

Adjuvant administration probiotic effects on sexual function in depressant men undergoing selective serotonin reuptake inhibitor treatment: a double-blinded randomized controlled trial

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Abstract

Background: Depression is a common psychiatric disorder worldwide, often linked to complications like impaired sexual function.

Aim: To determine the effect of the probiotic Lactofem combined with Escitalopram on severity of depression and sexual function in men diagnosed with mild to moderate depression undergoing SSRI treatment.

Methods: In a randomized controlled trial, 240 men with mild to moderate depression were assigned to 2 groups. The intervention group (119 participants) received Lactofem alongside Escitalopram, while the control group (121 participants) received only Escitalopram for 2 months.

Outcomes: Depression severity was measured by the Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI). Sexual function was assessed using the International Index of Erectile Function (IIEF) questionnaire at baseline and after treatment.

Results: Both groups showed significant improvement in depression scores ($P < .05$). The Lactofem group had a greater reduction in HDRS (6.42 ± 3.45 vs 8.61 ± 4.15 , $P < .05$) and BDI scores (27.63 ± 4.13 vs 30.24 ± 4.51 , $P < .05$). Sexual function improvements were significantly higher in the intervention group across all domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction (all $P < .05$).

Clinical Implications: Probiotics such as Lactofem may offer benefits as adjunctive therapy to reduce depression symptoms and improve SSRI-induced sexual dysfunction.

Strengths and Limitations: Strengths include a rigorous randomized design, validated tools, and large sample size. Limitations are recruitment from a single Iranian clinic with culturally homogenous, married men, absence of placebo, young patient age, and no long-term follow-up.

Conclusion: Adding Lactofem to Escitalopram treatment significantly reduces depression severity and enhances sexual function in men with mild to moderate depression.

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Trial registration: ClinicalTrials.gov identifier: <https://irct.behdasht.gov.ir/trial/67103>.

Keywords: probiotic; escitalopram; depression; sexual function; SSRI; men.

Introduction

Sexual dysfunction is a common and clinically significant adverse effect of antidepressant therapy, particularly among patients treated with selective serotonin reuptake inhibitors (SSRIs). Prevalence estimates range from approximately 30%–70% and include reduced libido, erectile dysfunction, delayed ejaculation, and impaired orgasm, which may substantially reduce treatment adherence and quality of life.^{1,2} Therefore, sexual dysfunction represents a major clinical challenge in the management of depressive disorders.³

The antidepressant effects of SSRIs are primarily mediated through enhancement of serotonergic neurotransmission;

however, increased serotonin activity may simultaneously inhibit dopaminergic and nitric oxide-dependent pathways that are critical for sexual desire, arousal, and orgasm.^{4,5} This complex neurochemical interaction explains why SSRIs may both induce sexual dysfunction and, in certain contexts, be therapeutically used to delay ejaculation in patients with premature ejaculation, reflecting dose- and context-dependent serotonergic effects on sexual function.^{5,6} Comparative evidence suggests that antidepressant classes differ substantially in their sexual side-effect profiles. Bupropion, a norepinephrine-dopamine reuptake inhibitor, is consistently associated with lower rates of sexual dysfunction and may

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improve sexual desire and orgasmic response when used either as a substitute for or an adjunct to SSRIs.^{7,8} These pharmacodynamic differences highlight the importance of individualized antidepressant selection to optimize both mood outcomes and sexual well-being.^{3,8} Phosphodiesterase type 5 (PDE5) inhibitors, including sildenafil and tadalafil, have been evaluated as adjunctive therapies for antidepressant-induced sexual dysfunction, particularly erectile dysfunction.^{9–11} These agents act via nitric oxide-mediated vasodilation and are generally well tolerated; however, they may cause adverse effects such as headache, flushing, dyspepsia, and mild reductions in blood pressure, with clinically significant hypotension occurring primarily in combination with nitrates or alpha-blockers.^{9,10}

