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Research Paper

Probiotic Add-on Therapy in the First-episode Schizophrenia: A Randomized Controlled Trial

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ABSTRACT

Background: Some evidence supports probiotics' beneficial effects on clinical symptoms of patients with schizophrenia and relieving unwanted frequently associated side effects of antipsychotic drugs such as constipation, obesity, and metabolic disorders.

Objectives: This study aimed to assess the effect of probiotic supplements on clinical psychiatry symptoms and metabolic indices in patients with schizophrenia.

Materials & Methods: First-episode schizophrenic patients were randomly assigned to probiotics and placebo groups in a randomized controlled trial that took 12 weeks. The primary outcomes were the brief psychiatric rating scale (BPRS) change scores and positive and negative syndrome scale (PANSS). The secondary outcomes were clinical global impression-improvement scale (CGI-S), blood pressure (BP), body mass index (BMI), lipid profiles, and fasting blood sugar (FBS).

Results: A total of 62 patients were considered for the intention-to-treat analysis (mean age, 34.7 years; 23 women; 39 men). The results showed no significant differences in the primary objectives between the probiotic and placebo groups. In the probiotic group, subjects had lower levels of all biochemical variables (triglycerides, cholesterol, and FBS) compared to the subjects in the placebo group (standardized mean difference -4.3, -2.8, and -4.6, respectively; $P<0.05$).

Conclusion: We found that by adding probiotics to oral antipsychotics, BPRS or PANSS scores do not improve. However, Cohen's d for biochemical variables showed a medium to large effect size. This study suggests probiotic supplementation may regulate and control triglycerides, cholesterol, and FBS levels. Future studies are recommended to demonstrate these findings in the confirmatory analysis.

Keywords: Probiotics, Microbiota, Schizophrenia, Mental disorders, Antipsychotic agents

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Highlights

- Probiotic supplements failed to improve schizophrenia symptoms more than placebo.
- Lipid profile and blood sugar were lower in the probiotic group.
- Probiotics can have beneficial effects on body mass index and blood pressure.

Introduction

Schizophrenia (SZ) is a chronic and serious psychiatric disorder. Its prevalence in the world population is about 1% [1]. The disease is characterized by positive symptoms, negative symptoms, and cognitive dysfunction, the latter two being particularly resistant to antipsychotics [2]. Cognitive impairment and negative symptoms present challenges in managing SZ [3-6]. Therefore, it is necessary to regularly evaluate new combinations of nutritional and pharmacological therapy for these symptoms. Then again, antipsychotic medications are associated with cardiometabolic adverse effects, including weight gain, dyslipidemia, insulin resistance or frank type 2 diabetes mellitus, and hypertension [7].

Research into the pathogenesis of schizophrenia has pointed to a potential role for the human microbiome and the gut-brain axis, which involves bidirectional communication between the central and enteric nervous systems [8]. Disturbed gut microbiota is linked to increased systemic inflammation [9], and consequent neural inflammation may be directly related to schizophrenia [10].

Preclinical studies have consistently demonstrated that fecal microbiota transplantation from patients with different psychiatric disorders leads to the development of the behavioral and physiological profiles of the disease in germ-free mice [11-15]. In this regard, 4 studies [16-19] have examined the relationship between schizophrenia and probiotics and found that probiotic supplementation reduced the positive and negative syndrome scale (PANSS) scores but not significantly. On the other hand, evidence suggests that probiotics can reduce constipation [16, 20], weight gain, and metabolic side effects [21] commonly associated with antipsychotic use. Probiotics may improve metabolic parameters through anti-inflammatory and insulin-resistance properties [22]. Dickerson et al. [16] showed that probiotic supplementation for 14 weeks can prevent common physical symptoms in patients with SZ but have no effects on the clinical syndrome scale.

Despite the high prevalence of dyslipidemia in schizophrenia and the increased risk of metabolic complications and cardiovascular disease, the focus in this population is primarily on managing psychotic symptoms, and their physical health is generally overlooked.

To date, few studies have examined the lessening of metabolic impairments in patients with SZ, and the evidence regarding the effects of probiotics on metabolic status is insufficient. Research on schizophrenia needs more randomized clinical trials (RCTs) to provide sufficient proof, draw reasonable conclusions, and consequently determine the effect of probiotic supplements on the clinical symptoms and metabolic status of patients with SZ [23]. This study aimed to assess the impact of probiotic supplementation on improving clinical signs and adverse metabolic effects commonly observed in patients with first-episode schizophrenia receiving antipsychotics.

