Probiotics as an Adjunctive Treatment for Fibromyalgia: Results from a Randomized Clinical Trial

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Abstract:

Objective: Fibromyalgia (FM) is a complex, chronic disorder. Recent research has highlighted the role of the gut microbiota in modulating various physiological systems through the gut-brain axis. In this context, probiotics have emerged as a potential therapeutic approach for FM. The

primary objective of this study was to evaluate the impact of multispecies probiotics over a 12 weeks period on pain and fatigue, and secondary on sleep disturbances, cognitive function, and emotional symptoms.

Methods: This study was a quadruple-blinded randomized controlled trial with a placebo control group. Participants were randomly assigned to the following groups: experimental (Teoliance HPI 10 (Laboratorios Therascience)), which contained *Lactobacillus acidophilus LA-3, Lactobacillus rhamnosus GG, Bifidobacteria BS01, Lactobacillus plantarum BG112, Streptococcus thermophilus SP4, Lactobacillus casei LCO3, Lactobacillus reuteri LR92* (revivification 10^9 germs per capsule, 1 capsule per day, n = 48), or placebo (n = 49). To assess the different clinical dimensions different questionnaries were administered (VAS, BPI, SF36, MOS, HAS, FIQ).

Results: Forty eight participants were assigned to the probiotic condition and 49 participants to the placebo condition. The findings revealed a heterogeneous response, but with notable improvements in pain and somnolence, as well as a potential protective role of probiotics. There was significant statistical difference in the pain intensity scale (BPI). In probiotic group pain decreased from 6.64 to 6.49 and in placebo group increased from 6.69 to 7.17 (p=0.03). Sleepiness improved in the probiotic group from 48.11 to 41.23. In the control group sleepiness score was worse (from 42.66 to 48.03) (p=0.003).

Conclusion: Probiotic supplementation may serve as an adjunctive approach in the management of fibromyalgia, particularly in reducing pain intensity and daytime sleepiness.

1. Introduction

Fibromyalgia (FM) is a complex, chronic disorder characterized by widespread musculoskeletal pain, fatigue, sleep disturbances, and cognitive dysfunction, affecting approximately 2–4% of the global population, predominantly women. Despite its high prevalence, the pathophysiology of FM remains incompletely understood, with the mechanisms underlying chronic pain still unclear and effective treatments remaining limited [1]. Recent research has highlighted the role of the gut microbiota in modulating various physiological systems, including the immune, endocrine, and nervous systems, through the gut-brain axis. Dysbiosis, or microbial imbalance, in the gut has been implicated in the pathogenesis of several chronic conditions, including FM [2,3].

The involvement of the intestinal microbiota in various diseases is becoming increasingly recognized. Emerging evidence suggests that alterations in the

composition of the gut microbiota may contribute to the development and exacerbation of FM symptoms. Studies have reported reduced levels of beneficial bacteria such as *Lactobacillus*, *Bifidobacterium*, and *Faecalibacterium prausnitzii*, alongside increased levels of pro-inflammatory bacteria, including *Clostridium* and *Bacteroides*, in FM patients [4]. Other studies have shown microbiota alterations, specifically reduced diversity, with a marked depletion of *Coproccocus*, in individuals with chronic widespread musculoskeletal pain, one of the hallmark symptoms of FM [5]. The gut microbiota plays a crucial role in various physiological functions, including the regulation of brain processes through a bidirectional communication network known as the gut microbiota–brain axis. This network exerts a wide range of effects, from energy metabolism to psychological well-being [6-9]. Microbial imbalances may lead to increased intestinal permeability, systemic inflammation, and altered neurotransmitter metabolism, all of which are associated with FM symptoms.

In this context, probiotics—live microorganisms that confer health benefits to the host when administered in adequate amounts—have emerged as a potential therapeutic approach for FM [10]. Although few clinical trials with small sample sizes have been conducted, some studies suggest that probiotic supplementation can significantly improve certain emotional symptoms in FM patients [11-12]. For instance, a double-blind, placebo-controlled trial demonstrated that daily administration of probiotics resulted in significant improvements in pain scores and quality of life in FM patients [13].