In recent years, growing evidence has highlighted the gut-brain axis as an important regulator of emotional and sexual health. Probiotics, through modulation of gut microbiota composition, may influence neuroendocrine signaling, systemic inflammation, and neurotransmitter pathways, including serotonergic transmission.¹² Emerging clinical trials suggest that probiotic supplementation may improve depressive symptoms and potentially attenuate antidepressant-associated sexual dysfunction, supporting a novel adjunctive therapeutic strategy.¹³ Despite increasing interest in this field, randomized controlled trials (RCTs) specifically evaluating probiotics as an adjunctive intervention for antidepressant-induced sexual dysfunction remain limited. Accordingly, the present study aimed to assess the effects of adjunct probiotic administration on sexual function in men receiving SSRI therapy, addressing an important gap in the current literature.

Methods

Participants

This study was a randomized clinical trial undertaken in men with depression treated with anti-depressants attending the Shahid Mofateh Clinic, Yasuj University of Medical Sciences, Yasuj, Iran was invited to participate in the study during 2024. This study is a RCT registered at the Iranian Registry of Clinical Trials, <https://irct.behdasht.gov.ir/trial/67103>, prospectively registered from May 17, 2024. In addition, this study was approved by the Yasuj University of Medical Sciences, Yasuj, Iran Ethics Committee with ethical code: IR.YUMS.REC.1401.078. An information sheet was offered to all women and informed written consent was obtained. All participants were aware that they could withdraw any time during the trial.

Recruitment of participants

Inclusion criteria: age 18–45 years; reading and writing literacy; having scoring less than 20 on the Hamilton Depression Rating Scale (HDRS), which indicates mild to moderate severity depression; being treated for at least 4 weeks with antidepressants; having penetrative intercourse at least once a month; having an emotionally satisfying relationship with a stable and sexually active partner for at least 1 year. Diagnosis of depression was verified by a specialist in psychiatry prior to inclusion.

Exclusion criteria: unwillingness of the patient during sampling, having speech or hearing problems, addiction to drugs and alcohol in patient or her partner, having sexual problem before taking antidepressants, having symptoms of psychosis, loss of relatives or friends during the last 6 months ago, known sexual problem in men, suffering from internal

diseases such as cardiovascular, thyroid, arthritis, diabetes, epilepsy, kidney infection, taking birth control pills or any drugs that affect sexual function, such as antihypertensives drugs, antihistamine H2 blockers, barbiturates.

Because no prior studies reported variance for sexual function with probiotics, and Romijn et al. (2017)¹⁴ provided parameters for depression severity rather than sexual function, we used these depression-based estimates to perform a preliminary sample size calculation using the following formula, resulting in a minimum of 120 participants per group.

$$N = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 (S_1^2 + S_2^2)}{\Delta^2}$$

$$1 - \alpha = \%95 \quad \beta = \%80.$$

$$S_1 = 13.2 \quad S_2 = 10.3 \quad \Delta^2 = 0.99$$

Randomization, hidden distribution, and blindness

Allocation to Lactofem plus SSRIs (Group A) or SSRIs alone (Group B) was done by “block” randomization method. Randomization tool was statistical software, and hiding method was done by envelopes in the package. This study was conducted as an open-label clinical trial. Because no placebo was provided to the control group, blinding of participants and investigators was not feasible.

Study design

After obtaining written consent from eligible people to enter the study, the subjects evaluated for 2 months. Before the intervention, depression severity measured using Beck and HDRS, and sexual function by International Index of Erectile Function (IIEF). After completing the questionnaires, the subjects were divided into 2 intervention and control groups.

Group A: SSRI antidepressant Escitalopram (10 mg, daily) plus Lactofem prescribed. Lactofem capsule (including *Lactobacillus acidophilus* 2×10^9 cfu/g, *Bifidobacterium bifidus* 2×10^9 cfu/g, *Lactobacillus ruti* 2×10^9 cfu/g, *Lactobacillus fermentum* 2×10^9 cfu/g; capsule weight of 500 mg bio-capsule) made by Iranian Zist-Takhmir Company administered orally and daily for 2 months.

Group B: SSRI antidepressant Escitalopram (10 mg, daily) alone prescribed.

Duration of intervention in 2 groups were 2 months.