Materials and Methods

Study patients

From March 2019 to June 2021, a randomized, double-blind, placebo-controlled trial was conducted at Shafa Hospital, Rasht City, Iran. This study included inpatients from the Psychiatric Department who met the eligibility criteria: 1) Aged between 18 and 60 years, 2) First-episode schizophrenia diagnosis according to the DSM-5, and 3) Clinically stable for 4 weeks or more. Clinical stability was defined as 1) No change in oral antipsychotics (olanzapine or risperidone) dosage, 2) Clinical global impressions-improvement of illness (CGI-S) score ≤4, and 3) Positive symptom score ≤4 in brief psychiatric rating scale (BPRS). The exclusion criteria were as follows: 1) Duration of positive symptoms exceeding two years, 2) Diagnosis of serious neurologic or cardiovascular disease, 3) Using any drug for weight loss, 4) A history of substance use or alcohol in the last three months (except nicotine or caffeine), 5) Receiving antibiotics for any reason in the last two weeks, 6) Mental retardation (intelligent quotient of <70), and 7) Pregnancy.

Study design

After enrollment in the clinical study, the patients were treated on an outpatient basis. All patients received probiotic supplements (FamiLact capsule, Zist Takhmir Co., Tehran, Iran) or a placebo once daily. FamiLact capsules (500 mg) contain gram-positive organisms and 38.5 mg Fructooligosaccharides. The microorganisms are 9×10^9 colony-forming units (CFU)/g of viable, lyophilized *Lactobacilli* (*Lactobacillus Acidophilus, Lactobacillus Casei, Lactobacillus Delbrueckii* Subsp. *Lactobacillus Bulgaricus*, and *Lactobacillus Rhamnosus*), 1.25×10^{10} of Bifidobacteria (*Bifidobacterium Longum* and *Bifidobacterium Breve*), and 1.5×10^{10} of *Streptococcus Salivarius* Subsp. *Thermophilus*.

Randomization and blinding

Patients who met the inclusion criteria were randomly assigned to probiotic and placebo groups (equal numbers) for 12 weeks. Randomization and blinding were performed by an independent pharmacist using a sealed coded envelope. Block randomization (size 4) was performed using a computer-generated random allocation sequence. The probiotic supplement and placebo were indistinguishable in appearance and content.

Outcome measures

The primary endpoints were assessing clinical symptoms using BPRS and PANSS. Secondary endpoints included the severity of psychiatric symptoms using CGI-S, clinical response, and biometric and biochemical measures. Clinical response was defined as a ≥25% reduction in BPRS score after 3 months. Biometric and biochemical variables included blood pressure (BP), body mass index (BMI), triglycerides (TG), total cholesterol, and fasting blood sugar (FBS). Lipid profiles and FBS were measured using an enzymatic kit (Pars Azmun, Tehran, Iran) with intra-assay CVs of less than 5%. Primary objectives were measured at baseline and then 4, 8, and 12 weeks after the study started. All secondary objectives were assessed at baseline and 12 weeks later.

Sample size

The required sample size was computed using the Stata statistical software, version 14 (StataCorp LP, College Station, TX, USA). Leucht et al. [24] demonstrated a 25% BPRS score reduction as "minimally improved." According to the included trials in this study, the standard deviation of the BPRS total score at baseline was 12.2. In addition, Leddy-Stacy and Rosenheck [25] suggested the minimum clinically important difference for the PANSS to be between 4.25 and 8.30 total points. From a previous study [18], we estimated the Mean±SD difference between active intervention and placebo group to be 70.9±11.4. Furthermore, we supposed that a 5-point difference in PANSS between active intervention and placebo would be clinically significant. Using analysis of covariance (ANCOVA) with a correlation coefficient of 0.7, 80% power, and 95% confidence at three measurement points, a total of 52 participants would be required. Accounting for a 20% loss, 62 participants (31 per arm) would be sufficient to estimate effect sizes for each of the two primary objectives.

Statistical analyses

We presented quantitative variables with Mean±SD and categorical variables with absolute frequencies and percentages. Data normality was assessed with the Shapiro-Wilk test. Repeated measures of analysis of variance (ANOVA) were used to analyze the effect of probiotics on primary objectives (BPRS and PANSS). Partial Eta squared (η^2) was used to calculate effect sizes for significant main effects, with the following standards to determine small (0.01-0.059), medium (0.06-0.139), and large (>0.14) effect sizes.

Secondary analyses were exploratory without formal sample size estimation. The clinical response variable was considered a categorical variable. A chi-squared test was performed to assess the effect of probiotics on the clinical response. The chi-squared test compared the proportion of patients with a CGI-S score of 1 or 2 (very much or much improved). Other secondary objectives were analyzed using analysis of variance/covariance (ANOVA/ANCOVA) after adjusting for the baseline levels of variables. We presented effect sizes as standardized mean differences (Cohen's d) or risk ratios (RR) with 95% confidence intervals (95% CI).