The selected probiotic species have been used previously to improve functions related to the gut–brain axis [15] and they are therefore expected to be capable of attenuating the cognitive and emotional changes caused by FM. The aim of the study was to determine whether probiotic treatment can be effective in improving the symptoms experienced by individuals with fibromyalgia. At no point was it intended to investigate the mechanisms through which probiotics might influence the expression of fibromyalgia.

Our hypothesis was that probiotic treatment could serve as an effective intervention for FM. The primary objective of this study was to evaluate the impact of multispecies probiotics over a 3-month period on pain and fatigue. The secondary objectives were to assess the effects of probiotics on sleep disturbances, cognitive function, and emotional symptoms.

2. Material and methods.

2.1 Study Design

This study was a randomized, quadruple-blind, placebo-controlled trial conducted between November 2020 and July 2023 at the Hospital de Sant Pau, a tertiary referral center in Barcelona, Spain, serving approximately 407,000 inhabitants.

Participants were recruited from the hospital's outpatient Fibromyalgia Unit. Inclusion criteria were: (1) female sex; (2) age ≥18 years; (3) diagnosis of fibromyalgia established at least one year prior to enrollment by a rheumatologist or internist, according to the 2010 American College of Rheumatology (ACR) criteria [14]; and (4) provision of written informed consent. Exclusion criteria included: use of antibiotics or probiotic supplements within the 6 months prior to inclusion; known allergy to any component of the study product; current participation in other clinical or psychological trials; pregnancy or breastfeeding; history of severe gastrointestinal disease or active malignancy; and presence of severe psychiatric disorders other than anxiety or depression.

This study was conducted in accordance with the Declaration of Helsinki and received approval from the Ethics Committee of Hospital de Sant Pau (IIBSP-FIB-2020-08).

2.2 Procedure

Participants were randomly assigned (1:1) to the experimental group or the placebo group. The experimental group received Teoliance HP

I10 (Laboratorios Therascience), a multi-strain probiotic formulation containing *Lactobacillus acidophilus* LA-3, *Lactobacillus rhamnosus* GG, *Bifidobacterium* BS01, *Lactobacillus plantarum* BG112, *Streptococcus thermophilus* SP4, *Lactobacillus casei* LCO3, and *Lactobacillus reuteri* LR92. Each capsule

contained a total of 10^9 Colony Forming Units (CFU). Participants were instructed to take one capsule daily.

The control group received placebo capsules composed of cellulose (provided by Therascience S.L.), which were indistinguishable from the active treatment in color, taste, and smell to ensure blinding. Clinical evaluations were performed at two time points: baseline (pre-intervention) and Week 12 (post-intervention).

2.3 Outcome Measures

Baseline demographic and clinical data were collected for all participants. To assess clinical outcomes, the following validated instruments were administered:

Pain Assessment: Pain intensity was evaluated using the Visual Analogue Scale (VAS) [16] (0–10 range) and the Brief Pain Inventory (BPI) [17], which assesses both intensity and interference with daily function (scores > 7 indicate severe interference).

Health-Related Quality of Life: The SF-36 Health Survey[18] was used to measure quality of life across eight physical and mental domains. Scores are standardized to a 0–100 scale, with higher values indicating better health status.

Symptom Impact and Mood: Sleep quality was measured via the MOS Sleep Scale[19] (higher scores indicate poorer sleep). Psychological distress was screened using the Hospital Anxiety and Depression Scale (HADS) [20], where scores ≥ 8 indicate clinically significant anxiety or depression. Finally, the Fibromyalgia Impact Questionnaire (FIQ) [21] assessed the overall negative impact of the disease on daily life.

2.4 Statistical Analyses

Descriptive statistics were calculated for all baseline and outcome variables. Continuous variables are expressed as Mean (SD), while categorical variables are reported as counts and percentages. The normality of the data distribution was assessed using the Shapiro-Wilk test.

Baseline comparisons between groups were performed using the χ^2 test for categorical variables and independent Student's t-tests for continuous variables. To evaluate the effects of the intervention, a repeated-measures analysis of variance (RM-ANOVA) was conducted, with Treatment (Probiotic vs. Placebo) as the between-subjects factor and Time (Baseline vs. Week 12) as the within-subjects factor. The primary statistical endpoint was the time × group interaction, which assesses differential changes between groups. Additionally, the mean change from baseline to Week 12 and its associated 95% Confidence Interval (95% CI) were calculated for all outcomes.