Outcome measure

- 1) The IIEF is a widely used, reliable self-report measure for assessing male sexual function, including erectile dysfunction, across 5 domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. Responses are rated on a Likert scale.¹⁵ Additionally, the Persian version of the IIEF has been validated in an Iranian male sample, showing excellent reliability and cultural relevance for use in Iranian populations.¹⁶
- 2) Measurement of depression: HDRS (version with 21 items; Persian version, including psychometric indices¹⁷ used in this research to examine the depression status of patients. The rating scale consisted of 21 items asking about symptoms related to depression, including low mood, suicidality, irritability, tension, loss of appetite,

loss of interest, and somatic symptoms. Answers were given on different rating scales ranging from 3-, 4-, or 5-point ratings: (eg, “insomnia early”: 0=no difficulty falling asleep; 1=complains of occasional difficulty falling asleep, ie, more than 0.5 hours; 2=complains of nightly difficulty falling asleep), with higher scores reflecting more marked depressive symptoms.¹⁸

- 3) The Beck Depression Inventory-II (BDI-II) is a widely used self-report tool to assess the severity of depressive symptoms. It consists of 21 items that cover affective, cognitive, and somatic symptoms related to depression, such as sadness, loss of pleasure, irritability, changes in appetite, and fatigue. Each item is rated on a 4-point Likert scale ranging from 0 (symptom absent) to 3 (severe symptoms), with total scores ranging from 0 to 63. Higher scores indicate greater severity of depression, categorized as minimal (0-13), mild (14-19), moderate (20-28) and severe (29-63) depression. The BDI-II is designed to reflect depression symptoms experienced over the past 2 weeks and has demonstrated strong reliability and validity across different populations.^{19,20}
- 4) Side effects, ie, fever, itching, diarrhea, vomiting, or other gastrointestinal symptoms, were recorded.

Statistics

Data analysis was done using descriptive statistics (frequency, percent, mean $\pm$ SD), and a comparison of these data was performed by χ^2 , independent *t*-test, and paired *t*-test. We used descriptive statistics as well as the Kolmogorov-Smirnov test to analyze the distribution of data. The statistical program for social sciences (Statistical Package for Social Sciences; SPSS, version 21; SPSS, Chicago, IL). *P* values were set at .05 for all analyses. In this study, sexual function was considered the primary outcome, and depression severity considered the secondary outcome. There were no missing values. Therefore, no missing imputation technique was used. This manuscript is in accordance with the PRISMA guidelines for reporting randomized trials.

Result

1) Sample characteristics

A total of 244 patients were assessed for eligibility and randomly assigned to 2 groups (122 patients per group). Ultimately, 240 patients completed the follow-up (119 in the probiotic group and 121 in the control group). Four patients were lost to follow-up: 3 in the intervention group and 1 in the control group, due to unwillingness to continue the study.

The patient allocation process is illustrated in Figure 1. At baseline, there were no significant differences between the probiotic and control groups regarding demographic or clinical characteristics. The mean age of participants was 39.63 ± 11.78 years in the probiotic group and 40.28 ± 10.95 years in the control group ($P = .65$). Most participants in both groups had a university degree (51.3% vs 42.1%), while fewer had only a high school education (10.9% vs 14.9%). The mean BMI was 22.96 ± 1.80 kg/m² in the probiotic group, and 23.16 ± 1.20 kg/m² in the control group ($P = .29$). The duration of depressive illness was similar between groups (3.42 ± 1.32 years vs 3.47 ± 1.26 years; $P = .76$).

2) Comparison of sum score of sexual function between group

As presented in Table 1, the domains of erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction were significantly higher in the probiotic group compared with the control group ($P < .05$). Additionally, within the probiotic group, there was a statistically significant improvement in intercourse satisfaction and overall satisfaction subscales before and after the intervention ($P < .05$).

3) Comparison of sum score of depression between group

According to Table 2, depression severity was significantly lower in the probiotic group compared with the control group ($P < .05$). Moreover, paired *t*-test results indicated a statistically significant improvement in depression severity before and after treatment in both the probiotic ($P < .05$) and control ($P < .05$) groups.