Data were analyzed according to the intention-to-treat principle using the Stata statistical software. To handle missing data, we used simple mean imputation [26]. Also, we used subgroup analysis, comparing the baseline characteristics between completers and dropouts. Statistical tests were two-tailed. P≤0.05 were considered to indicate statistical significance.

Results

Of 62 enrolled patients, 55(88.7%) completed the study. There were no significant differences in baseline characteristics between 7 patients who dropped out at

week 8 or 12 and completers (Supplementary Table 1). Figure 1 depicts the flow of patients' enrolment through the study according to the consolidated reporting trial standards (CONSORT) statement. Table 1 presents the patients' characteristics at baseline. None of the variables with a P<0.05 were strong confounders for primary and secondary objectives [27, 28].

Primary outcomes

Clinical psychiatric symptoms (BPRS and PANSS) improved in both groups at 12 weeks (Table 2), and repeated measure ANOVA revealed a significant effect of time on these outcomes with medium effect sizes (Figure 2, Figure 3). The mean BPRS score was reduced from 44.4 to 29.4 in the probiotic group and 45.4 to 32.6 in the placebo group. However, the results indicated no significant group effect on clinical symptoms (P=0.296).

The mean total score of PANSS was reduced by 26.3, from 64.7 at the baseline to 38.4, after receiving antipsychotic drugs and probiotics for 12 weeks and by 21.2, from 61.45 at the baseline to 40.3, in the placebo group. Also, we observed no significant difference in PANSS score improvement between the two groups (P=0.995). Similar trends were also observed for all subscales of the PANSS (Supplementary Table 1). Mean differences of primary objectives at varying times and results of repeated measure ANOVA could be observed in Table 3.

In addition, we calculated effect sizes using Cohen's d formula to examine the extent of treatment effects within the group. Effect sizes were classified as small (0.20–0.49), medium (0.50–0.79), and large (0.80 and more). Large effect sizes were observed in the BPRS and the PANSS in the probiotic group at 4 weeks (0.87 and 1.52), at 8 weeks (1.47 and 2.30), and at 12 weeks (2.02 and 2.73).

