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Probiotics Plus Dietary Fiber Supplements Attenuate Olanzapine-Induced Weight Gain in Drug-Naïve First-Episode Schizophrenia Patients: Two Randomized Clinical Trials

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Background and Hypothesis: **Antipsychotic-induced weight gain is associated with alterations to the composition of the gut microbiota. The purpose of this study was to determine the effect of probiotics plus dietary fiber on antipsychotic-induced weight gain.** ***Study Design:*** **Two sequential, randomized clinical trials were conducted. In Study 1, 90 drug-naïve, first-episode schizophrenia patients were randomized to receive either olanzapine plus probiotics or olanzapine monotherapy for 12 weeks. In Study 2, 60 drug-naïve, first-episode schizophrenia patients were randomly assigned to receive either olanzapine plus probiotics and dietary fiber or olanzapine monotherapy for 12 weeks.** ***Study Results:*** **In Study 1, no significant differences in weight gain were observed between the two groups. The insulin resistance index (IRI) was lower in the olanzapine plus probiotics group compared with the olanzapine monotherapy group at week 12 (estimated mean difference, −0.65, [95% confidence interval (CI), −1.10 to −0.20]; $p = .005$). In Study 2, weight gain was lower in the probiotics plus dietary fiber group than in the olanzapine monotherapy group at week 12 (estimated mean difference −3.45 kg, [95% CI, −5.91 to −1.00]; $p = .007$). At week 12, IRI increased significantly in the olanzapine monotherapy group (mean, 1.74; standard deviation (SD) = 1.11, $p < .001$), but not in the olanzapine plus probiotics and dietary fiber group (mean 0.47, SD = 2.16, $p = .35$) with an estimated mean difference of −0.95 between the two groups [95% CI, −1.77 to −0.14]; $p = .022$).** ***Conclusions:*** **These results provide support for the efficacy and safety of probiotics plus dietary fiber in attenuating antipsychotic-induced weight gain in drug-naïve, first-episode schizophrenia patients.**

Key words: schizophrenia/weight gain/probiotics/dietary fiber/insulin resistance

Introduction

Second-generation antipsychotics (SGAs) are widely used as first-line medications to treat schizophrenia. However, antipsychotic-induced weight gain, insulin resistance, and metabolic disturbances are concerning.[1] These side effects not only affect patients' compliance with antipsychotic medications, but also cause substantial morbidities, such as diabetes, cardiovascular disease, and strokes, which can ultimately lead to premature death.[2,3] Olanzapine is a widely used SGAs, and it is one of the most efficacious antipsychotic drugs in patients with schizophrenia.[4] In the Second-Generation Antipsychotic Treatment Indication Effectiveness and Tolerability in Youth Study, 84% of participants who were administered olanzapine gained more than 7% of their baseline body weight during the first 3 months.[5] Despite these data, there are currently few trials examining the prevention of weight gain and metabolic side effects among patients taking antipsychotics.

The mechanism of antipsychotic-induced weight gain and metabolic disturbances has not been elucidated.[6] Previous studies have indicated that antipsychotic-induced weight gain and metabolic dysfunctions were partly attributable to gut microbiome alterations.[7–9] Bahra et al.[10] showed that risperidone-treated mice exhibited significant weight gain due to shifts in the gut microbiome and suppression of energy expenditure. A study showed that the body weight of adolescents

with psychiatric illness had significantly increased with chronic risperidone treatment, and this increase was associated with a significantly higher *Firmicute*:*Bacteroidetes* ratio compared with antipsychotic-naïve controls.[9] Additionally, rats chronically treated with olanzapine showed altered fecal microbiota profiles, which might have been associated with olanzapine-induced metabolic changes.[11] These findings suggest that microbiota alterations may mediate antipsychotic-induced weight gain and metabolic dysfunction.

The gut contains approximately 500–1000 different microorganisms.[12] The gut microbiota in germ-free mice plays an important role in regulating energy harvest and storage, as well as weight gain and fat composition.[13] Probiotics are live microorganisms (including *Bifidobacterium* and *Lactobacillus*) that confer multiple health benefits.[14–16] Vitamin D supplementation with probiotics improved clinical symptoms and metabolic dysfunctions in patients with schizophrenia treated with chlorpromazine and anticholinergic agents for 6 months.[17] However, few studies have explored the attenuation of metabolic disturbances in patients with schizophrenia,[18] and sufficient evidence for the effects of probiotics on these patients is still lacking.

Dietary fiber is a non-digestible, fermented ingredient that functions as a substrate for bacterial metabolism, resulting in growth and changes in the activity of microbiota.[16] Zhao et al.[15] found that dietary fiber induced a greater reduction in body weight and improved blood lipid profiles and glucose control in individuals with diabetes mellitus. Despite these encouraging results, its efficacy in schizophrenia is controversial.[19] Kao et al.[20] found that dietary fiber supplementation (B-GOS®) alone improved the metabolic index in rats but was not effective for improving weight and body mass index (BMI) in patients with schizophrenia who were stable on antipsychotic drugs for >3 months.

