Review

Therapeutic advances in fibromyalgia: one year in review 2026

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Received on May 14, 2026; accepted in revised form on May 26, 2026.

Clin Exp Rheumatol 2026; 44: 1069-1081.

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Key words: fibromyalgia, central sensitisation, pharmacological therapy, complementary therapies, neuromodulation, gut-brain axis, phenotype-driven treatment

Competing interests: none declared.

ABSTRACT

Fibromyalgia (FM) is a chronic nociplastic pain syndrome characterised by widespread pain, fatigue, sleep disturbances and cognitive impairment, with a significant impact on health-related quality of life (HRQoL). Despite the availability of several therapeutic options, management remains challenging and often requires a personalised and multidimensional approach.

Over the past year, growing attention has been directed toward both emerging pharmacological strategies and innovative non-pharmacological interventions. Among pharmacological treatments, low-dose naltrexone (LDN) continues to show potential benefits in modulating neuroinflammation and central sensitisation. Cannabinoids and other neuromodulatory agents have also been investigated, with preliminary evidence suggesting a role in symptom control. In addition, novel approaches involving serotonergic modulation, including psychedelic compounds such as psilocybin, are being explored in early-phase studies.

Intravenous lidocaine remains a potential option in selected refractory patients, although recent evidence has not substantially expanded its clinical role. Similarly, interest in nutraceuticals and antioxidant compounds is increasing, particularly in relation to mitochondrial function and oxidative stress.

Non-pharmacological interventions remain a cornerstone of FM management. Recent studies highlight the importance of structured physical activity, including supervised exercise programs and digitally supported rehabilitation. Emerging approaches such as neuromodulation techniques, including non-invasive brain stimulation and vagal nerve stimulation, are gaining attention. Complementary and body-oriented interventions are also being explored for their potential impact on pain perception and emotional well-being.

Overall, current evidence supports a biopsychosocial and multimodal approach, integrating pharmacological and non-pharmacological strategies tailored to individual patient profiles. Future research should focus on better phenotyping of patients and on identifying predictors of treatment response to optimise personalised management.

Introduction

Fibromyalgia (FM) is a chronic and complex pain syndrome, currently classified among nociplastic pain conditions, characterised by widespread musculoskeletal pain, fatigue, non-restorative sleep, and cognitive disturbance. The disorder predominantly affects women and is frequently associated with multiple comorbidities, including mood disorders, irritable bowel syndrome and other functional somatic syndromes. Despite its high prevalence and significant impact on HRQoL, FM remains a challenging condition in both diagnosis and management.

Over the last decade, increasing evidence has shifted the understanding of FM from a purely peripheral or inflammatory condition to a disorder involving central pain processing, with alterations in pain modulation, neuroinflammation and possible contributions from neuroendocrine and autonomic

dysfunction. However, the heterogeneity of clinical presentations suggests that FM likely represents a spectrum of conditions rather than a single entity, reinforcing the need for individualised therapeutic strategies.

From a therapeutic perspective, current management is based on a multidimensional approach integrating pharmacological and non-pharmacological interventions. Nevertheless, conventional treatments often provide only partial relief, and a substantial proportion of patients remain symptomatic, highlighting the need for novel and more effective strategies.

In this context, the past year has seen growing interest in emerging therapies targeting central sensitisation, neuroimmune mechanisms, and the biopsychosocial dimensions of the disease. At the same time, innovations in non-pharmacological approaches, including digital health interventions and neuromodulation techniques, are contributing to reshape the therapeutic landscape.

The aim of this review is to provide an updated overview of the most relevant therapeutic advances in FM over the last year, with a particular focus on emerging treatments and innovative approaches that may contribute to a more personalised and effective management of this condition.

Pharmacological therapies in fibromyalgia: innovations and repositioning

In recent years, advances in the pharmacological management of FM have been driven less by the introduction of entirely new drug classes and more by a progressive refinement of existing treatments, the development of new formulations, and an improved understanding of the neurobiological mechanisms underlying nociplastic pain. The 2025 literature confirms this trend, highlighting a shift toward mechanism-based and domain-oriented therapeutic strategies.

Among emerging pharmacological options, the most relevant innovation is represented by sublingual cyclobenzaprine (TNX-102 SL), which received regulatory approval in the United States in August 2025 (1). Unlike traditional oral formulations, this sublingual preparation allows rapid transmucosal absorption and a pharmacokinetic profile better aligned with nighttime administration, targeting sleep disturbances, one of the core domains of FM.

Evidence supporting its use derives from randomised trials and recent meta-analyses. In a pooled analysis of four randomised controlled trials including 1,684 patients, TNX-102 SL significantly increased the proportion of patients achieving ≥30% and ≥50% pain reduction compared with placebo, and improved patient global impression of change (2). However, the impact on overall disease burden, as measured by the revised Fibromyalgia Impact Questionnaire (FIQR), was not consistently significant, suggesting that its clinical benefit may be more domain-specific, particularly on pain and sleep. A second meta-analysis involving nearly 2,000 patients confirmed modest but statistically significant improvements in daily pain scores, sleep quality and quality of life, with a generally acceptable tolerability profile, although transient oral adverse effects and sedation were more frequent (3).

These findings position TNX-102 SL as a meaningful innovation from a regulatory and pharmacokinetic standpoint, but not as a breakthrough in terms of overall disease modification.

Another area of renewed interest concerns skeletal muscle relaxants, a heterogeneous class including cyclobenzaprine, tizanidine, and baclofen. A recent meta-analysis of 14 randomised trials (n=1,851) evaluated their effects across multiple domains, including pain, sleep, fatigue, depressive symptoms, and HRQoL (4). The results indicate a small but statistically significant reduction in pain, accompanied by improvements in sleep and, to a lesser extent, depressive symptoms. In contrast, the effect on fatigue and global disease impact appears limited.

Importantly, these benefits are counterbalanced by a higher incidence of adverse events, particularly sedation, fatigue and sensory disturbances, leading to increased treatment discontinuation. Within this class, cyclobenzaprine remains the most extensively studied agent, whereas data on other muscle relaxants are sparse and less conclusive. Overall, these findings support a selective and phenotype-driven use, particularly in patients with prominent sleep disturbances or myofascial features.