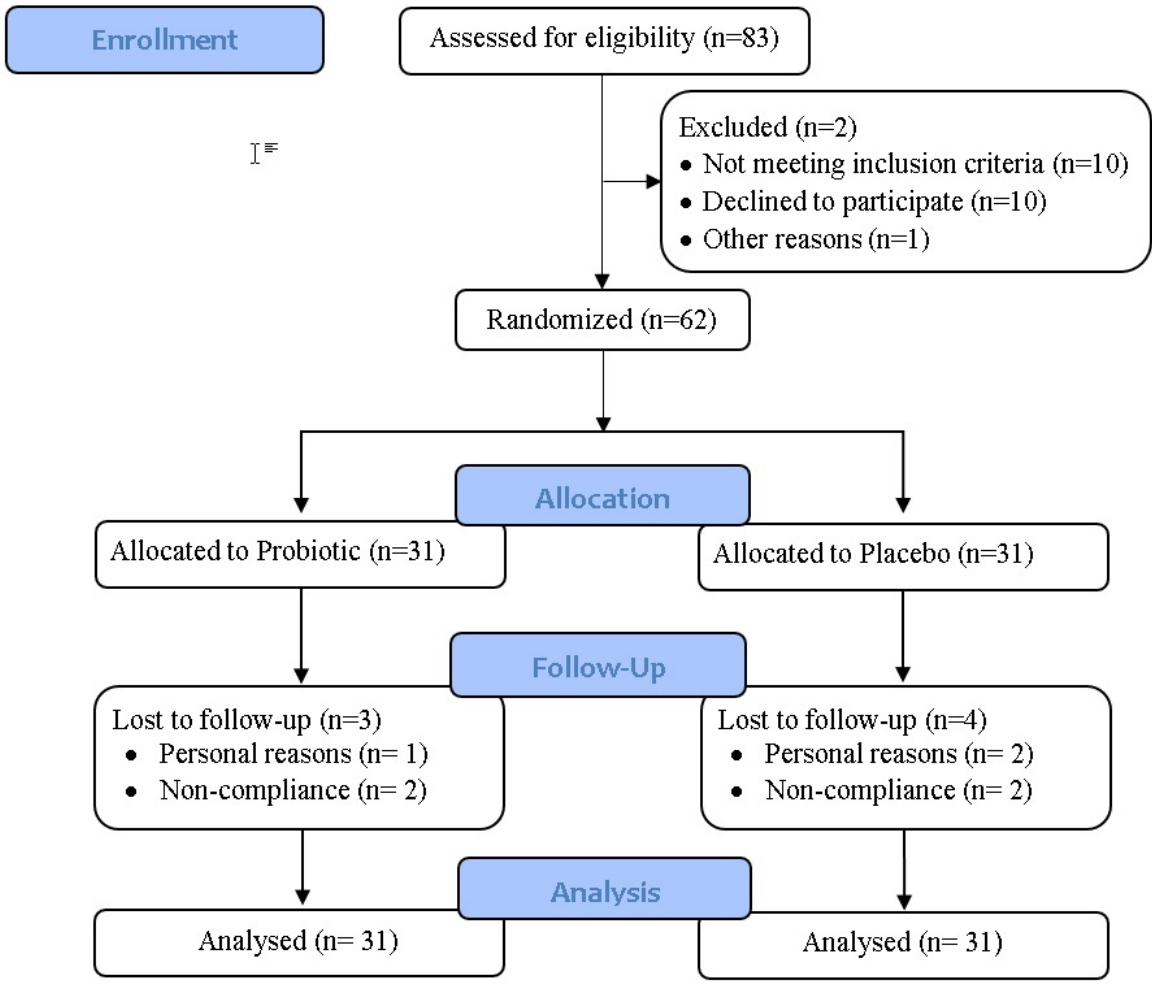

Figure 1. Overview of patients' flow chart

Table 1. Baseline demographics of the patients* (n=31)

Variables		Mean±SD/No. (%)		P
		Probiotic	Placebo	
Age (y)		34.2±10.2	36.5±10.8	0.39
Female		11(35.5)	12(38.7)	0.79
Smoker		23(74.2)	21(67.7)	0.58
Body weight (kg)		73.8±7.9	74.5±10.3	0.77
BMI (kg/m^2)		27.3±2.6	27.5±2.9	0.78
Location	Urban	21(67.7)	23(742)	0.58
	Rural	10(23.3)	8(25.8)	
Having a job		14(25.8)	17(54.8)	0.45
Education level (y)		9.0±5.0	8.4±5.5	0.64
Married		14(45.2)	15(48.4)	0.80
Blood pressure (mm Hg)	Systolic	116.5±9.5)	114.5±13.6	0.52
	Diastolic	79.7±8.3)	77.5±9.4	0.33
FBS (mg/dL)		90.6±9.1	91.8±10.7	0.64
TG (mg/dL)		105.8±27.4	110.3±58.1	0.70
Cholesterol (mg/dL)		152.4±27.6	153.1±26.7	0.92
Drug	Risperidone	22(71.0)	20(61.3)	0.59
	Olanzapine	9(29.0)	11(38.7)	
Chlorpromazine equivalent dosage (mg)		487.1±138.4	506.5±106.3	0.54
CGI-S score	2	6(19.4)	5(16.1)	0.18
	3	16(51.6)	19(61.3)	
	4	9(29.0)	7(22.6)	
PANSS	Negative	13.0±3.2	12.4±2.8	0.44
	Positive	13.3±3.0	12.5±3.5	0.34
	General	38.4±7.4	36.5±9.5	0.38
	Total	64.7±12.6	61.4±14.6	0.34
BPRS		45.4±12.0	44.4±8.8	0.71

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Abbreviations: BMI: Body mass index; FBS: Fasting blood sugar; TG: Triglyceride; CGI-S: Clinical global impression-improvement scale; PANSS: Positive and negative syndrome scale; BPRS: Brief psychiatric rating scale.

*To determine the equivalence of baseline characteristics, we used the t-test for continuous variables and the chi-squared test for dichotomous variables.

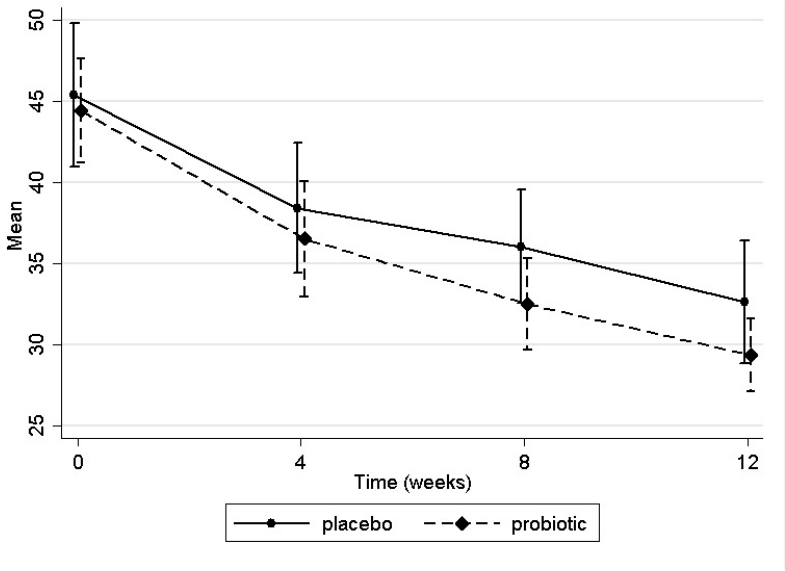

Figure 2. Change in brief psychiatric rating scale in the probiotic and placebo groups

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The bar indicated a 95% CI.

