alterations in FM similar to IBS; SIBO association	Narrative review; no formal synthesis

Abbreviations: FM: Fibromyalgia; fMRI: Functional magnetic resonance imaging; FMT: Fecal microbiota transplantation; IBS: Irritable bowel syndrome; SIBO: Small intestinal bacterial overgrowth.

in a tertiary-care multicomponent treatment program reported that 73.2% scored above the threshold for elevated depressive symptoms on the Center for Epidemiologic Studies Depression Scale at baseline. This reflects a treatment-seeking, severity-enriched sample assessed by a self-report screening instrument rather than a clinical diagnosis of major depressive disorder, and is therefore not directly comparable to community-based prevalence estimates.¹³ Higher baseline depression scores predicted poorer functional outcomes after a multicomponent treatment program, even after controlling for pain severity and other clinical variables.¹³ Patients whose depression was effectively treated during the program, however, showed significant improvements in functional status at five-month follow-up, suggesting that depression is a modifiable risk factor for poor outcomes in FM.¹³

The bidirectional relationship between pain and psychological symptoms is well established. Chronic pain can trigger or worsen depression and anxiety through sleep disruption, functional impairment, and social isolation, while depression and anxiety can amplify pain perception via altered descending pain modulation, increased attention to pain, and catastrophizing.^{1,12} Emerging evidence suggests that gut microbiome dysbiosis may be a shared mechanism linking pain and psychological symptoms in FM.^{5,12}

6.2. Microbiome–brain network associations

Nhu *et al.*⁵ provided novel insight into the relationships between gut microbiome composition, psychological symptoms, and brain network function in FM. Using 16S rRNA gene sequencing, psychological assessments (e.g., Beck Depression Inventory, State-Trait Anxiety Inventory), and resting-state fMRI, they showed that specific gut bacterial taxa were associated with depressive symptom severity and with altered functional connectivity in brain networks involved in emotional processing and pain modulation. Increased abundance of *Phascolarctobacterium* in patients with FM correlated positively with Beck Depression Inventory scores and was associated with altered functional connectivity in the salience network, a brain network critical for integrating emotional and sensory information and directing attention to salient stimuli. The salience network, anchored by the anterior insula and anterior cingulate cortex, is consistently implicated in both chronic pain and depression. These findings suggest that gut microbiome composition may shape psychological symptoms in FM through modulation of brain network function, possibly via metabolite-mediated signaling.⁵

Systematic reviews synthesizing evidence across multiple studies conclude that intestinal dysbiosis and increased gut permeability in FM are associated with

higher levels of psychological distress, although the directionality and causality of these relationships remain to be clarified.¹² Proposed mechanisms include microbiome-mediated modulation of neurotransmitter synthesis (particularly serotonin and GABA), immune-mediated cytokine signaling affecting brain function, and direct effects of microbial metabolites on neuronal excitability and synaptic plasticity.^{7,12}

6.3. Metabolite–immune–mood interactions

Jakobsson *et al.*⁹ identified interactions between microbially produced bile acids, immune activation, and mental well-being in FM.⁹ Elevated levels of secondary bile acids in patients with FM were associated with increased anti-satellite glial cell IgG autoantibody titers and poorer scores on mental well-being questionnaires. These findings suggest that altered bile acid metabolism may contribute to psychological symptoms through immune-mediated mechanisms, possibly involving autoimmune processes or chronic low-grade inflammation.⁹

Bile acids can cross the blood–brain barrier and directly modulate neuronal function through activation of FXR and Takeda G protein-coupled receptor 5 expressed in the brain.¹⁹ They also influence peripheral immune cell function and cytokine production, which can indirectly affect CNS function through immune-to-brain signaling.¹⁹ The association between bile acid alterations, autoantibody production, and mental well-being in FM suggests that microbiome-driven metabolic and immune perturbations may contribute to the burden of psychological comorbidities in this population.⁹

6.4. Intervention effects on psychological outcomes

Microbiome-targeted interventions show early evidence of improving psychological outcomes in FM, consistent with a role for gut dysbiosis in neuropsychiatric symptoms, though placebo-controlled evidence is required before causal conclusions can be drawn.^{8,18} In a randomized controlled trial, eight weeks of synbiotic supplementation (combined *Lactobacillus* and *Bifidobacterium* strains + fructooligosaccharides) in patients with FM produced significant reductions in perceived stress, anxiety, and depression scores compared with baseline.¹⁸ These psychological improvements occurred alongside normalization of HPA axis function, reduced inflammatory markers (e.g., C-reactive protein, IL-6), and improvements in quality of life.¹⁸