As this was an exploratory pilot study, no formal sample size calculation was performed a priori to detect a prespecified effect; findings should therefore be interpreted as hypothesis-generating. Consistent with this exploratory aim, analyses were performed on a per-protocol basis, including only participants who completed the study and maintained adherence to the intervention. This approach was chosen to evaluate the potential physiological efficacy of the probiotic in compliant participants as a proof-of-concept.

Statistical analyses were performed using IBM SPSS 29.0. Statistical significance was defined as a two-sided p-value < 0.05.

3. Results

3.1 Participant Characteristics

A total of 97 women with fibromyalgia were enrolled and randomized to the probiotic group (n = 48) or the placebo group (n = 49). During the 12-week follow-up, 15 participants withdrew from the study: eight in the probiotic arm (two due to diarrhea, six for reasons unrelated to the intervention) and seven in the placebo arm (one due to diarrhea, six unrelated). Consequently, 40 participants in the probiotic group and 42 in the placebo group completed the protocol and were included in the final analyses.

Baseline characteristics were well-balanced between the two groups (Table 1). The mean age was 55.4 (SD 8.2) years in the probiotic group and 55.4 (SD 7.9) years in the placebo group. Mean BMI was 25.7 (SD 3.8) kg/m² and 24.4 (SD 3.9)

kg/m², respectively. No statistically significant differences were observed for any demographic or clinical variable at baseline.

Figure 1. Flow diagram of the progress through the phases of the trial.