Among repositioned therapies, low-dose naltrexone (LDN) represents one of the most discussed options. Although a recent meta-analysis did not demonstrate superiority over controls in chronic pain overall, a signal of efficacy emerged in the FM subgroup (5). The proposed mechanism involves modulation of microglial activation and downstream neuroinflammatory pathways, including reduction of pro-inflammatory cytokines and central sensitisation processes. However, the current evidence remains limited by small sample sizes, heterogeneity, and methodological constraints.

Intravenous lidocaine remains a potential option in selected refractory patients, particularly in the context of central sensitisation, although recent evidence has not substantially expanded its clinical role and its use remains limited to specialised settings.

An even more experimental field is that of psychedelic compounds, including psilocybin, LSD (lysergic acid diethylamide), and DMT (N,N-dimethyltryptamine). Recent reviews suggest that these agents may modulate pain perception through 5-HT2A (serotonin) receptor activation, enhancement of neuroplasticity, and reorganisation of affective-cognitive networks involved in chronic pain (6). Their potential relevance to FM lies in the overlap between nociplastic pain, mood disorders, and altered central processing. However, clinical evidence in FM is currently lacking.

At the interface between pharmacology and supportive therapy, nutraceutical approaches continue to generate interest. High-dose omega-3 supplementation has been associated with improvements in pain indices (WPI, VAS), symptom severity, and functional scores (FIQR), possibly through anti-inflammatory and membrane-modulating effects (7). Similarly, combinations including CoQ10 (coenzyme Q10), magnesium, and tryptophan have shown beneficial effects on pain, sleep and functional impact, although prima-

Table I. Pharmacological therapies in FM.

Therapy/class	Mechanism of action	Evidence (2025)	Clinical benefit	Limitations	Suggested clinical phenotype
SNRIs (duloxetine, milnacipran)	Descending modulation; neuroimmune effects	(9, 10)	~30–50% responders; pain + mood	Variable response	Anxiety/depression
Gabapentinoids (pregabalin, gabapentin)	α2δ calcium channels	(11, 12)	Pain + sleep	Sedation, weight gain	Sleep disturbance
Cyclobenzaprine SL (TNX-102 SL)	Sleep modulation	(2, 3)	Pain + sleep	Limited FIQR effect	Hyperarousal
Skeletal muscle relaxants	Central muscle tone	(4)	Small effect	AEs, discontinuation	Myofascial
Low-dose naltrexone (LDN)	Microglial modulation	(5)	Subgroup benefit	Limited data	Neuroimmune
Psychedelics	5-HT2A, neuroplasticity	(6)	Theoretical rationale	No FM trials	Pain + trauma
Omega-3 (high-dose)	Anti-inflammatory	(7)	Pain reduction	Small studies	Metabolic
CoQ10 + Mg + tryptophan	Mitochondrial support	(8)	Pain + sleep	No fatigue effect	Fatigue phenotype

Pharmacological therapies in FM provide moderate and domain-specific benefits, mainly on pain, sleep and mood, with substantial interindividual variability and limited impact on overall disease burden.

Table II. Manual and complementary therapies in fibromyalgia (2025 evidence).

Therapy/approach	Mechanism of action	Evidence (2025)	Clinical benefit	Limitations	Suggested clinical phenotype
Acupuncture	Modulation of nociceptive pathways; endogenous opioid release; autonomic regulation	Systematic reviews and comparative studies (52, 56)	Small but significant pain reduction; improvement in function	Heterogeneity; sham effects	Chronic pain, somatic symptoms
Dry needling	Trigger point inactivation; reduction of peripheral nociceptive input	Clinical/comparative studies (52)	Local pain reduction	Operator-dependent; limited long-term data	Myofascial phenotype
Myofascial release/manual therapy	Soft tissue modulation; muscle relaxation; central pain modulation	Systematic/ observational data (53)	Short-term improvement in pain, stiffness, sleep	Limited durability	Muscle tension, stiffness
Massage/lymphatic techniques	Autonomic modulation; ↓ sympathetic activity; improved circulation	Clinical studies/ reviews (53)	Improvement in pain, anxiety, sleep	Poor standardisation	Dysautonomia, anxiety
Body-oriented therapies	Modulation of interoception and body representation	Mechanistic/qualitative studies (43, 54)	Improved body awareness and coping	Limited RCT evidence	High somatic awareness
Multimodal complementary approaches	Integrated peripheral + central modulation	Meta-analyses/ integrative studies (39-43)	Greater benefit when integrated	Hard to isolate effects	Multidomain phenotype

Manual and complementary therapies show modest but clinically relevant effects, mainly on pain, muscle tension and sleep. The 2025 evidence supports their use as adjunctive and tailored interventions, particularly when integrated into multimodal treatment programs rather than used as stand-alone therapies. RCT: randomised controlled trial.

ry endpoints such as fatigue were not consistently improved (8).

In parallel with these emerging strategies, established pharmacological treatments, particularly serotonin-norepinephrine reuptake inhibitors (SNRIs) and gabapentinoids, remain the cornerstone of FM management, although their role has been reinterpreted in light of recent evidence.

Overall, these agents provide moderate efficacy, with approximately 30-50% of patients achieving clinically meaningful pain reduction, but with substantial interindividual variability (9, 10). This has led to a paradigm shift from a disease-centred to a patient- and mechanism-centred approach, in which treatment is tailored according to dominant symptom domains and comorbidities.

SNRIs, such as duloxetine and milnacipran, act by enhancing descending inhibitory pathways through increased availability of serotonin and norepinephrine. Recent data highlight the particularly relevant role of the noradrenergic system in modulating spinal nociceptive transmission (10). In addition to their neuronal effects, monoaminergic agents may also influence neuroimmune mechanisms, including microglial activation and cytokine production (*e.g.* TNF-α, IL-1β, IL-6), thereby contributing to the modulation of central sensitisation (10).