Secondary outcomes

Clinical responses in the probiotic and placebo groups were observed in 11 patients (39.3%) and 15 patients (55.6%), respectively (RR: 0.72; 95% CI, 0.42%-1.24%; X^2=1.46; P=0.23). In terms of CGI-S, a score of 1 or 2 was observed in 19 patients (54.3%) in the probiotic group and 16 patients (45.7%) in the placebo group (RR: 1.20; 95% CI, 0.70%-2.06%; X^2=0.44; P=0.51). Adjusting for baseline values, the systolic blood pressure and BMI were similar in the two groups. The mean diastolic blood pressure was 82.1(5.2) mm Hg with probiotics and 75.6(4.6) mm Hg with placebo (Cohen's d: 4.79; 95% CI, 2.78%-6.80%; P<0.001). Interestingly, statistical analyses showed lower levels of all three biochemical variables (FBS, triglyceride, and cholesterol) in the probiotic group compared to the placebo group (P<0.05). The Cohen's d for these biochemical variables were 0.70, 1.57, and 0.68, respectively. The magnitude of these values was interpreted as a medium-large effect size. Table 4 shows the results of ANOVA/ANCOVA analyses in detail.

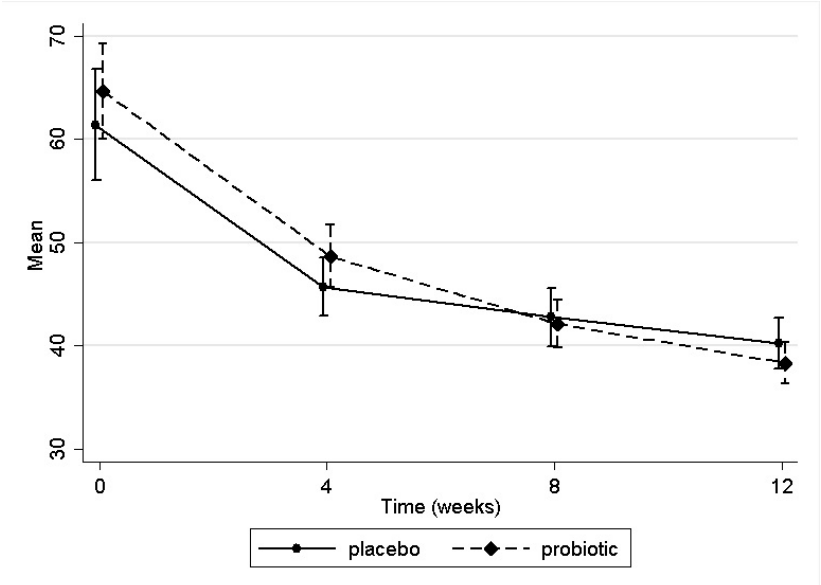

Figure 3. Changes in positive and negative syndrome scale total score in the probiotic and placebo groups

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The bar indicated a 95% CI.

Table 2. Primary and secondary outcomes at 12 weeks between probiotic and placebo groups

Variables		Mean±SD/No. (%)	
		Probiotic (n=28)	Placebo (n=27)
PANSS	Negative	8.0(1.4)	8.4(1.8)
	Positive	8.1(1.6)	8.4(2.1)
	General	22.3(4.4)	23.5(4.0)
	Total	38.4(5.2)	40.3(6.3)
BPRS		29.4(5.7)	32.6(9.5)
Clinical response		11(39.3)	15(55.6)
CGI-S	1	0(0.0)	3(11.1)
	2	19(6739)	13(48.2)
	3	9(32.1)	11(40.7)
BMI (kg/m^2)		25.5(2.8)	26.7(3.1)
Blood pressure (mm Hg)	Systolic	114.3(7.2)	112.6(11.6)
	Diastolic	82.1(5.2)	75.6(4.5)
FBS (mg/dL)		93.3(6.7)	97.7(5.8)
TG (mg/dL)		115.8(36.8)	128.3(29.7)
Cholesterol (mg/dL)		158.6(23.1	176.8(30.1)

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Abbreviations: BMI: Body mass index; FBS: Fasting blood sugar; TG: Triglyceride; CGI-S: Clinical global impression-improvement scale; PANSS: Positive and negative syndrome scale; BPRS: Brief psychiatric rating scale.

Post-hoc analysis

The Mean±SD weight of patients in the probiotics and placebo groups was 81.9(9.1) kg and 85.1(11.0) kg, respectively. Patients in the probiotic group gained 7.9 kg, while those in the placebo group gained 10.6 kg. The difference in weight between the two groups was not significant (P=0.08). We identified individuals who experienced a weight gain of 7% or more [29]. In the first three months, 62.5% of individuals in the olanzapine group and 70.0% in the risperidone group gained weight by 7% or more from baseline in the probiotic group. However, the corresponding values in the placebo group were 100.0% and 66.7%, respectively.