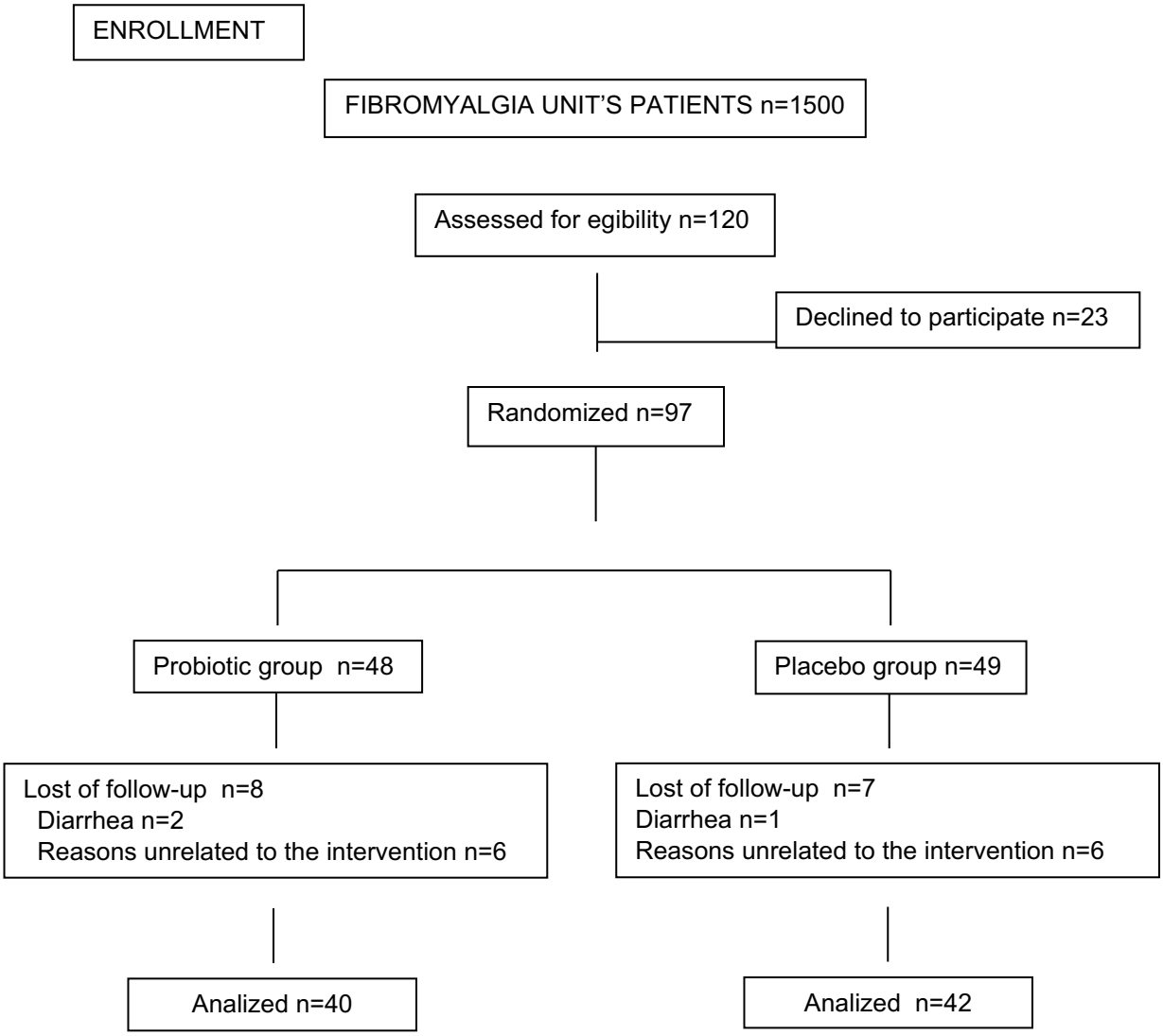


Table 1. Demographic characteristics in the Probiotic and Placebo groups.

Demographic characteristics			
	Probiotic	Placebo	P
Participants	48	49	
Age	55.38 (8.17)	55.36 (7.91)	0.98
Superior Educational level	68.7%	69.4%	0.67
Time with FM (years)	10.34 (7.42)	9.23 (6.47)	0.43
Any CNS treatment	83,6%	84,8%	0.77
BMI (kg/m^2)	25.7 (3.74)	24.42 (3.93)	0.82

Mean scores and standard error of the means (in parentheses) are shown.
FM fibromyalgia, BMI Body Mass Index; CNS Central Nervous System

Table 2. Basal Questionnaires and Physiological outcomes.

	Probiotic	Placebo	P
VAS	7.22 (1.71)	7.75 (1.23)	0.18
BPI intensity	6.64 (1.72)	6.69 (1.47)	0.86
BPI Impact	6.82 (2.19)	7.05 (1.69)	0.90
SFP36			
Physical function	42.57 (21.53)	45.26 (20.19)	0.26
Physical role	16.22 (27.14)	14.74 (27.93)	1.00
Bodily pain	22.65 (18.55)	17.56 (15.44)	0.29
General health	34.43 (17.67)	32.54 (17.28)	0.56
Vitality	26.62 (18.86)	22.95 (17.12)	0.38
Social function	39.19 (27.82)	34.61 (21.36)	0.43
Emotional role	27.76 (40.30)	31.62 (43.22)	0.56
Mental health	42.81 (21.06)	42.46 (14.44)	0.89
MOSS			
Sleep disturbance	55.34 (25.07)	57.11 (25.51)	0.89
Sleepiness	48.10 (21.43)	42.66 (22.58)	0.59
HAD Anxiety	11.49 (4.86)	12.61 (4.25)	0.29
HAD Depression	10.16 (5.17)	10.41 (4.21)	0.51
FIQ	71.00 (15.14)	75.77 (12.05)	0.13

Mean scores and standard error of the means (in parentheses) are shown.

3.2 Main outcome. Effect of probiotic in pain scales.

Outcomes for pain assessments are presented in Table 3. The Visual Analogue Scale (VAS) showed no significant time x group interaction ($p = 0.50$), with overlapping confidence intervals for mean changes in the probiotic (-0.03; 95%

CI: -0.48 to 0.43) and placebo arms (-0.24; 95% CI: -0.68 to 0.19). Conversely, BPI Pain Intensity revealed a significant time x group interaction (p = 0.035), indicating divergent trajectories: the probiotic group demonstrated a mean reduction of -0.15 (95% CI: -0.56 to 0.26), whereas the placebo group exhibited a significant increase of +0.47 (95% CI: 0.07 to 0.87). No significant time x group interaction was observed for BPI Pain Interference (p = 0.39).