Gabapentinoids, particularly pregabalin, remain among the most evidence-supported agents for nociplastic pain, acting via modulation of voltage-gated calcium channels (α2δ subunit) and reduction of excitatory neurotransmitter release. However, recent literature has increasingly focused on safety. Gabapentin has been associated with weight gain in up to 25% of patients, sedation, and increased risk of respiratory depression, particularly when combined with opioids or other sedatives (11). Despite these concerns, a large observational study involving more than 57,000 older adults found no increased risk of falls compared with duloxetine (HR 0.52), suggesting a complex and context-dependent safety profile (12).

Taken together, the 2025 evidence does not introduce a large number of new pharmacological agents but significantly refines the clinical positioning of existing therapies, emphasising the need for individualised, multidomain, and mechanism-oriented treatment strategies.

Most agents act through central mechanisms, including modulation of descending inhibitory pathways (SNRIs), synaptic transmission (gabapentinoids) and neuroimmune processes. Emerging therapies, such as low-dose naltrexone and psychedelics, further support the role of neuroinflammation and neuroplasticity, although evidence remains preliminary.

Treatment response is highly variable across clinical profiles, with different drug classes showing greater efficacy in specific clinical profiles (*e.g.* mood disorders, sleep disturbance, myofascial features).

Collectively, the 2025 evidence supports a transition toward a mechanism-based, pharmacological approach, integrated within multimodal management strategies (Fig. 1).

Take-home messages

- No major breakthrough drugs emerged in 2025, but the field is evolving through *new* formulations, drug repositioning, and mechanism-based approaches rather than novel molecules.
- SNRIs and gabapentinoids remain the pharmacological backbone, with moderate efficacy and significant interindividual variability, confirming the need for personalised treatment strategies.
- Cyclobenzaprine sublingual (TNX-102 SL) represents the most relevant innovation, improving pain and sleep, although its impact on overall disease burden remains limited.
- Emerging therapies, such as low-dose naltrexone and psychedelics, highlight a shift toward neuroimmune modulation and central mechanisms, but current evidence remains preliminary.
- Overall, the 2025 evidence supports a transition from a "one drug fits all" approach to a phenotype-driven, multidomain treatment model, targeting pain, sleep, mood, and fatigue.

Non-pharmacological therapies in fibromyalgia: current innovations and multimodal approaches

Exercise and rehabilitation

Exercise remains the most consistently supported non-pharmacological intervention in FM. The 2025 literature confirms that the main innovation is not simply "exercise", but how exercise is delivered, supervised and maintained over time. Notably, exercise has a crucial role, being able to improve some etiopathogenetic mechanisms as well as related behaviours/conditions (stress, obesity, unhealthy lifestyle). Furthermore, exercise helps to prevent/manage other chronic diseases, which may affect FM patients, and to foster well-being and healthy ageing. According to the available literature, the most effective programs result from a structured and personalised exercise prescription, encompassing a clear definition of modality, intensity, frequency, duration and progression of physical activity, tailored on FM patient's conditions, FM severity, needs and clinical goals. Since FM symptoms can represent actual barriers to exercise execution, progression of exercise dose is mandatory to foster patient compliance. It is crucial to start with a low-demanding protocol and progressively increase intensity only when the patient feels she/he can manage it without adverse effects (13). Comparative exercise studies also suggest that different exercise modalities may variably influence pain, fatigue and functional outcomes, supporting the need for individualised rehabilitation strategies in FM patients (14). Digital and supervised rehabilitation represents one of the most relevant 2025 developments. Zhang *et al*. (15) evaluated a remote network technology-supervised exercise program combined with pregabalin and duloxetine. Both supervised and unsupervised groups improved, but long-term supervised exercise produced more reliable improvements in pain, sleep and HRQoL, supporting the role of adherence, feedback and structured follow-up.

Aquatic exercise also remains relevant. Although some studies included mixed rheumatic populations or ME/CFS cohorts, the overall message is that low-to-moderate intensity, self-paced aquatic activity may be useful for patients with fatigue, poor tolerance to land-based exercise or fear of symptom worsening (16, 17). The AquaHigh trial, however, did not show superiority of high-intensity interval aquatic training over moderate continuous aquatic training in Patient-Reported Outcome Measures (PROMs) and quality-adjusted life years (QALYs), suggesting that intensity alone is not the key factor (17).

Mind-body exercise approaches are also gaining attention. Qigong and Ba-Duan-Jin studies suggest improvements in pain, fatigue, sleep, mood and function. In the RCT comparing Ba-Duan-Jin with pregabalin, both interventions improved pain, fatigue, sleep and depression, with sustained benefits at follow-up; exploratory functional Magnetic Resonance Imaging (fMRI) data suggested possible modulation of brain networks, especially the parahippocampal gyrus (18, 19).

FIBROWALK and BBAT (Basic Body Awareness Therapy) represent structured multidomain rehabilitation models. FIBROWALK studies support the feasibility of online or blended programs, while BBAT delivered online showed effects comparable to face-to-face therapy (20). These findings point toward accessible, scalable and phenotype-oriented rehabilitation.