After treatment, the mean BDI score in the probiotic group decreased from 36.94 ± 2.31 to 27.63 ± 4.13 , changing from severe to moderate depression, whereas the control group decreased from 36.74 ± 2.21 to 30.24 ± 4.51 , remaining in the severe range. The between-group effect size (Cohen's *d*) was approximately 0.61, indicating a moderate and clinically meaningful effect of probiotics.

Similarly, HDRS scores decreased from 18.40 ± 2.36 to 6.42 ± 3.45 in the probiotic group (mild/minimal depression) compared with 17.94 ± 2.37 to 8.61 ± 4.15 in the control group (still mild depression), with a between-group effect size of 0.60. These results provide both statistical significance and clinically interpretable improvements in depressive symptoms.

After treatment, the between-group effect sizes were moderate for both HDRS ($d = 0.60$) and BDI ($d = 0.61$), indicating clinically meaningful improvements beyond statistical significance.

4) Side effects

No side effects were reported in either group.

Discussion

This study investigated the effects of adjunctive administration of the probiotic Lactofem in men with mild to moderate depression receiving Escitalopram. In the present study, adjunctive Lactofem administration with SSRIs significantly reduced depressive symptoms and improved multiple domains of sexual function—including erectile function, sexual desire, orgasm, and overall satisfaction—compared with SSRIs monotherapy.

Sexual dysfunction is a well-recognized adverse effect of SSRIs, commonly resulting in reduced libido, erectile difficulties, delayed or absent orgasm, and other sexual issues, affecting both men and women.^{21,22} Overall, 57%-73% of patients on SSRIs report some form of sexual dysfunction, which can reduce quality of life and treatment adherence.^{21,23} Emerging evidence highlights the gut-brain axis as an important modulator of both mental and sexual health. The gut microbiota can influence systemic inflammation, produce neuroactive metabolites, and regulate hormonal balance, all of which impact mood, stress, and sexual function.^{13,24} A recent systematic review demonstrated that probiotic

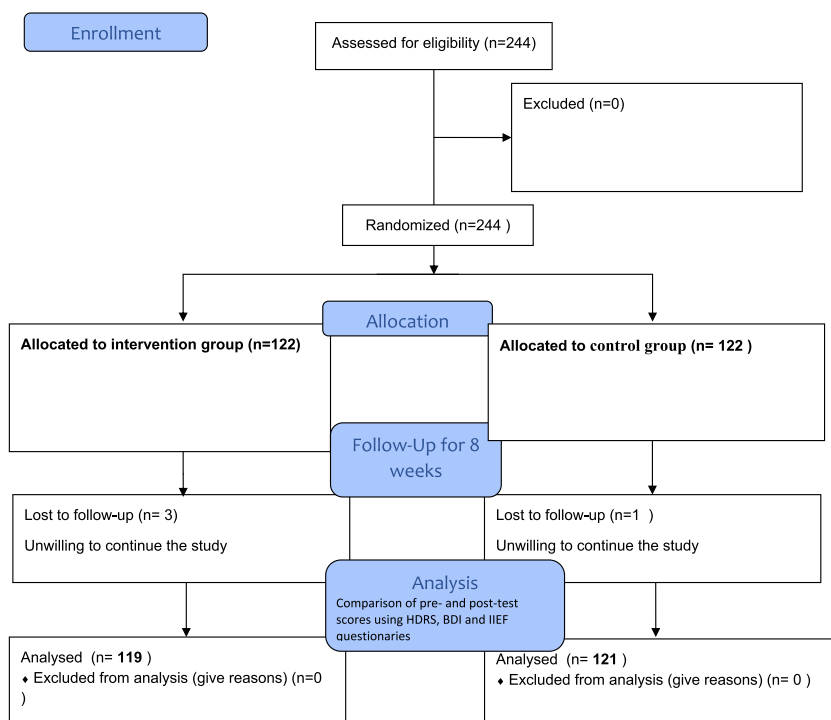


Figure 1 The patient allocation process.