3.3 Secondary outcomes.

Secondary endpoints are detailed in Table 3. Subjective Sleep Quality (MOSS) yielded the study's most robust time x group interaction (p = 0.003). This result was driven by a significant improvement in the probiotic group (mean change: -6.87; 95% CI: -12.64 to -1.10) contrasted against worsening scores in the placebo group (+5.37; 95% CI: -0.25 to 10.99). SF-36 Physical Functioning showed a trend toward significance for the time x group interaction (p = 0.066), characterized by score maintenance in the probiotic group (+0.68; 95% CI: -3.66 to 5.01) versus a significant decline in the placebo group (-5.00; 95% CI: -9.11 to -0.78). No significant time x group interactions were found for FIQ Total Score (p = 0.65), Objective Sleep (MOSTS, p = 0.22), or HADS scores (Anxiety p = 0.94; Depression p = 0.86), with 95% CIs crossing zero in both groups.

Table 3. Baseline and Post-intervention Scores for Pain, Sleep, and Mood Following 12-week Probiotic Supplementation.

Variable	Group	Baseline, Mean (SD)	Week 12, Mean (SD)	Δ Mean [95% CI]	p
Pain Assessment					
VAS Pain	Probiotic	7.22 (1.72)	7.20 (1.56)	−0.03 [-0.48, 0.43]	0.500
	Placebo	7.75 (1.23)	7.51 (1.69)	−0.24 [-0.68, 0.19]	
BPI Pain Intensity	Probiotic	6.64 (1.72)	6.49 (1.76)	−0.15 [-0.56, 0.26)	**0.035**
	Placebo	6.70 (1.47)	7.17 (1.90)	+0.47 [0.07, 0.87]	
BPI Pain Interference	Probiotic	6.82 (2.20)	6.72 (2.12)	−0.10 [-0.56, 0.37]	0.398
	Placebo	7.05 (1.69)	7.22 (2.05)	+0.18 [-0.27, 0.63]	
Quality of Life (SF-36)					
Physical Functioning	Probiotic	42.57 (21.53)	43.24 (22.71)	+0.68 [-3.66, 5.01]	0.066
	Placebo	45.26 (20.19)	40.26 (19.33)	−5.00 [-9.11, -0.78]	
Role Physical	Probiotic	16.22 (27.14)	16.22 (30.74)	0.00 [-8.49, 8.49]	0.284
	Placebo	14.74 (27.93)	8.33 (20.14)	−6.41 [-14.68, 1.85]	
Bodily Pain	Probiotic	22.65 (18.55)	24.35 (16.42)	+1.70 [-2.93, 6.33]	0.823
	Placebo	17.56 (15.44)	18.54 (16.12)	+0.97 [-3.53, 5.48]	

General Health	Probiotic	34.43 (17.67)	33.19 (16.34)	−1.24 [-4.75, 2.27]	0.184
	Placebo	32.54 (17.28)	28.00 (17.64)	−4.54 [-7.96, -1.12]	
Vitality	Probiotic	26.62 (18.86)	23.78 (21.00)	−2.84 [-8.82, 3.15]	0.852
	Placebo	22.95 (17.12)	20.90 (17.20)	−2.05 [-7.88, 3.78]	
Social Functioning	Probiotic	39.19 (27.82)	43.58 (30.42)	+4.39 [-2.25, 11.03]	0.341
	Placebo	34.62 (21.36)	34.55 (23.65)	−0.06 [-6.53, 6.40]	
Role Emotional	Probiotic	27.76 (40.31)	32.43 (43.38)	+4.67 [-7.31, 16.65]	0.290
	Placebo	31.62 (43.22)	27.34 (39.64)	−4.27 [-15.94, 7.39]	
Mental Health	Probiotic	42.81 (21.06)	42.60 (25.42)	−0.22 [-4.81, 4.37]	0.512
	Placebo	42.46 (14.44)	40.13 (20.91)	−2.33 [-6.80, 2.14]	
Impact & Sleep					
FIQ Total Score	Probiotic	71.00 (15.14)	67.41 (17.11)	−3.59 [-7.45, 0.27]	0.658
	Placebo	75.77 (12.05)	73.42 (12.47)	−2.35 [-6.37, 1.68]	
MOSTS (Objective)	Probiotic	55.34 (25.07)	53.92 (26.61)	+1.42 [-6.91, 4.08]	0.227
	Placebo	57.12 (25.51)	60.38 (24.55)	+3.27 [-2.08, 8.62]	