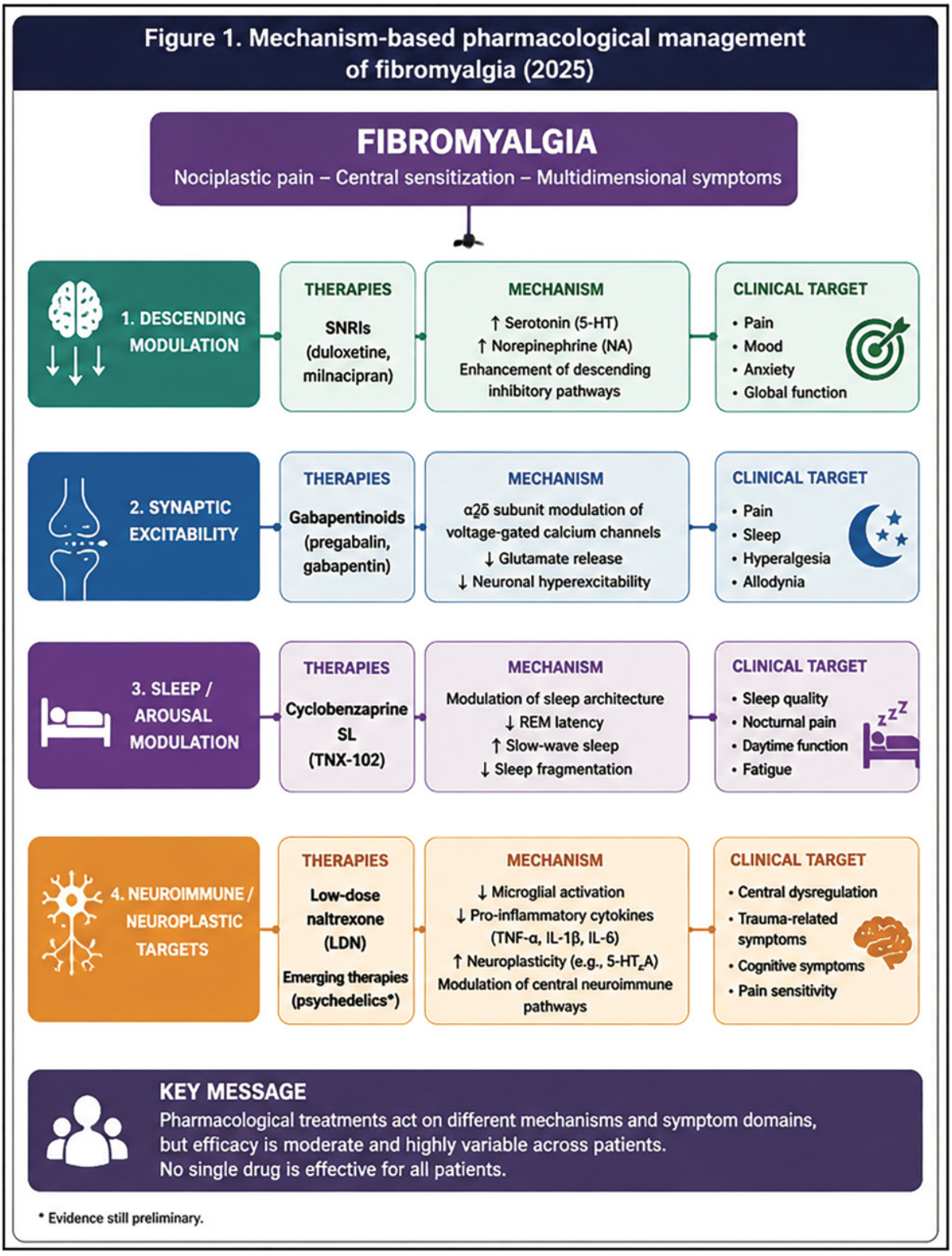


Fig. 1. Mechanism-based pharmacological management of fibromyalgia.
Pharmacological treatment of fibromyalgia is increasingly conceptualised as a mechanism-based approach, targeting distinct components of nociplastic pain, including impaired descending inhibition, synaptic hyperexcitability, sleep dysregulation, and neuroimmune activation. Current drug classes act on specific neurobiological pathways. SNRIs enhance descending inhibitory control, gabapentinoids reduce neuronal hyperexcitability, and cyclobenzaprine primarily modulates sleep architecture. Emerging therapies, such as low-dose naltrexone and psychedelic compounds, further support the relevance of neuroinflammation and neuroplasticity in symptom generation. However, these mechanisms translate into domain-specific clinical effects, mainly involving pain, sleep, and mood, with limited impact on fatigue and global disease burden. A key finding from the 2025 literature is the marked interindividual variability in treatment response, suggesting that pharmacological efficacy is strongly dependent on the patient's dominant clinical and biological profile. Accordingly, pharmacological therapy should not be viewed as a uniform strategy, but rather as a targeted intervention aligned with underlying mechanisms and integrated within a broader multimodal treatment framework.

Clinical implications: exercise should remain first-line, but the 2025 evidence supports moving from generic advice to structured, supervised, personalised and digitally supported programs, especially in patients with low adherence or high fatigue (13, 20, 21) (Fig. 2).

Take-home messages

- Exercise remains the most evidence-supported non-pharmacological intervention in FM, particularly when personalised and progressively adapted to symptom severity (13-20).
- The 2025 literature emphasises that treatment delivery (supervision, adherence and digital support) may be more important than the specific type of exercise itself (14, 19, 20).
- Mind–body approaches such as Qigong and Ba-Duan-Jin may improve pain, fatigue, sleep and emotional well-being, with possible effects on brain network modulation (18, 19).
- Structured and phenotype-oriented rehabilitation programs should be preferred over generic exercise recommendations, especially in patients with fatigue, low adherence or fear-avoidance behaviors (13, 19-21).

Instrumental therapies and neuromodulation

The 2025 literature shows increasing interest in instrumental and neuromodulatory approaches, but the evidence remains heterogeneous. These interventions target central sensitisation, autonomic imbalance and neuroplasticity, but most data derive from small trials or heterogeneous reviews.

Among neuromodulation techniques, Transcranial Direct Current Stimulation (tDCS) is one of the most studied. A narrative review including 31 RCTs suggests that tDCS, particularly targeting Primary Motor Cortex (M1) or Dorsolateral Prefrontal Cortex (DLPFC), may reduce pain, although effects on fatigue, mood and sleep are less consistent (22). A recent RCT (randomised controlled trial) showed that dual site tDCS combined with therapeutic exercise improved fatigue, sleep quality and HRQoL (23). However, another study found that adding M1-tDCS to mindfulness abolished some beneficial effects of mindfulness on emotion regulation, indicating that protocol interactions are complex (24).

Neurofeedback is an emerging approach. EEG-based neurofeedback targeting the pregenual anterior cingulate cortex (pgACC) and the primary somatosensory cortex (S1) connectivity was feasible and safe, but showed comparable improvements in active and placebo groups, questioning current efficacy despite strong mechanistic rationale (25).