In the gut, probiotics competitively inhibit other microbes to confer health benefits. The addition of dietary fiber promotes gut microbiome carbohydrate fermentation, which is the main activity of human gut microbiota.[16] Probiotics, especially in combination with dietary fiber, improved glycemic conditions in pre-diabetic individuals.[21] Thus, we hypothesized that probiotics and/or dietary fiber supplementation might be useful for patients with schizophrenia. We performed two clinical trials (Study 1 and Study 2) to evaluate the efficacy of probiotics and probiotics plus dietary fiber in attenuating olanzapine-induced weight gain.

Methods

Study Design

Both studies were randomized clinical trials. In Study 1, we assessed the effect of probiotics alone on weight gain in drug-naïve patients with first-episode schizophrenia being treated concurrently with antipsychotics. In Study 2, we evaluated the effects of probiotics plus dietary fiber on olanzapine-induced weight gain and metabolic disturbances. The study protocols were approved by the ethics committee of the Second Xiangya Hospital, Central South University, and the studies were conducted in accordance with the Declaration of Helsinki.

Participants

All participants were recruited by investigators from the Department of Psychiatry of the Second Xiangya Hospital at Central South University, China. Participants for Study 1 were recruited from November 30, 2017, to February 01, 2019, and participants for Study 2 were recruited from February 15, 2019, to May 05, 2020. The inclusion/exclusion criteria and all procedures were the same in the two studies. Patients with schizophrenia (aged 18–50 years) were diagnosed according to the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Only patients who experienced the first episode of schizophrenia were enrolled. None of the patients had used antipsychotics or recreational drugs for at least 3 months before enrollment. The trial was registered at clinicaltrials.gov, Identifier NCT03379597.

The following exclusion criteria were applied: (1) patients with inflammatory bowel disease, previous gastrointestinal tract surgery, or colon diseases; (2) patients who had used probiotics or antibiotics ≤4 weeks before the study or long-term laxative use; (3) patients with intellectual disabilities or addictive disorders; (4) patients with specific systemic or metabolic disorders, such as diabetes mellitus, dyslipidemia, cardiovascular diseases, or hypertension; (5) pregnant or lactating patients.

Written informed consents were obtained from all the participants after they received a complete description of the study.

Randomization and Masking

In Study 1, 90 participants were randomly assigned (1:1) in blocks of four to either 12-week olanzapine (15–20 mg/day) plus probiotics (Bifico, tipple live bacteria oral capsule, 840 mg twice daily, Shanghai Xinyi Pharmaceutical Inc., Shanghai, China) treatment or 12-week olanzapine alone treatment (15–20 mg/day). In Study 2, 60 participants were randomly assigned (1:1) in blocks of four to either a 12-week olanzapine (15–20 mg/day) and probiotics (840 mg twice daily) plus dietary fiber (30 g twice daily) treatment or a 12-week olanzapine (15–20 mg/day) alone treatment. The participants in both studies were assigned using a computer-based random number generator. A research nurse who was not present during the treatment administration conducted the randomization. The treating clinicians were not blinded to the groups, but blinded independent assessors evaluated al the primary and most of the secondary outcomes.

Bifico is a commonly used probiotics supplement in China containing live *Bifidobacterium*, *Lactobacillus*, and *Enterococcus* at concentrations ≥5.0 × 10^7 CFU/g. The dietary fiber (Perfect China Co., Zhongshan, China) included two modified and simplified formulas.[15] Formula No. 1 was a powder preparation containing bitter melon (*Momordica charantia*) and oligosaccharides (fructo-oligosaccharides and oligoisomaltoses). Formula No. 2 was a powder preparation containing kudzu starch, inulin, and resistant dextrin.[15] Participants in the dietary fiber group consumed 10 g of Formula No. 1 and 20 g of Formula No. 2 twice daily. The two formulas were weighed, pre-mixed, and packaged for each meal dose before giving to the participants.

The participants' adherence to the treatments was evaluated at each visit via pill count. Good adherence was defined as taking >80% of the prescribed dosage for the given interval. If a participant was non-adherent, the participant and caregiver were counseled on the importance of taking the study medication as prescribed.

Procedures

Identical data collection procedures were used for each study. The baseline assessments included demographics, a comprehensive medical history, physical examination, anthropometric measurements (weight and height), and the Positive and Negative Symptom Scale (PANSS) scores. The baseline laboratory tests included fasting glucose, lipids and insulin, liver and renal function, routine blood tests, and an electrocardiogram. The baseline laboratory evaluations were repeated during follow-up visits at weeks 4, 8, and 12. Psychopathologic symptoms were reevaluated using the PANSS at week 12, and adverse effects were assessed using the Treatment Emergent Symptom Scale (TESS) throughout the trials.