MOSS (Subjective)	Probiotic	48.11 (21.43)	41.23 (24.42)	−6.87 [-12.64, -1.10]	**0.003**
	Placebo	42.66 (22.58)	48.03 (21.91)	+5.37 [-0.25, 10.99]	
Mood (HADS)					
Anxiety (HAD-A)	Probiotic	11.49 (4.86)	11.57 (5.18)	+0.08 [-0.93, 1.09]	0.947
	Placebo	12.62 (4.25)	12.74 (4.30)	+0.13 [-0.86, 1.11]	
Depression (HAD-D)	Probiotic	10.16 (5.17)	9.89 (5.66)	−0.27 [-1.25, 0.71]	0.866
	Placebo	10.41 (4.22)	10.56 (4.87)	+0.15 [-0.80, 1.11]	

Data expressed as Mean (SD). Δ Change: mean difference (Baseline–Week 12); 95% CI: 95% confidence interval. Intergroup p-values calculated via ANOVA on mean changes. Bold indicates $p < 0.05$. VAS, Visual Analogue Scale; BPI, Brief Pain Inventory; SF-36, Short Form-36 Health Survey (PF: Physical Functioning; RF: Role Physical; BP: Bodily Pain; GH: General Health; VT: Vitality; SF: Social Functioning; RE: Role Emotional; MH: Mental Health); FIQ, Fibromyalgia Impact Questionnaire; MOSTS/MOSS, Sleep Quality Scales (Objective/Subjective); HADA/HADD, Hospital Anxiety and Depression Scale (Anxiety/Depression).

Figure 2. BPI Intensity evolution

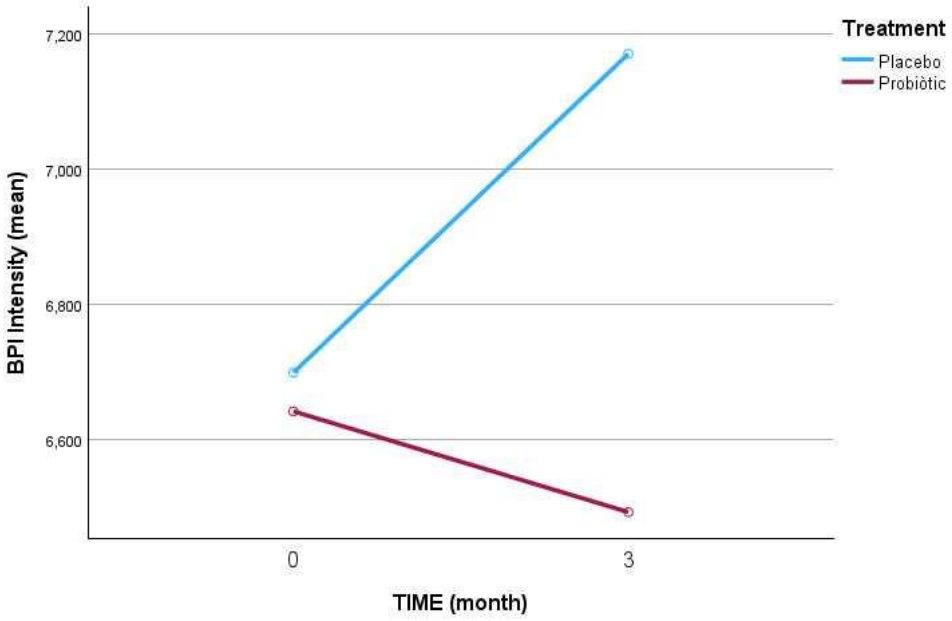
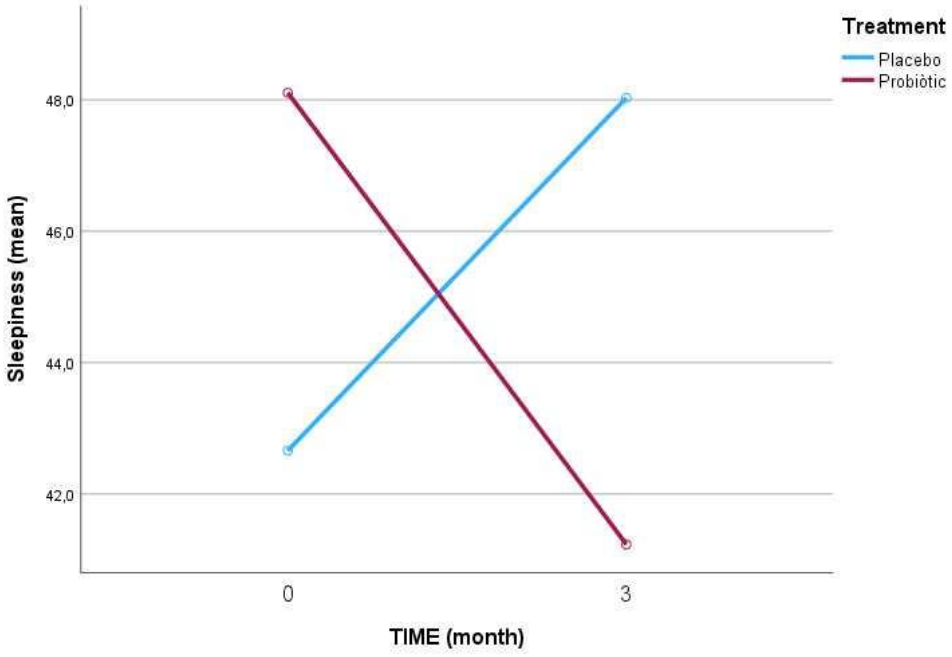