Vagal nerve stimulation is also increasingly studied. Reviews on transcutaneous auricular Vagal Nerve Stimulation (taVNS or tVNS) suggest potential benefit across chronic pain conditions, including FM, likely through modulation of autonomic balance and inflammatory pathways, but protocols and outcomes remain highly variable (26).

Virtual reality (VR) and photobiomodulation are additional emerging areas. VR-based interventions show potential improvements in pain, fatigue and HRQoL, although evidence remains heterogeneous (27, 28). Photobiomodulation appears promising, particularly for fatigue, but lacks standardisation (29).

Shockwave therapy has also been explored. Although some studies did not show statistically significant differences, clinically meaningful improvements in pain and patient-reported outcomes suggest a possible role in selected patients (30).

Practical interpretation: instrumental therapies should be considered adjunctive and phenotype-driven, particularly in refractory patients, but are currently limited by heterogeneity and lack of standardised protocols (Fig. 2).

Take-home messages

- Neuromodulation techniques such as tDCS and vagal nerve stimulation target central sensitisation, autonomic imbalance and neuroplasticity mechanisms (22-26).
- Current evidence suggests modest but potentially clinically relevant benefits on pain, fatigue, sleep and HRQoL, particularly when combined with rehabilitation strategies (22).
- Neurofeedback, virtual reality and photobiomodulation remain promising but still experimental approaches, limited by heterogeneous protocols and small studies (24, 26-28).
- Instrumental therapies should currently be considered adjunctive and phenotype-driven interventions rather than stand-alone treatments (21-30).

Oxygen-ozone therapy

Oxygen-ozone therapy represents an emerging complementary intervention receiving increasing attention, although evidence remains preliminary. Observational and retrospective studies on major autohaemotherapy (MAH) consistently show improvements in pain, functional impact and HRQoL. Kuculmez (31) reported a reduction in VAS from 9 to 3 after treatment, with sustained benefits at 3 months. Üşen *et al*. (32) confirmed improvements in pain, FIQ, fatigue, sleep and mood, with partial relapse at 6 months. Tertemiz *et al*. (33), in a larger cohort, observed significant improvements in VAS, FIQ, SF-36 and PSQI.

The most innovative contribution comes from a randomised double-blind trial using ozonated water enema, which showed significant improvements in pain, WPI, anxiety and sleep, along with a reduction in duloxetine use and measurable changes in the gut microbiome (34).

Proposed mechanisms include modulation of oxidative stress, activation of antioxidant pathways, mitochondrial effects, and regulation of inflammatory mediators. The microbiota findings also support a potential interaction with the gut-brain axis.

Clinical positioning: oxygen-ozone therapy may be considered an emerging complementary option, particularly in refractory or multisystem patients, but remains limited by small sample sizes, heterogeneous protocols and lack of long-term controlled data (Fig. 2).

Take-home messages

- Observational and retrospective studies suggest that oxygen-ozone therapy may improve pain, fatigue, sleep and HRQoL in FM patients (31-33).
- The randomised trial on ozonated water enema represents one of the most innovative findings of 2025, suggesting possible modulation of the gut microbiome and gut-brain axis (34).