In the open-label FMT trial by Fang *et al.*⁸, transplantation of healthy donor microbiota into patients with FM was associated with increases in serum serotonin and GABA, decreases in glutamate, and reductions in

pain intensity and quality-of-life impairment. The trial did not specifically report psychological outcomes, but the normalization of neurotransmitter profiles suggests potential benefits for mood and anxiety, given the roles of serotonin and GABA in emotional regulation.

These intervention studies are preliminary and limited by small sample sizes and the absence of placebo controls in some cases, but together, they provide proof-of-concept evidence that altering gut microbiome composition can modulate psychological symptom severity in FM.^{8,10,18} The mechanisms likely involve several routes acting in parallel: restoration of neurotransmitter balance, reduction of systemic inflammation, normalization of HPA axis function, and direct effects of microbial metabolites on brain function.^{7,12,18}

Systematic reviews emphasize the need for larger, well-controlled trials with assessment of both somatic and psychological outcomes before the therapeutic potential of microbiome-targeted interventions for psychological comorbidities in FM can be established.^{10,12} The convergence of observational and interventional evidence nonetheless supports the gut–brain axis as a promising therapeutic target.^{5,12,18}

7. Diagnostic criteria and emerging biomarker approaches

7.1. Current clinical diagnostic criteria

Fibromyalgia diagnosis remains primarily clinical, based on patient-reported symptoms and the exclusion of alternative diagnoses.³ The evolution of diagnostic criteria reflects an ongoing effort to improve sensitivity, specificity, and clinical utility while capturing the multidimensional nature of the disorder.³

The ACR 1990 classification criteria defined FM as chronic widespread pain (pain in all four body quadrants and the axial skeleton for more than three months) and tenderness at ≥ 11 of 18 specific tender points on digital palpation.³ These criteria standardized research and clinical recognition but were criticized for reliance on a subjective tender-point examination with poor inter-rater reliability, failure to capture non-pain symptoms (e.g., fatigue, cognitive dysfunction, sleep disturbances), exclusion of patients with fewer than 11 tender points despite otherwise typical presentations, and gender-related bias, as women generally exhibit a higher number of tender points than men.³

The ACR 2010 preliminary diagnostic criteria eliminated the tender-point examination and introduced the WPI, assessing the number of painful body regions (0–19), and the SSS, assessing fatigue, unrefreshed sleep,

cognitive symptoms, and somatic symptoms (0–12).³ FM is diagnosed when WPI ≥ 7 and SSS ≥ 5 , or WPI ≥ 3 –6 and SSS ≥ 9 , with symptoms present for more than three months and no alternative explanation.³ The ACR 2016 revision further refined these criteria by incorporating a generalized pain criterion (pain in at least four out of five body regions) and modifying the SSS to improve specificity, and is now widely used in both clinical practice and contemporary trials of microbiome-based interventions.^{3,8,13}

7.2. Limitations of symptom-based diagnosis

Although these criteria (as discussed in Section 7.1) improved on earlier tender-point-based approaches, FM diagnosis remains challenging because there are no definitive laboratory tests, imaging findings, or histopathological markers.³ Reliance on subjective symptom reporting can lead to diagnostic uncertainty, delays of years between symptom onset and diagnosis, and potential overlap with other chronic conditions—such as myalgic encephalomyelitis/chronic fatigue syndrome, irritable bowel syndrome, and autoimmune disorders.^{3,11,20}

Symptom-based criteria also do not capture underlying pathophysiological heterogeneity within the FM population.¹ Emerging evidence suggests that FM encompasses multiple pathophysiological subtypes characterized by distinct patterns of central sensitization, immune activation, psychological comorbidities, and microbiome dysbiosis.^{1,5,6} Objective biomarkers reflecting these mechanisms could allow more precise diagnosis, prognostic stratification, and personalized therapeutic selection.