Figure 3. MOSS Sleepiness evolution



4. Discussion

This study assessed the effects of a 12-week probiotic supplementation regimen in patients with fibromyalgia, focusing on pain, sleep quality, quality of life, cognitive function, and mental health. The probiotic combination was selected based on previously documented benefits related to the gut-brain axis interaction

[15]. The participants in our study were comparable in terms of age, fibromyalgia duration, and physical and social characteristics to those included in other probiotic studies. At baseline, the mean Fibromyalgia Impact Questionnaire (FIQ) score was 72.56, indicating that the cohort was severely affected by the condition. Most participants were receiving pharmacological treatments aimed at alleviating fibromyalgia symptoms, including benzodiazepines, antidepressants, NSAIDs, paracetamol and tramadol, with no changes in medication during the study period.

The findings revealed a heterogeneous response, but with notable improvements in pain and somnolence, as well as trends suggesting a potential protective role of probiotics.

Regarding pain, a significant reduction in the Brief Pain Inventory (BPI) intensity scores was observed in the probiotic group, compared to a worsening in the placebo group ($p = 0.03$). This result does not support the widely known “placebo effect” [22] observed in pain-related conditions, including fibromyalgia [23]. Such effects have been reported in similar trials[11]. It is also possible that the improvement observed in some patients could be related to the therapeutic interaction with specialists, who help patients better manage chronic pain [23]. The BPI impact dimension showed a trend toward improvement, although this was not statistically significant, with the placebo group exhibiting a deterioration. Despite this, no significant changes were observed in the Visual Analogue Scale (VAS), which worsened in both groups over time. This discrepancy may be attributed to the differing sensitivities of the instruments: the VAS provides a unidimensional assessment of global pain [24], whereas the BPI captures multidimensional aspects (intensity and interference), allowing for greater sensitivity to subtle changes [25]. While studies on this topic are limited and results are mixed, a trial by Calandre et al. did not find significant improvements in pain following 12 weeks of probiotic treatment, using the VAS [26], while Asland et al. did report improvements after 8 weeks of probiotic treatment using the same scale [13].

In terms of quality of life, as measured by the SF-36, no statistically significant differences were found between the probiotic and placebo groups. However, the

probiotic group exhibited trends toward stability or improvement, whereas the placebo group showed trends toward deterioration across all evaluated domains, particularly in physical functioning (p=0.06) and general health perception (p=0.18). Increases in social functioning and emotional role were also noted in the probiotic group, suggesting a potential protective effect, though insufficient to reach statistical significance within the study period. The FIQ slightly improved in both groups, without a significant difference; however, the post-treatment mean FIQ in the probiotic group was below 70 (67.41 ± 17.10). This result is consistent with the hypothesis that improvements in pain may be associated with better physical and emotional functioning, as well as enhanced social role performance.