Table 1 Comparison depression severity between groups.

Variable ^a	Probiotic group (n = 119)	Control group (n = 121)	P value ^b	Cohen's d (between groups) ^d
Hamilton Depression Rating Scale (HDRS)				0.60
Before treatment	18.40 ± 2.36	17.94 ± 2.37	.13	
After treatment	6.42 ± 3.45	8.61 ± 4.15	.05	
P value (within-group) ^c	<.001	<.001		
Beck Depression Inventory (BDI)				0.61
Before treatment	36.94 ± 2.31	36.74 ± 2.21	.48	
After treatment	27.63 ± 4.13	30.24 ± 4.51	.05	
P value (within-group) ^c	.05	.05		

^aMean ± SD ^bindependent *t* test ^cpaired *t* test ^dCohen's *d* values were calculated using pooled standard deviations. Effect sizes of 0.2, 0.5, and 0.8 were considered small, moderate, and large, respectively. After treatment considered as time point.

interventions can significantly improve sexual function, especially in patients experiencing antidepressant-induced sexual dysfunction. Improvements were noted in reproductive parameters, sperm quality, and hormone-related sexual outcomes.²⁴

In men, although no direct RCT has yet examined probiotic effects on sexual function in men on SSRIs, mechanistic data suggest that gut microbiota and its metabolites can influence hormones and inflammatory pathways relevant to erectile function and other sexual domains in men.^{12,24} These benefits are likely mediated through modulation of systemic inflammation, neuroactive metabolites, and the gut–brain axis.^{12,24} Although formal minimal clinically important difference (MCID) values for the total IIEF-15 score have not been universally established,²⁵ the observed categorical change in the erectile function subscale (from mild-to-moderate to mild erectile dysfunction (ED)) provides an indirect measure of clinically meaningful improvement. Improvements in other subscales were numerical but did not cross categorical severity thresholds. Similarly, enhancements in sexual desire, orgasm, and overall satisfaction subscales in the probiotic group are consistent

with previous studies showing probiotics can improve sexual function and satisfaction in patients receiving SSRIs.^{12,13,24} Mechanistically, probiotics may reduce stress, improve mood, and modulate neuroendocrine pathways, thereby supporting sexual desire and satisfaction.^{12,13}

Although some studies have reported inconsistent or inconclusive results, particularly regarding different strains, dosages, and populations,^{26–28} the present study specifically evaluated men with mild to moderate depression, enhancing the relevance of our findings to this population. These discrepancies highlight the importance of strain-specific research and careful consideration of intervention duration, dosage, and patient characteristics in future trials. Importantly, our study demonstrates the feasibility and potential clinical benefit of Lactofem as an adjunctive therapy for depression and associated sexual dysfunction in men. However, it is acknowledged that the ideal duration to observe full effects of probiotics is not yet fully established, and longer-term studies are warranted to determine sustained efficacy. Additionally, stratifying patients based on factors such as baseline depression severity, comorbidities, and age could further optimize probiotic interventions and enhance clinical applicability.

Table 2 Comparison sexual function scores between groups.

Variable ^a	Probiotic group (n = 119)	Control group (n = 121)	P value ^b
Erectile function			
Before treatment	14.08 ± 6.29	13.74 ± 6.21	.59
After treatment	18.10 ± 4.59	14.88 ± 3.49	<.001
P value (within-group) ^c	<.001	0.23	
Orgasmic function			
Before treatment	6.78 ± 3.22	6.96 ± 2.94	.64
After treatment	8.73 ± 2.38	6.35 ± 1.94	<.001
P value (within-group) ^c	<.001	0.35	
Sexual desire			
Before treatment	4.68 ± 1.94	4.90 ± 1.54	.70
After treatment	5.88 ± 1.81	3.96 ± 1.65	<.001
P value (within-group) ^c	.09	0.07	
Intercourse satisfaction			
Before treatment	4.45 ± 2.33	3.90 ± 1.54	.97
After treatment	5.68 ± 1.94	4.46 ± 2.20	.05
P value (within-group) ^c	.91	0.07	
Overall satisfaction			
Before treatment	6.71 ± 1.24	5.58 ± 1.04	.06
After treatment	7.71 ± 1.24	5.68 ± 0.52	<.001
P value (within-group) ^c	.08	0.32	
Total score			
Before treatment	36.70 ± 7.79	35.08 ± 7.28	P = .11
After treatment	46.10 ± 5.94	35.33 ± 4.88	P < .001
P value (within-group) ^c	P < .001	P = .23	