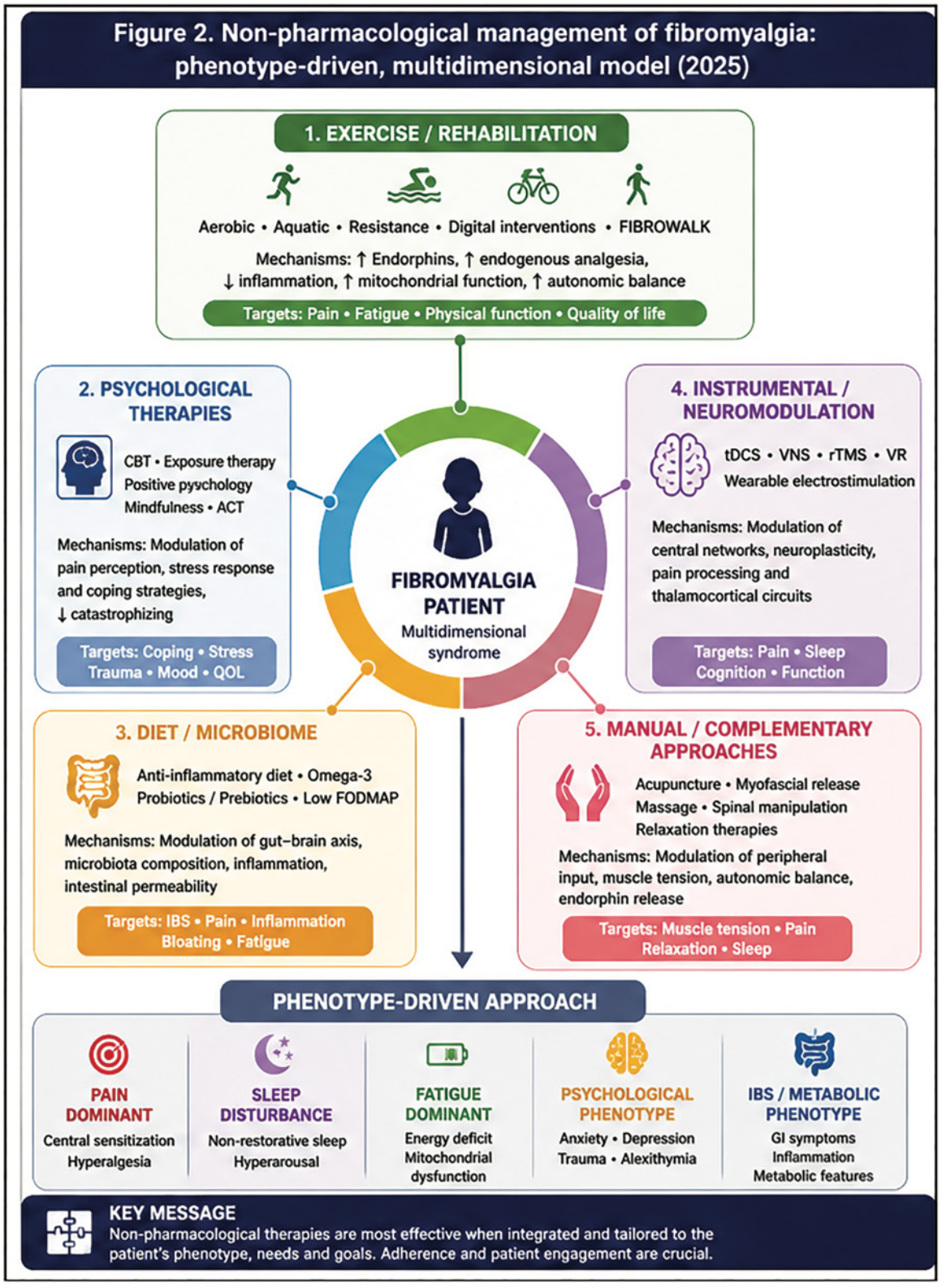


Fig. 2. Multidimensional, phenotype-driven model of non-pharmacological therapies in fibromyalgia
Non-pharmacological management of fibromyalgia is based on a multidimensional framework, integrating exercise, psychological therapies, diet and microbiome modulation, neuromodulation techniques, and manual/complementary approaches. Each intervention targets specific pathophysiological mechanisms, including central sensitisation, autonomic dysregulation, mitochondrial dysfunction, neuroimmune activation, and gut-brain axis alterations, and contributes to the modulation of key clinical domains such as pain, fatigue, sleep disturbance, and functional impairment. A central concept emerging from the 2025 literature is that treatment response is strongly phenotype-dependent. Clinically relevant subgroups include pain-dominant, sleep disturbance, fatigue-dominant, psychological, and IBS/metabolic phenotypes. Accordingly, non-pharmacological therapies are most effective when selected and combined based on the patient's dominant clinical profile, rather than applied as uniform interventions.

- Proposed mechanisms include antioxidant effects, modulation of inflammatory mediators and mitochondrial support (31-34).
- Despite encouraging findings, current evidence remains preliminary and limited by small sample sizes and lack of long-term controlled studies (31-34).

Psychological, educational and self-management interventions

Psychological and educational interventions remain central in FM management, and the 2025 literature reinforces their role not as "ancillary" treatments, but as therapies targeting key mechanisms of symptom amplification, including catastrophising, fear-avoidance, emotional dysregulation, alexithymia and maladaptive illness behaviour (35-37).

A major theme is the continued relevance of Cognitive Behavioural Therapy (CBT)-based approaches, particularly when delivered in accessible formats. Hedman-Lagerlöf *et al*. (36) evaluated the cost-effectiveness of online exposure-based CBT compared with traditional online CBT in fibromyalgia. The study suggested that exposure-based CBT may be cost-effective, although differences in clinical efficacy and costs between the two approaches were not statistically robust, indicating that the main value may lie in accessibility and scalability rather than superiority of one CBT model over another.

Psychological treatment is also expanding beyond classical CBT. A randomised pilot study comparing brief psychodynamic therapy with CBT showed that both approaches reduced anxiety symptoms and pain intensity, with no clear superiority of one over the other. Interestingly, alexithymia and attachment dimensions predicted post-treatment pain and psychological outcomes, suggesting that emotional processing and relational patterns may influence therapeutic response (36-37). This is clinically relevant because it supports a more personalised psychological approach rather than a uniform CBT-only model.

The role of alexithymia is further supported by a prospective observational study in which duloxetine combined with aerobic exercise improved both pain and alexithymia scores over six months. The correlation between reduction in alexithymia and pain improvement suggests that difficulty in identifying and expressing emotions may be linked to symptom persistence and treatment response (37). In the context of FM, this strengthens the rationale for interventions targeting emotional awareness, body perception and affective regulation. Recent best-practice recommendations further emphasise the importance of tailoring psychological interventions according to emotional processing, coping strategies and patient-specific clinical characteristics (38).

Among newer psychological approaches, positive psychotherapy has been evaluated in an RCT including 72 patients. A 10-session program significantly improved pain perception, daily functioning and mental health compared with controls, with significant effects on VAS, FIQ and General Health Questionnaire-28 (GHQ-28) domains including anxiety, depression, social functioning and somatic symptoms (39). Although replication is needed, this study is important because it shifts the focus from symptom control alone to resilience, resources and positive coping.

Relaxation-based interventions also continue to show benefit. Progressive muscle relaxation exercises applied twice weekly for eight weeks, significantly improved pain, kinesiophobia and functional status in an RCT of 85 patients (40). This supports their role in patients with fear of movement, muscle tension and high autonomic arousal, especially when integrated into broader rehabilitation programs.

Educational and self-management interventions represent another important area. A systematic review and meta-analysis focused on health education interventions showed significant reductions in pain intensity and improvements in disease impact and quality of life (41). A second meta-analysis evaluating the addition of structured educational programs to standard fibromyalgia treatment confirmed benefits on symptom severity, depression, anxiety, sleep quality and physical function (42). These findings suggest that education is not simply informative, but may act therapeutically by improving symptom interpretation, coping and adherence.

Qualitative evidence further clarifies why self-management programs work. Hu *et al*. (43) showed that patients experience self-management interventions as complex and multidimensional, with group cohesion, personalisation and post-intervention support emerging as key determinants of success. The lack of continued support after structured programs was identified as a major barrier, reinforcing the need for long-term follow-up rather than isolated short interventions.

Finally, the 2025 literature highlights the relevance of trauma and psychological comorbidity. A systematic review on FM and post-traumatic stress disorder (PTSD) confirmed an association between PTSD and FM, with some evidence linking PTSD to greater symptom severity (44). This supports the need to screen for trauma-related symptoms and to consider trauma-informed psychological approaches in selected patients.