Table 3. Comparing clinical symptoms using PANSS and BPRS between probiotic and placebo groups at 4, 8, and 12-weeks of intervention

Outcome	Mean Difference (95% CI)			Result of RM-ANOVA*	
	4 weeks	8 weeks	12 weeks	Effect size**	P
PANSS	3.0 (-1.8, 7.7)	-0.6 (-5.4, 4.2)	-1.9 (-6.7, 2.9)	<0.001	0.995
BPRS	-1.9 (-6.7, 2.9)	-3.5 (-8.4, 1.3)	-3.3 (-8.2, 1.6)	0.02	0.296

PANSS: Positive and negative syndrome scale; BPRS: Brief psychiatric rating scale.

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*Repeated measures analysis of variance, **Partial eta squared.

Table 4. Comparing biometric outcomes at 12 weeks between probiotic and placebo groups*

Variables		Probiotic	Placebo	MD	SMD	P
Blood pressure	Systolic	113.4(1.3)	113.5(1.3)	-0.15	-0.08	0.935
	Diastolic	82.0(4.8)	75.7(4.8)	6.28	4.79	<0.001
Body mass index (kg/m^2)		30.6(2.1)	31.6(2.1)	-1.09	-1.96	0.056
Triglycerides		112.6(16.6)	131.3(15.7)	-18.70	-4.30	<0.001
Cholesterol		161.0(18.7)	174.7(17.6)	-13.70	-2.78	0.008
Fasting blood sugar		93.1(4.0)	97.9(3.7)	-4.80	-4.60	<0.001

*MD: Mean difference; SMD: Standardized mean difference.

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Discussion

Antipsychotic medication is associated with side effects, including metabolic dysregulation, constipation, and cognitive impairment. Probiotics have been investigated as a potential intervention to prevent or reduce these side effects with several studies reporting promising results. A recent meta-analysis showed the effects of probiotic supplementation in several psychiatric disorders [30]. However, it is uncertain whether probiotics improve clinical symptoms in SZ patients. We could not observe any significant effects of the intervention on BPRS and PANSS (effect size of 0.02 for BPRS and <0.001 for PANSS). This result was consistent with previous studies [16, 31]. Dickerson treated SZ patients with probiotic or placebo supplementation in a randomized controlled trial. The researchers did not observe a significant difference in psychiatric symptom scores between probiotic and placebo-supplemented groups [16]. Similarly, two subsequent studies reported no significant difference in PANSS scores in probiotic supplementation [18, 19].

Contrary to these studies, Ghaderi et al. [17] observed an improvement in general and total PANSS scores in patients with chronic schizophrenia after taking probiotics and vitamin D for 12 weeks. However, it had no effects on negative and positive subscales and BPRS scores. The current disagreements could be explained through different doses of probiotics, various study designs, and participants' diverse characteristics. We used an add-on design where all patients received standard therapy with either probiotics or placebo. Although this design is common in therapy trials for different diseases, such studies are not directly informative about a drug as monotherapy. Therefore, a larger research may need to be conducted to find a significant difference.

The present trial showed the positive effects of probiotic supplementation on weight, FBS, and lipid profile (metabolic indices). In line with the present study, Ghaderi et al. [17] reported the beneficial effects of vitamin D and probiotics on lipid profiles and glycemic control in chronic schizophrenia. Kang et al. [32] conducted an RCT to assess the efficacy and safety of probiotic supplements in mitigating antipsychotic-induced metabolic disturbance and increased body weight. Drug-naïve first-episode schizophrenia patients were randomly assigned to receive olanzapine plus probiotics or olanzapine alone. After 12 weeks of treatment with the addition of probiotics, the researchers found a nominal level of significant differences in BMI and body weight between treatments. Still, these changes became non-significant after adjusting for increased appetite. Lipid profiles (triglycerides, total cholesterol, high-density lipoprotein, and low-density lipoprotein) significantly increased in both groups (P<0.0001). However, only total cholesterol shows a significant difference between the two treatment groups (P=0.028). Another study [31] compared the effects of probiotics and dietary fiber on weight gain and metabolic disturbances in drug-naïve, first-episode schizophrenia patients receiving olanzapine. After 12 weeks, FBS and lipid profiles (except for HDL-C) showed no significant difference between the two groups. Huang et al. [33] assessed the effects of probiotics and dietary fiber alone or in combination on weight gain due to atypical antipsychotics in patients with schizophrenia or bipolar disorder. The study found that probiotics plus dietary fiber significantly reduced weight and prevented further deterioration of metabolic disturbances, and probiotics or dietary fiber alone could prevent further weight gain. Huang et al. [34] conducted two sequential, randomized clinical trials and reported that probiotics plus dietary fiber could reduce weight gain in drug-naïve, first-episode schizophrenia patients receiving antipsychotic drugs. The first study showed insignificant differences

in weight gain between the olanzapine plus probiotics group and the olanzapine alone group at week 12. In the second study, the probiotics plus dietary fiber group gained less weight than the olanzapine alone group at week 12. The authors also found that probiotic supplementation significantly improved cognitive function and lowered FBS levels in these patients.