^a Mean ± SD ^b independent *t* test ^c paired *t* test

In summary, this study provides evidence that adjunctive Lactofem improves both depressive symptoms and sexual function in men treated with SSRIs. The beneficial effects are likely mediated via the gut–brain axis, anti-inflammatory pathways, and serotonergic modulation. These findings underscore the therapeutic potential of probiotics in addressing SSRI-related sexual dysfunction and highlight the need for further RCTs to confirm these effects and establish optimal treatment parameters.

Strengths and limitations

The present study possesses several strengths. It employed a rigorous RCT design with well-defined inclusion criteria at baseline. The questionnaires used were adapted from previously validated instruments, and a sufficiently large sample size was included to enhance the statistical power of the analysis.

Several limitations should be noted. First, all participants were recruited from a university referral clinic, and all were married and residing in Iran, which may limit generalizability to unmarried individuals or other socio-cultural contexts. Second, the study lacked a placebo control and was open-label, so performance or expectation bias cannot be excluded; future trials should consider a double-blind, placebo-controlled design. Third, the relatively young age of participants may have reduced side effects from SSRIs, and prior use of SSRIs, probiotics, or PDE5 inhibitors was not assessed, though randomization likely balanced these factors. The 8-week follow-up primarily reflects short-term outcomes, limiting assessment of delayed or persistent sexual side effects, and the minimum required sexual activity at baseline may have constrained the observable changes. The absence of post-intervention follow-up prevents evaluation of the durability of probiotic effects. Additionally, sample size was estimated from depression outcomes, so the study may have been underpowered to detect smaller effects in sexual

function. Finally, while improvements in depression may have contributed to enhanced sexual function, the greater benefits in the probiotic group suggest a potential independent effect of probiotics. Future studies with larger samples and factorial designs are needed to clarify the specific contributions of SSRIs, probiotics, and depression improvement.

Conclusion

In conclusion, considering the limitations mentioned above, the results of the current first RCT study suggest that 8 weeks of probiotic consumption may improve depression severity in men with mild to moderate depression, sexual function, and sexual satisfaction in SSRI-treated men.

Author contributions

S.-A.T.: (Conceptualization-Equal, Data curation-Equal, Methodology-Equal, Writing—review & editing-Equal. M.S.: Data curation-Equal, Investigation-Equal, Writing—review & editing-Equal. M.H.M.-A.: Data curation-Equal. N.H.: Data curation-Equal, Writing—review & editing-Equal. Z.H.: Data curation-Equal. F.B.: Conceptualization-Equal, Data curation-Equal, Investigation-Equal, Project administration-Equal, Software-Equal, Supervision-Equal, Writing—original draft-Equal, Writing—review & editing-Equal.

Supplementary material

Supplementary material is available at *The Journal of Sexual Medicine* online.

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Conflicts of interest

The authors declare no conflict of interest.

Data availability

The primary data for this study is available from the authors on direct request. N.H.M., M.S., S.A.T., M.H.M., Z.H.M., F.B. contributed in conception, design, and drafting of the manuscript. N.H.M., M.S., M.H.M., Z.H.M. contributed in data collection. F.B., S.A.T. contributed in manuscript drafting. All authors approved the final version for submission. N.H.M. and F.B. oversaw the study.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. It was approved by the ethics committee of Yasuj University of Medical Sciences Ethics Committee, Yasuj, Iran (IR.YUMS.REC.1401.078). Written informed consent was gained from all patients; all participants were informed that they could withdraw at any point during the trial. This study was registered prospectively at the Iranian Registry of Clinical Trials (www.irct.ir). Trial registration: IRCT20160524028038N14.

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