Clinical positioning: psychological interventions should be selected according to the dominant phenotype. CBT and exposure-based CBT may be particularly useful in patients with fear-avoidance, catastrophising and disability; psychodynamic or emotionally focused approaches may be considered when alexithymia, relational vulnerability or trauma-related features are prominent; relaxation and positive psychotherapy may be useful in patients with autonomic arousal, anxiety and low self-efficacy. Overall, the 2025 evidence supports a shift from generic psychological support to individualised psychological treatment.

Take-home messages

- Psychological interventions remain a core component of FM management and increasingly target emotional regulation, catastrophising, trauma and maladaptive illness behaviour (35-42).
- CBT-based interventions remain supported, but emerging evidence suggests that psychodynamic, posi-

tive psychology and emotionally focused approaches may also be useful in selected phenotypes (35-37).
- Educational and self-management interventions appear therapeutically relevant beyond simple information delivery, improving coping strategies, symptom interpretation and adherence (39-43).
- The 2025 literature supports a shift toward individualised and trauma-informed psychological approaches rather than uniform psychological support models (35, 36, 42).

Diet, nutrition and gut microbiome

Dietary and nutritional approaches are increasingly investigated in FM, particularly in relation to the gut-brain axis, low-grade inflammation and metabolic factors, although the overall quality of evidence remains heterogeneous and often limited by small sample sizes and lack of standardised protocols.

A central area of investigation concerns FM in association with irritable bowel syndrome (IBS). A systematic review and meta-analysis evaluating interventions in patients with comorbid FM-IBS showed that pharmacological treatments (including pregabalin and cyclobenzaprine) significantly reduced pain scores, whereas dietary interventions produced mixed results, with benefit limited to selected subgroups (45). Probiotics did not demonstrate significant benefit compared with placebo, suggesting that microbiota-targeted interventions may not be universally effective but could be relevant in specific phenotypes. The relevance of the gut-brain axis is further supported by emerging data linking gastrointestinal function, oral health and systemic inflammation to central sensitisation mechanisms. A recent systematic review also highlighted the potential role of Mediterranean and low-antigen anti-inflammatory dietary patterns in modulating FM symptoms through metabolic and inflammatory pathways (46). A recent review highlighted how alterations in the gut microbiota and oral microbiome may contribute to neuroinflammation and chronic pain states, including FM, through immune activation, cytokine release and neural signalling pathways (47).

One of the most innovative contributions in 2025 comes from a randomised double-blind trial evaluating ozonated water enema, which demonstrated significant improvements in pain, WPI, anxiety and sleep, along with a reduction in duloxetine use and measurable changes in the gut microbiome composition (34).

Nutritional supplementation has also been explored. A randomised clinical study on high-dose omega-3 fatty acids reported significant improvements in pain intensity, WPI, symptom severity and FIQ scores, with associated changes in serum calcium and magnesium levels (7). Similarly, a trial evaluating a combination of coenzyme Q10, magnesium and tryptophan suggested improvements in pain, sleep and functional impact, although fatigue (primary endpoint) was not significantly improved (8).

Additional indirect evidence comes from broader intervention studies. A systematic review on non-pharmacological strategies for sleep disturbance in FM identified exercise, weight loss and behavioural interventions as potentially beneficial, highlighting the role of metabolic and lifestyle factors in symptom modulation (48).

Emerging perspectives also include more experimental approaches. A comprehensive review on chronic pain management discussed faecal microbiota transplantation (FMT) as a potential future strategy to modulate the gut microbiome in chronic pain conditions, including FM, although current evidence remains preliminary (49). Similarly, research on psychedelic-assisted therapy in IBS suggests that targeting gut-brain interactions and central processing may have implications for FM, particularly in overlapping conditions (50).

Overall, the 2025 literature reinforces the concept that diet is not a primary stand-alone therapy, but rather a modulator of disease expression, acting through gut microbiota composition, immune and inflammatory pathways, metabolic and micronutrient balance, and gut-brain signalling

Clinical positioning: dietary and microbiome-related interventions should be considered in a tailored manner, particularly in patients with IBS, dysbiosis, metabolic abnormalities or prominent gastrointestinal symptoms. Nutritional supplementation (*e.g.* omega-3, CoQ10-based combinations) may provide additional benefit in selected patients, but current evidence does not support routine use. More robust and standardised trials are needed to define their role in clinical practice. Emerging observational and preclinical evidence has also raised interest in GLP-1 receptor agonists as potential modulators of pain, fatigue and neuroinflammation in FM, although dedicated clinical trials are still lacking and their role remains speculative (51)

Take-home messages
- Increasing evidence supports a role of the gut-brain axis, microbiota alterations and metabolic factors in FM symptom modulation (45, 47).
- Nutritional interventions and supplementation (*e.g.* omega-3, CoQ10-based combinations) may provide benefit in selected phenotypes, although evidence remains heterogeneous (7, 8).
- Emerging approaches such as microbiota modulation and GLP-1 receptor agonists suggest potential interactions between metabolism, neuroinflammation and chronic pain mechanisms (51).
- Dietary and microbiome-related approaches should currently be considered adjunctive and personalised interventions rather than stand-alone therapies (45-47).

Manual and other complementary therapies

Manual and complementary therapies remain widely used in FM, and the 2025 literature confirms their role as adjunctive interventions targeting specific symptom domains, rather than disease-modifying strategies. Although overall effect sizes remain modest, these therapies continue to be clinically relevant due to their impact on pain, muscle tension, autonomic regulation and patient engagement.

Among these approaches, acupuncture and dry needling are the most studied (52). Evidence from recent systematic reviews and comparative analyses suggests small but significant improve-

ments in pain and function, particularly when compared with usual care rather than sham interventions. Still, results remain inconsistent due to heterogeneity in treatment protocols and patient populations. Importantly, emerging interpretations indicate that these interventions are more effective in patients with a predominant myofascial phenotype, where reduction of peripheral nociceptive input may contribute to modulation of central sensitisation (49).