A recent study in rats indicated that co-administration of antibiotics ameliorated impairment in the microbiota and metabolic disorders due to olanzapine, including weight gain, visceral fat deposition, increased plasma-free fatty acids, and macrophage infiltration into adipose tissue [35]. Zhai et al. [36] indicated an early-onset nature of HDL-C abnormalities in drug-naïve first-episode schizophrenia patients. After an average of 22.7 days of antipsychotic exposure, lipid abnormalities, and insulin resistance markers were significantly elevated. Moreover, results of the recovery after an initial schizophrenia episode (RAISE) study [37] showed that after an average of 47.3 days of antipsychotic treatment, 48.3% of subjects were obese or overweight, 56.5% had dyslipidemia, 10.0% had hypertension, and 13.2% had metabolic syndrome. Therefore, improving metabolic indices in the probiotic group could be important, and the microbiota may be a novel approach for treating metabolic comorbidity in patients with schizophrenia.

Conclusions

We found no significant group effect on clinical psychiatric symptoms (BPRS and PANSS) in patients in the first episode of psychosis. Exploratory analyses have shown significant positive effects of probiotics on triglyceride, cholesterol, and FBS levels. Probiotics may have potential benefits in preventing or reducing antipsychotic side effects, particularly metabolic dysregulation. Therefore, an add-on probiotic strategy may be considered in patients with schizophrenia.

Study limitations

This study had some limitations. First, we did not control for non-pharmacological interventions prescribed to reduce antipsychotic-induced weight gain. Dietary counselling, exercise interventions, cognitive and behavioural strategies could have significant positive effects on weight loss, waist circumference, triglycerides, fasting blood sugar and insulin [38]. Secondly, as this was a 12-week trial, the beneficial effects of probiotic supplements on clinical signs of schizophrenia might be observed in studies with longer durations. The short study period may not have allowed sufficient time for intervention to impact outcomes. It is necessary for a long-term, confirmatory study to reinforce the current analyses. Thirdly, CGI-I has been considered a secondary objective in this study, thus our finding about this variable is exploratory and should be confirmed by more studies. Fourthly, the beneficial effects of probiotic supplements on cardiovascular risk factors are exploratory findings and our study was not designed to determine these effects. This must be tested in RCTs with acceptable power. Lastly, risperidone or olanzapine have different receptor profiles and consequently exhibit distinct adverse metabolic and endocrine effects, although the number of patients taking each medications did not show a significant difference.

Ethical Considerations

Compliance with ethical guidelines

All study procedures were done in compliance with the ethical guidelines of the Declaration of Helsinki 2013. The trial was registered at the Iranian Registry of Clinical Trials (IRCT) (Code: IRCT20120603009934N2). The protocol was approved by the Ethics Committee of Guilan University of Medical Sciences (GUMS), Iran (Code: IR.GUMS.REC.1397.456). All subjects or their legal guardians signed informed consent before the start of the study.

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Authors contributions

Conceptualization and methodology, writing, review, and editing: All authors; Investigation and writing the original draft: Seyede Melika Jalali; Resources and supervision: Robabeh Soleimani and Mir Mohammad Jalali.

Conflict of interest

The authors declared no conflict of interest.

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Supplementary Table 1. Antipsychotic treatment effect on psychopathological symptoms*

Group		Time			
		Baseline	Week 4	Week 8	Week 12
Total	Probiotic	64.7(12.6)	48.7(7.9)	42.1(5.9)	38.4(5.2)
	Placebo	61.4(14.6)	45.7(7.3)	42.8(7.2)	40.3(6.3)
Positive	Probiotic	13.3(3.0)	10.0(2.6)	8.9(1.9)	8.1(1.6)
	Placebo	12.5(3.5)	9.4(2.3)	8.4(2.0)	8.4(2.1)
Negative	Probiotic	13.0(3.2)	9.9(2.3)	8.7(1.6)	8.0(1.4)
	Placebo	12.4(2.8)	9.5(1.9)	8.9(2.3)	8.4(1.8)
General	Probiotic	38.4(7.4)	28.8(4.2)	24.5(3.8)	22.3(4.4)
	Placebo	36.5(9.5)	26.8(4.6)	25.4(4.5)	23.5(4.0)

Group		Between Groups		Time Main Effect		Group-time interaction	
		P	Effect Size	P	Effect Size	P	Effect Size
Total	Probiotic Placebo	0.995	<0.001	<0.001	0.75	0.044	0.07
Positive	Probiotic Placebo	0.746	0.002	<0.001	0.543	0.24	0.025
Negative	Probiotic Placebo	0.877	<0.001	<0.001	0.562	0.17	0.030
General	Probiotic Placebo	0.930	<0.001	<0.001	0.681	0.03	0.053

Effect size: Partial eta squared.