7.3. Microbiome-based biomarkers

The consistent finding of gut microbiome dysbiosis in FM has prompted investigation of microbiome-based diagnostic biomarkers.^{5,6,21} Minerbi *et al.*¹⁹ compared the gut microbiomes of women with FM and healthy controls, identifying bacterial taxa whose abundance discriminated cases from controls and correlated with symptom severity; a machine-learning classifier built on these features achieved promising performance in cross-validation, although the cohort was geographically restricted and replication in independent populations is needed.¹⁹

Nhu *et al.*⁵ demonstrated that specific gut bacterial taxa, particularly *Phascolarctobacterium* and *Faecalibacterium*, were associated with FM diagnosis and symptom severity and were found to mediate relationships between gut dysbiosis and brain network alterations. Microbiome signatures may therefore function as both diagnostic markers and indicators of underlying pathophysiological mechanisms.

Critical reviews emphasize substantial challenges in translating microbiome findings into clinically useful diagnostic tests, including heterogeneity of findings across studies, the absence of standardized protocols for sample collection, processing, and analysis, confounding by diet and medications, the need for large independent validation cohorts, and unclear diagnostic thresholds.^{11,14} Despite this, the convergence of evidence from multiple studies supports continued investigation of microbiome-based biomarkers as adjunctive diagnostic tools.^{5,6}

7.4. Metabolomic and proteomic signatures

Metabolomic profiling has identified alterations in circulating metabolites in FM, with bile acid signatures showing particular promise.^{9,19} Minerbi *et al.*¹⁹ showed that serum bile acid profiles could discriminate patients with FM from healthy controls with high accuracy using machine learning, and that bile acid alterations correlated quantitatively with symptom severity, suggesting potential utility for monitoring disease activity and treatment response as well as for diagnosis.

Jakobsson *et al.*⁹ confirmed elevated secondary bile acids in an independent FM cohort and showed associations with autoantibody levels and mental well-being, further supporting the diagnostic and pathophysiological relevance of bile acid profiling. They noted that validation in larger, independent cohorts is needed before clinical implementation.

Proteomic approaches have also identified candidate biomarkers. Studies analyzing plasma protein profiles in women with FM have reported correlations between specific protein patterns and pain intensity, sensitivity, and psychological distress, although findings have been inconsistent across cohorts and analytic platforms. Specific proteins implicated in immune activation, inflammation, and neuronal signaling have been reported, although replication in independent cohorts and validation against standardized clinical phenotypes remain necessary.^{9,19}

7.5. Integrative multimodal approaches

Expert reviews and consensus statements have argued for integrative, multimodal approaches to FM diagnosis combining clinical assessment with objective biomarkers that reflect neurophysiological, immunological, metabolic, and microbiome perturbations.¹ Such approaches could address the pathophysiological heterogeneity of FM, allow for the identification of distinct subtypes, and guide personalized treatment.¹

Combining microbiome profiling with metabolomic signatures (e.g., bile acids, SCFAs), proteomic markers (e.g., cytokines, autoantibodies), and neurophysiological

assessments (e.g., quantitative sensory testing, neuroimaging) could provide a more comprehensive pathophysiological profile for individual patients.^{1,5,19} Machine learning and artificial intelligence may help integrate these high-dimensional datasets into clinically useful diagnostic and prognostic algorithms.¹⁹

Translating multimodal biomarker panels into clinical practice will require attention to cost, accessibility, standardization, regulatory approval, and demonstration of clinical utility beyond existing symptom-based criteria.¹⁴ Large, prospective studies with rigorous validation in diverse populations are necessary to move these approaches from research tools to clinical applications.¹⁴

It should be noted that the biomarker candidates described in this section—including microbiome signatures, bile acid profiles, and proteomic markers—should currently be classified as exploratory rather than clinically validated diagnostic tools. Available evidence is largely derived from small, geographically restricted cohorts without external validation. Reported diagnostic performance metrics (e.g., area under the curve, sensitivity, specificity) have been generated mainly through internal cross-validation, which can substantially overestimate real-world diagnostic accuracy. None of these biomarkers have been validated in independent external cohorts of sufficient size and diversity, and none have been tested against the incremental diagnostic utility provided by ACR 2010/2016 clinical criteria alone. Before these markers can inform clinical decisions, prospective validation studies with pre-specified performance thresholds and assessment of added clinical value are required.