Similarly, manual therapies, including myofascial release and massage-based interventions, have shown short-term improvements in pain, stiffness and sleep quality. These effects are likely mediated by a combination of peripheral and central mechanisms, including mechanical modulation of soft tissues, activation of descending inhibitory pathways and autonomic nervous system regulation. Nevertheless, durability of effect remains uncertain due to limited long-term data and methodological variability across studies (50). A relevant conceptual development in 2025 is the increasing focus on body perception and interoception. Massage therapy and related approaches, including lymphatic techniques, may contribute to improvements in pain, anxiety and sleep quality, likely through autonomic modulation, particularly reduction of sympathetic overactivity. However, protocols remain poorly standardised, limiting comparability across studies (53).

Patients with FM frequently present altered body representation and increased somatic hypervigilance, and manual or body-oriented therapies may act by modulating central sensory integration processes. This aligns with earlier mechanistic evidence suggesting that symptom perception is influenced by cognitive-emotional and interoceptive factors (54).

Recent randomised data also suggest a potential role for warm acupuncture in selected FM patients, particularly in those with increased cold sensitivity and altered pain perception (55).

Another important finding is the role of these therapies within multimodal and integrative treatment programs. Evidence suggests that manual and complementary interventions are combined with exercise, psychological therapies and education, rather than used in isolation. This is consistent with broader findings on self-management and educational interventions (39-43).

Across studies, a consistent finding is that response to manual and complementary therapies is highly phenotype-dependent. Patients with myofascial pain, muscle tension, autonomic dysregulation and high somatic awareness appear more likely to benefit, whereas those with predominant central sensitisation or severe fatigue may show limited response.

Take-home messages

- Manual and complementary therapies may provide modest but clinically relevant improvements in pain, muscle tension, anxiety and sleep quality (52-54, 56).
- Acupuncture, dry needling and myofascial techniques appear more effective in patients with predominant myofascial or autonomic phenotypes (52, 53).
- Body-oriented therapies may influence interoception, somatic awareness and autonomic regulation, supporting their integration within multidimensional treatment models (43, 54).
- The greatest benefit is observed when complementary therapies are integrated into multimodal rehabilitation programs rather than used in isolation (38, 40-43).

Conclusion

The analysis of the literature published in 2025 provides a coherent and clinically meaningful picture of FM management. Rather than the emergence of single transformative therapies, the year is characterised by a progressive refinement of mechanism-based and phenotype-oriented approaches, reflecting a deeper understanding of the complexity of the syndrome.

Across both pharmacological and non-pharmacological domains, treatment efficacy remains moderate and highly variable, confirming that FM cannot be effectively managed through a uniform therapeutic strategy. Instead, current evidence supports a multidimensional model in which different interventions act on distinct components of the syndrome, including central sensitisation, neuroimmune activation, autonomic dysregulation and psychosocial factors.

From a mechanistic perspective, several converging pathways emerge. Pharmacological therapies such as serotonin-norepinephrine reuptake inhibitors (SNRIs) and gabapentinoids act on descending inhibitory pathways and synaptic transmission, while also demonstrating potential neuroimmune effects, including modulation of microglial activity and pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 (9). Emerging approaches, including low-dose naltrexone and psychedelic compounds, further reinforce the relevance of central neuroimmune and neuroplastic mechanisms, although clinical evidence remains preliminary.

Similarly, non-pharmacological interventions exert their effects through both peripheral and central pathways. Exercise and rehabilitation influence pain modulation, autonomic balance and mitochondrial function, while psychological therapies act on cognitive-emotional processing, stress response and behavioural adaptation (35-40). Dietary and microbiome-related studies highlight the importance of the gut-brain axis, with growing evidence linking microbiota composition, inflammation and symptom expression (45-47). Instrumental approaches, including neuromodulation and wearable electrostimulation, further emphasise the role of central network modulation and neuroplasticity, although lack of standardisation remains a major limitation.

One of the most relevant conceptual advances in 2025 is the increasing focus on patient phenotyping. Rather than treating FM as a homogeneous condition, the literature supports the identification of clinically meaningful subgroups based on dominant domains, such as central sensitisation and widespread pain; sleep disturbance and hyperarousal; fatigue and energy metabolism impairment; psychological distress, trauma and alexithymia; gastrointestinal and metabolic features

This approach is supported by consistent evidence showing that treatment

response varies significantly according to these profiles, both for pharmacological therapies (*e.g.* SNRIs in patients with mood disorders, gabapentinoids in sleep disturbance) and for non-pharmacological interventions (*e.g.* exercise adherence, psychological therapies, dietary modulation).

Previous yearly reviews have already highlighted the transition toward multidimensional and personalised management strategies in FM (56). Importantly, the 2025 literature indicates that integration and personalisation are more relevant than the choice of any single intervention. Multimodal programs combining exercise, psychological therapies, education and selected pharmacological or complementary treatments consistently demonstrate greater and more sustained benefits than isolated approaches. Within this framework, adherence, patient engagement and continuity of care emerge as critical determinants of outcome.

Despite these advances, significant limitations persist, including heterogeneity of study design, small sample sizes, short follow-up and lack of standardised outcome measures, which limit comparability and the strength of clinical recommendations.

At the same time, a key unresolved issue becomes increasingly evident. Despite the large number of available studies and therapeutic options, no intervention has demonstrated a robust and universal effect across all patients and symptom domains. Most treatments produce domain-specific and variable benefits, typically on pain, sleep or HRQoL, while fatigue, cognitive symptoms and global disability remain difficult to modify.

This suggests that the main limitation may not lie solely in the lack of effective treatments, but in the continued application of uniform therapeutic strategies applied to a biologically and clinically heterogeneous condition. What is still missing is a reliable way to identify which patient is most likely to respond to which treatment, and at which stage of disease.

In this context, the key unmet need is accurate patient stratification. Future research should move beyond average treatment effects and focus on phenotype-based trial design, integrating clinical, biological and possibly biomarker-driven approaches. Without this step, even potentially effective therapies may appear only modestly beneficial, as responders and non-responders continue to be analysed together.

From a clinical perspective, FM should no longer be approached as a single therapeutic target, but as a multidimensional syndrome requiring tailored combinations of interventions matched to the patient's dominant mechanisms and symptom profile. The challenge is no longer identifying treatments for FM, but understanding which patients are more likely to benefit from specific therapeutic strategies.

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