For sleep outcomes, probiotics significantly reduced daytime sleepiness (p=0.03), while the placebo group experienced worsening. A nonsignificant trend toward improvement in sleep disturbances was also observed (p=0.23). These results align with findings from other studies that assessed sleep disturbances using the Pittsburgh Sleep Quality Index [13]. Although a different study did not show positive results, it had important methodological differences, including a shorter treatment duration (4 weeks), a smaller sample size (15 participants), and a different probiotic formulation (not using *Streptococcus*) [27]. These findings are clinically relevant, as sleep dysfunction is a core feature of fibromyalgia and contributes to exacerbation of pain, fatigue, and cognitive impairment. The reduction in daytime sleepiness may reflect modulation of the gut-brain axis and improved wakefulness regulation, warranting further investigation.

Regarding mental health, no significant differences were observed in anxiety or depression scores (HADS: p=0.95 and p=0.54, respectively). It is important to note that participants had high baseline anxiety levels (mean 11.8) and moderate depression (mean 0.9). This suggests that probiotics may not have exerted measurable short-term effects on emotional symptoms, possibly due to the severity of the condition in this population. However, other studies have demonstrated positive results in this area, particularly when anxiety and depression were measured using the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) [13]. Gut microbiota may influence central nervous system activity through mechanisms such as short-chain fatty acid production,

tryptophan metabolism, neuroactive compound synthesis (e.g., GABA, serotonin precursors), and immune modulation [28,29]. The increase in tryptophan and serotonin precursors could help alleviate anxiety and depression. Given the high prevalence of these mental health issues in fibromyalgia, and their impact on pain and quality of life, the lack of significant effects in this domain limits the broader interpretation of our findings. However, trends suggesting improvements in mental health and emotional role within the quality-of-life domains were observed in the probiotic group, indicating a potential benefit in these areas.

The treatment duration in our study was longer than that in other similar studies, which typically administered treatment for only 8 weeks. This may have contributed to more lasting and consistent effects. However, further studies with longer follow-up periods are necessary to assess the long-term effects of probiotic treatment. Our systematic review highlights the potential of microbiota modulation as a therapeutic strategy for managing fibromyalgia symptoms [30]. These findings could have important clinical implications. It is well established that the most effective treatment for fibromyalgia involves a combination of pharmacological and non-pharmacological interventions, with a multidisciplinary approach [31]. Probiotics could be considered as an adjunct to the regular treatment of these patients.

The main limitations are the exploratory, single-center design and the absence of a formal a priori sample-size calculation, which limit power to detect small or moderate effects; nonetheless, each arm included >45 participants and analyses were conducted with rigorous statistical methods on high-quality data. We used a per-protocol approach to estimate efficacy among adherent participants; although this may reduce generalizability if losses were differential, baseline characteristics were similar between completers and non-completers. Dietary intake (including other fermented foods) was not controlled, and unmeasured external factors (stress, climate, socioeconomic conditions) could have influenced symptoms. These findings should therefore be considered hypothesis-generating, and future multicenter trials should prespecify intentio-to-treat analyses with appropriate missing-data handling and formal sample-size calculations.

5. Conclusion

Probiotic supplementation may serve as an adjunctive approach in the management of fibromyalgia, particularly in reducing pain intensity and daytime sleepiness, while also preserving certain domains of quality of life. Furthermore, probiotics represent a cost-effective treatment, which is particularly important for patients with fibromyalgia due to their limitations to maintain a normal work life. Additionally, probiotics are generally well tolerated. However, these results should be interpreted with caution, given the methodological limitations of the study, including the small sample size, short intervention duration, and clinical heterogeneity. Future multicenter trials with larger cohorts, extended supplementation periods, and the inclusion of microbiota assessments, inflammatory biomarkers, and sensitive neurocognitive tests are essential to better elucidate the therapeutic potential of probiotics in fibromyalgia.

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