8. Therapeutic implications: Microbiome-targeted interventions

8.1. Fecal microbiota transplantation

Fecal microbiota transplantation, the transfer of fecal material from a healthy donor to a recipient to restore a balanced gut microbiome, has emerged as a promising therapeutic approach for FM based on findings from animal models and early-phase human trials.^{2,8,10}

The translational study by Cai *et al.*² showed that FMT from patients with FM into germ-free mice induced pain behaviors and immune and metabolic alterations, and that replacing the FM microbiota with healthy donor microbiota reversed these phenotypes. This proof-of-concept evidence supports a causal contribution of the gut microbiome to at least the pain-related features of FM in mice, providing experimental rationale for human FMT trials, although translation from germ-free murine models to symptomatic patients carries well-known limitations.

Fang *et al.*⁸ conducted an open-label, randomized trial in which 45 participants with FM were allocated to either oral FMT capsules from healthy donors or a non-placebo control arm; the report does not provide a detailed description of what the control group received beyond standard care, which limits causal inference about the FMT intervention itself. Patients receiving FMT from healthy donors showed significant reductions in pain intensity, improvements in quality of life, and favorable changes in serum neurotransmitter profiles (increased serotonin and GABA, decreased glutamate) compared with baseline. The trial lacked a placebo control, which is a meaningful limitation given the placebo response in pain trials; however, the magnitude of clinical improvement and the associated biochemical changes suggest potential therapeutic effects.

A systematic review by Martín Pérez *et al.*¹⁰ evaluated the effectiveness of FMT in nociplastic pain conditions, including FM, chronic fatigue syndrome, and irritable bowel syndrome. The review included 13 studies with 409 participants and concluded that FMT may reduce pain intensity and fatigue and improve quality of life, particularly in FM and irritable bowel syndrome.¹⁰ Proposed mechanisms include restoration of gut microbial balance, modulation of systemic inflammation and neuroinflammation, and normalization of neurotransmitter signaling.¹⁰ They noted that current evidence is insufficient for widespread clinical use due to methodological limitations, small sample sizes, inconsistent outcomes, and variability in FMT protocols (e.g., donor selection, preparation methods, administration routes, dosing).¹⁰

Key obstacles for FMT in FM include the absence of large, placebo-controlled randomized trials; the lack of standardized protocols; uncertainty about optimal donor selection criteria; potential safety concerns regarding transmission of pathogens and long-term microbiome stability; and regulatory and ethical considerations. The convergence of mechanistic evidence from animal models with the early-phase human signals nonetheless supports continued investigation.

The available evidence for FMT in FM must be interpreted with considerable caution. The strongest mechanistic data derive from germ-free murine models, which differ fundamentally from symptomatic human FM in immune maturity, microbial baseline, and pain physiology. The only published human FMT trial (Fang *et al.*⁸) lacked a placebo arm, enrolled a relatively small sample size ($n = 45$), and did not report blinded outcome assessment. The magnitude of the reported placebo response in FM pain trials—typically 20–40%—suggests that uncontrolled trials cannot reliably attribute observed

improvements to FMT itself. Donor selection, preparation method, administration route, dosing frequency, and follow-up duration were not standardized. Safety data beyond the short term are absent. FMT should therefore be regarded as an experimental approach for FM pending rigorous placebo-controlled trials, and should not be used outside research settings.

8.2. Probiotic and synbiotic supplementation

Probiotic (live beneficial bacteria) and synbiotic (combined probiotic and prebiotic) supplementation are more accessible and scalable than FMT.¹⁸ Several studies have examined these interventions in FM with encouraging results.¹⁸

Hinchado *et al.*¹⁸ conducted a randomized controlled trial of synbiotic supplementation (combined *Lactobacillus* and *Bifidobacterium* strains + fructooligosaccharides) in patients with FM.¹⁸ After eight weeks, participants receiving synbiotics showed significant improvements in quality of life, reductions in perceived stress, anxiety, and depression, and favorable changes in immunoneuroendocrine markers, including normalization of cortisol dynamics and reduced inflammatory cytokines. The study also found that effects were influenced by co-diagnosis with chronic fatigue syndrome, indicating that patient subgroups may respond differentially to microbiome interventions.

A systematic review by Dipalma *et al.*⁴ explored human studies of microbiome modulation (e.g., probiotics, prebiotics, synbiotics, dietary interventions) targeting neuroinflammation, cognition, and mood in conditions relevant to FM. The review concluded that microbiome-targeted interventions show promise for improving psychological symptoms and cognitive function through modulation of neuroinflammation and neurotransmitter systems, but that evidence specific to FM remains limited.