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Supplementary Table 2. Baseline comparisons between completers and non-completers due to lost to follow-up*

Variables		Completers (n=55)			Non-completers (n=7)		
		Mean±SD/No. (%)	Min	Max	Mean±SD/No. (%)	Min	Max
Female		21(38.2)			2(28.6)		
Smoking		39(70.9)			5(71.4)		
Age (y)		34.7±10.6	18	53	26.1±26.0	18.0	38.0
Having a job		28(50.9)			3(42.9)	7.0	12.0
Education level	<12 years 12-14 years >14 years	36(65.5) 8(14.6) 11(20.0)			5(71.4) 1(14.3) 1(14.3)		
Married		26(47.3)			3(42.9)		
Drug	Risperidone Olanzapine	37(62.3) 18(32.7)			5(71.4) 2(28.6)		
Chlorpromazine equivalent dosage (mg)		498.2±120.9	300	600	485.7±146.4	300	600
Weight (kg)		74.3±9.4	55.7	102.4	72.8±6.6	62.6	82.2
Body mass index (kg/m$^{2)}$)		27.7±2.7	22	37.6	25.1±1.7	23	28.1
Fasting glucose (mmol/L)		91.3±9.9	73	105	90.1±10.5	76	102
Blood pressure	Systolic Diastolic	116.7±11.5 79.2±9.0	100 60	140 90	105.7±7.9 73.9±6.3	100 60	120 80
Triglyceride (mmol/L)		108.4±46.4	58	245	105±36.3	76	168
Cholesterol (mmol/L)		154.9±25.1	100	195	136.4±37.0	98	198
CGI-S score	2 3 4	10(18.2) 31(56.4) 14(25.5)			1(14.3) 4(57.1) 2(28.6)		
PANSS		61.9±13.4	47	93	72±12.9	56	92
BPRS		43.1±9.6	27	60	59.3±4.2	56	68

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Abbreviations: CGI-S: Clinical global impression-improvement scale; PANSS: Positive and negative syndrome scale; BPRS: Brief psychiatric rating scale.

*Completers and non-completers have no significant difference in all baseline characteristics.

CONSORT 2010 Checklist of information to include when reporting a randomised trial*

Section/Topic		Item No	Checklist Item	Reported on Page No.
Title and abstract		1a	Identification as a randomized trial in the title	Title page
		1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CONSORT for abstracts)	Abstract (1)
Introduction	Background and objectives	2a	Scientific background and explanation of the rationale	2
		2b	Specific objectives or hypotheses	2
Methods	Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3
		3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
	Participants	4a	Eligibility criteria for participants	3
		4b	Settings and locations where the data were collected	3
	Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	3-4
	Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	3
		6b	Any changes to trial outcomes after the trial commenced, with reasons	-
	Sample size	7a	How sample size was determined	4
		7b	When applicable, explanation of any interim analyses and stopping guidelines	-
	Randomization: Sequence generation	8a	Method used to generate the random allocation sequence	3
		8b	Type of randomization; details of any restriction (such as blocking and block size)	3
	Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	3
	Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	3
	Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes), and how	3
		11b	If relevant, a description of the similarity of interventions	3
	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	4
		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	4
Results	Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	4
		13b	For each group, losses and exclusions after randomization, together with reasons	4-5
	Recruitment	14a	Dates defining the periods of recruitment and follow-up	3
		14b	Why the trial ended or was stopped	-

Section/Topic		Item No	Checklist Item	Reported on Page No.
Results	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
	Numbers analysed	16	For each group, the number of participants (denominator) included in each analysis and whether the analysis was by originally assigned groups	Table 2
	Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Tables 3, 4
		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	5
	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	5
	Harms	19	All important harms or unintended effects in each group (for specific guidance, see CONSORT for harms)	-
Discussion	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	8
	Generalisability	21	Generalisability (external validity, applicability) of the trial findings	7-8
	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	-
Other information	Registration	23	Registration number and name of trial registry	2
	Protocol	24	Where the full trial protocol can be accessed, if available	2
	Funding	25	Sources of funding and other support (such as the supply of drugs), role of funders	9

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*We strongly recommend reading this statement in conjunction with the CONSORT 2010 explanation and elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomized trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: For those and up-to-date references relevant to this checklist, see www.consort-statement.org.