Probiotic and synbiotic interventions have advantages in safety, accessibility, and ease of administration compared with FMT. Key limitations include heterogeneity in strains, doses, and formulations across studies; limited understanding of optimal strain selection; variable efficacy across individuals, possibly reflecting baseline microbiome composition and host factors; and a need for larger, longer-duration trials with comprehensive outcome assessment.

8.3. Metabolite-based therapies

Identification of specific microbial metabolites, particularly SCFAs and bile acids, as mediators of gut–brain axis crosstalk in FM has motivated investigation of metabolite-based therapeutic approaches.^{9,19}

Strategies aimed at enhancing endogenous SCFA

production, including increased dietary fiber intake and prebiotic supplementation, have been proposed as adjunctive approaches in FM, although direct trials with SCFA-specific clinical endpoints in this condition are lacking.^{4,7} Translation of SCFA-based strategies into human FM trials with well-defined microbiome and metabolite endpoints remains an open priority.^{4,7}

Bile acid modulation is another potential avenue. Given the associations between altered bile acid profiles, symptom severity, and immune activation in FM, interventions targeting bile acid metabolism, including bile acid sequestrants, FXR agonists, and dietary modifications affecting bile acid composition, merit investigation.^{9,19} No human trials of bile acid-targeted therapies in FM have been reported to date.¹⁹

Dietary strategies that modulate gut microbiome composition and metabolite production—such as the Mediterranean diet, a low-fermentable-oligosaccharides, disaccharides, monosaccharides, and polyols diet, or fiber supplementation—may also influence FM symptoms through gut–brain pathways, although rigorous controlled trials are lacking.^{4,11}

Table 3 presents the summary of interventional studies targeting the gut microbiome in FM.

9. Critical appraisal and methodological challenges

Formal assessment of study quality or risk of bias using standardized tools (e.g., AMSTAR-2 for systematic reviews, RoB 2 for randomized trials, ROBINS-I for observational studies, SYRCLE for animal studies, or GRADE for evidence certainty) was not performed in this narrative review. The risk of bias across included studies is therefore discussed qualitatively. It should be noted that the degree of certainty in the evidence supporting assertions about causation, diagnosis, and treatment potential may be lower than what is implied by narrative synthesis alone, given the predominance of small cross-sectional studies, open-label trials, and animal experiments in this literature.

Despite substantial progress, several methodological limitations constrain causal inference and clinical translation in this field.^{6,10–12,14}

Sample sizes have often been small ($n < 50$), reducing power to detect taxonomic differences and increasing the risk of false-positive findings; larger cohorts ($n > 100$) are needed for adequate power and subgroup analyses.^{6,11} Most studies are cross-sectional, which precludes assessment of temporal dynamics, causality, and microbiome stability over time; longitudinal designs tracking microbiome changes in relation to symptom fluctuations, treatment

Table 3. Summary of interventional studies targeting the gut microbiome in fibromyalgia

Study (year)	Intervention; <i>n</i>	Outcomes	Risk of bias
Fang <i>et al.</i> ⁸ (2024)	Open-label RCT; FMT (oral capsules) vs. standard care; <i>n</i> = 45	Significant reductions in pain (NRS) at 2–12 months; increased serum serotonin and GABA; decreased glutamate	High: No placebo control; open-label; no blinded outcome assessment; one site; no detailed control arm description
Hinchado <i>et al.</i> ¹⁸ (2023)	RCT; synbiotics (<i>Lactobacillus</i> + <i>Bifidobacterium</i> + fructooligosaccharides) vs. control; <i>n</i> not specified per arm	Reduced perceived stress, anxiety, depression; improved quality of life; normalized cortisol; reduced C-reactive protein and interleukin-6	Moderate: RCT but relatively small; subgroup by CFS comorbidity; short duration (eight weeks); self-reported outcomes
Martín Pérez <i>et al.</i> ¹⁰ (2025)	Systematic review; FMT in nociplastic pain; 13 studies, <i>n</i> = 409	FMT may reduce pain and fatigue in FM and IBS; improvements in quality of life; promising mechanistic signals	Reviews include low-quality primary studies; significant heterogeneity in protocols; mostly open-label trials
Dipalma <i>et al.</i> ⁴ (2025)	Systematic review; probiotics/prebiotics/synbiotics in neuroinflammation and mood	Microbiome-targeted interventions improve psychological symptoms and cognition through neuroinflammation modulation; limited FM-specific evidence	Narrative synthesis; indirect evidence from non-FM populations

Abbreviations: CFS: Chronic fatigue syndrome; FM: Fibromyalgia; FMT: Fecal microbiota transplantation; GABA: γ -aminobutyric acid; NRS: Numeric rating scale; IBS: Irritable bowel syndrome; RCT: Randomized controlled trial.

responses, and disease progression are essential to establish causal relationships.^{11,14}

Diet, medications (e.g., antibiotics, proton pump inhibitors, opioids, antidepressants), comorbid conditions (e.g., irritable bowel syndrome, obesity, psychiatric disorders), and lifestyle factors (e.g., physical activity, sleep quality, stress) shape gut microbiome composition but are often inadequately controlled or reported.^{6,11,14} Variability in DNA extraction protocols, sequencing platforms (16S rRNA gene sequencing versus shotgun metagenomics), bioinformatics pipelines, and taxonomic databases also complicates cross-study comparisons and meta-analyses; standardized protocols and reporting guidelines (e.g., the STORMS checklist) are needed.^{11,14}

Most studies report taxonomic differences without functional validation through metabolomics, metatranscriptomics, or mechanistic experiments; integration of multi-omics approaches and functional assays is essential to move beyond descriptive associations.^{11,14} Pain and psychological outcomes are highly susceptible to placebo effects, yet several FMT and probiotic trials in FM have lacked placebo controls, making rigorous double-blind designs essential for definitive assessment of therapeutic efficacy.^{8,10}

Additionally, most studies were conducted in Western populations with limited ethnic and geographic diversity; thus, replication in diverse populations is needed to

assess generalizability and identify population-specific microbiome signatures.¹¹ Although several pathways linking gut microbiota to CNS function have been proposed (e.g., metabolites, immune signaling, vagal afferents, neuroendocrine modulation), the relative contributions and interactions of these pathways in FM are not yet fully understood; mechanistic studies using animal models, human experimental medicine approaches, and systems biology integration are needed.^{7,11}

Addressing these challenges will require coordinated multi-center efforts with standardized protocols, large samples, detailed phenotyping, longitudinal designs, and integration of multi-omics and mechanistic approaches.^{11,14} International consortia and data-sharing initiatives could accelerate progress and enable rigorous meta-analyses.¹¹

10. Future directions and research priorities

Several key research priorities emerge from the current state of evidence and the gaps identified above.

- Large, well-powered prospective studies with detailed phenotyping (e.g., clinical symptoms, psychological assessments, quantitative sensory testing, neuroimaging), multi-omics profiling (e.g., metagenomics, metabolomics, proteomics, transcriptomics), and detailed metadata collection (e.g., diet, medications, comorbidities, lifestyle) are needed to establish reliable microbiome signatures,

assess temporal dynamics, and identify causal relationships.^{11,14}

- (ii) Integration of human observational findings with mechanistic experiments in animal models, *in vitro* systems, and human experimental medicine studies is needed to clarify the pathways linking gut microbiota to pain, neuroinflammation, and psychological symptoms.^{2,11} Key questions include which microbial metabolites are most relevant, what the relative contributions of immune, neural, and endocrine pathways are, and how host genetics and environmental factors modulate gut–brain interactions.
- (iii) FM likely encompasses multiple pathophysiological subtypes with distinct microbiome signatures, immune profiles, and treatment responses.^{1,5,6} Data-driven clustering approaches that integrate clinical, microbiome, metabolomic, and neuroimaging data could identify clinically meaningful subtypes and inform personalized treatment.¹
- (iv) Large, multi-center, double-blind, placebo-controlled randomized trials of FMT, probiotics and synbiotics, and metabolite-based therapies are needed to determine therapeutic efficacy, optimal protocols, and safety.¹⁰ Trials should include comprehensive outcome assessment (e.g., pain, fatigue, psychological symptoms, quality of life, functional status) and mechanistic endpoints (e.g., microbiome composition, metabolites, immune markers, neurotransmitters).¹⁰
- (v) Independent validation of candidate diagnostic and prognostic biomarkers (e.g., microbiome signatures, bile acids, proteomics) in large, diverse cohorts is essential before clinical implementation.¹⁹ Studies should assess diagnostic accuracy, clinical utility, cost-effectiveness, and integration with existing diagnostic criteria.
- (vi) Controlled trials of dietary interventions (e.g., Mediterranean diet, fiber supplementation, a low-fermentable-oligosaccharides, disaccharides, monosaccharides, and polyols diet) and lifestyle modifications (e.g., exercise, stress reduction, sleep hygiene) that modulate gut microbiome composition and function could provide accessible, low-risk therapeutic strategies.^{4,11}
- (vii) Most research to date has focused on adult women in Western countries.¹¹ Studies in pediatric populations, men, and diverse ethnic and geographic groups are needed to assess generalizability and identify population-specific factors.¹¹
- (viii) Investigation of gut–brain axis mechanisms in relation to established FM treatments (pharmacotherapy, cognitive-behavioral therapy, exercise) could identify predictors of treatment response and opportunities

for combination approaches.¹

- (ix) Development and adoption of standardized protocols for sample collection, processing, sequencing, and analysis, along with data-sharing initiatives and public repositories, would support meta-analyses and accelerate discovery.^{11,14}
- (x) Engagement with regulatory agencies, industry partners, and patient advocacy groups will be essential to establish translational pathways for microbiome-based diagnostics and therapeutics.¹⁰

11. Conclusion

The gut–brain axis has become a central pathophysiological pathway in FM, linking intestinal microbiome dysbiosis, altered metabolite production, immune activation, and CNS dysfunction. Evidence from animal models, observational human studies, and early-phase trials indicates that gut microbiota may contribute to pain perception, neuroinflammation, neurotransmitter balance, and psychological symptoms through multiple connected mechanisms, with causal evidence being primarily derived from animal experiments and requiring validation in rigorous human trials. Specific taxonomic alterations, particularly reduced abundance of beneficial commensal bacteria such as *Faecalibacterium* and increased abundance of potentially pro-inflammatory taxa, have been consistently documented in patients with FM. Metabolomic profiling has identified alterations in bile acid and SCFA profiles that correlate with symptom severity and may serve as diagnostic biomarkers and therapeutic targets.

Psychological comorbidities, particularly depression and anxiety, are highly prevalent in FM and are associated with specific microbiome signatures, altered brain network connectivity, and poorer functional outcomes. Microbiome-targeted interventions, including FMT and synbiotic supplementation, have shown early promise in improving both somatic and psychological symptoms, supporting the gut–brain axis as a viable therapeutic target. Current evidence is limited by small sample sizes, methodological heterogeneity, and the lack of rigorous placebo-controlled trials.

Diagnosis of FM remains primarily clinical and symptom-based in the absence of definitive biomarkers. Emerging multimodal approaches integrating microbiome profiling, metabolomics, proteomics, and neurophysiological assessments hold promise as objective diagnostic aids and for the identification of pathophysiological subtypes to guide personalized treatment. Substantial validation in large, diverse cohorts is required before clinical implementation.

The field is at a transitional moment, with sound mechanistic foundations and promising early-phase clinical signals set against methodological challenges that must be addressed before findings can be translated into clinical practice. Large, longitudinal, well-controlled studies with standardized protocols, detailed phenotyping, and mechanistic validation are essential priorities. Integration of gut–brain axis insights with existing neurobiological, psychological, and therapeutic frameworks may help move the care of FM toward precision medicine approaches that address the complex, multifactorial nature of the condition. Current evidence supports a potentially modifiable mechanistic contribution of the gut microbiome to FM pathophysiology, with implications for therapeutic innovation that must be weighed against the methodological limitations of the existing literature.

Among the strategies reviewed, the most actionable therapeutic targets are restoration of a eubiotic microbiome through FMT or synbiotic supplementation, modulation of SCFA and secondary bile acid metabolism to dampen neuroinflammation and normalize neurotransmitter signaling, and correction of HPA axis and immune dysregulation through microbiome-directed interventions; multimodal biomarker panels further offer a route toward patient stratification that could match these strategies to the subgroups most likely to benefit.

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The authors declare they have no competing interests.

Author Contributions

Conceptualization: Victoria Tischer Sawka, Guilherme Welter Wendt

Supervision: Guilherme Welter Wendt

Writing—original draft: Victoria Tischer Sawka

Writing—review & editing: Victoria Tischer Sawka, Guilherme Welter Wendt

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