Outcomes

The primary outcomes were changes in body weight and BMI. The BMI was calculated as the weight (in kg) divided by the height (in m) squared.

The secondary outcomes were insulin, insulin resistance index (IRI), fasting glucose, and changes in lipid metabolism, including triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). IRI was calculated using a homeostatic model assessment formula for insulin resistance (HOMA-IR = fasting insulin [mIU/L] × fasting glucose [mmol/L]/22.5).

Statistical Analysis

Changes in primary and secondary outcomes in weeks 4, 8, and 12 were analyzed for each treatment group. A random-effects linear mixed model was employed to compare the outcomes measures between the groups over time, in which the baseline characteristics variables (age, sex, duration of illness, and olanzapine dose) and the relevant baseline outcome scores were included as fixed effects.[22] An unstructured variance–covariance matrix was used within Akaike's information criterion. We used the restricted maximum likelihood estimation and examined significant effects by simple-effects tests. Summary statistics, including means, medians, and standard deviations, were calculated for all the variables at baseline and each follow-up. Post-hoc least square estimates of means and standard errors were obtained, and corrections for multiple testing were performed using Dunnett's test to compare the follow-up outcomes with the baseline. The analyses were performed using SPSS 25.0 (IBM, Armonk, NY), and a two-sided p-value of .05 was considered statistically significant.

The sample size was calculated to demonstrate a treatment difference of 5.0 kg in weight changes from baseline to week 12, based on 90% power, a two-sided significance level of 5%, a standard deviation (SD) of 5.0, and 20% of patients lost to follow-up. The estimated number required for each treatment group was 27.

This report followed the CONSORT 2010 guidelines and related recommendations for reporting parallel group randomized trials and clinical trials, as well as calls for transparency in the reporting of clinical and preclinical research.

Results

Study 1

A total of 126 patients were screened for eligibility; of which, 17 did not meet the inclusion criteria or fell within the exclusion criteria and 19 declined to participate. Subsequently, 90 patients were assigned to either an olanzapine plus probiotics group or an olanzapine monotherapy group. Finally, 88.2% of the patients completed the 12-week intervention (figure S1). The mean olanzapine dosage in Study 1 was 19.1 mg/day (SD = 1.77).

Approximately 32% of the patients were women and 37% were cigarette smokers. The mean age was 24.1 years (SD = 5.30), the illness duration was approximately 11.3 months (SD = 3.55), and the total PANSS score was approximately 79.7 points (SD = 6.38). The baseline characteristics and outcomes were not different between the groups ($p > .05$), except for LDL-C ($p = .003$) (table 1).

The primary outcomes were the changes in weight and BMI during the follow-up period. After adjusting for baseline weight, there were no significant main effects for time-by-group interaction in weight ($F = 0.42$, $df = 3,75$, $p = .52$). Similar results were observed in BMI using random-effects modeling ($F = 0.53$, $df = 3,75$, $p = .47$). Compared with the baseline, the body weight and BMI values increased significantly for both groups during the period ($p < .001$). The patients in the olanzapine monotherapy group exhibited a weight gain

Table 1. Baseline Characteristics of the Patients by Treatment Groups in Study 1

	Olanzapine plus probiotics (*N* = 39)		Olanzapine alone (*N* = 37)		
	Mean	SD	Mean	SD	Normal range
Age, y	24.82	5.64	23.43	4.89	
Duration of illness, mo	11.49	3.51	11.08	3.64	
Dose of olanzapine, mg	19.36	1.59	18.85	1.92	
Weight, kg	55.63	7.54	56.75	8.35	
Body mass index, kg/m^2	21.26	2.59	21.25	1.69	18.5–23.9 kg/m^2
Fasting glucose, mmol/L	4.41	0.39	4.40	0.37	3.90–6.10 mmol/L
Fasting insulin, μIU/mL	8.07	2.88	7.85	1.72	6.40–15.0 uIU/mL
IRI	1.59	0.59	1.54	0.38	<2.67
Triglyceride, mmol/L	0.86	0.41	0.72	0.26	<1.71 mmol/L
Cholesterol, mmol/L	3.75	0.58	3.70	0.48	2.90–5.20 mmol/L
HDL-C, mmol/L	1.21	0.18	1.23	0.14	>1.04 mmol/L
LDL-C, mmol/L**	2.39	0.44	2.10	0.36	<3.12 mmol/L
Total score of PANSS	79.77	5.37	79.65	7.37	
	N	%	*N*	%	
Female	11	28	13	35	
Male	28	72	24	65	

Med, median; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
**$p < .01$, compared between the two treatment groups.

of 7.91 kg (SD = 4.23) after 12 weeks, while patients in the olanzapine plus probiotics group gained 7.39 kg (SD = 4.45) at week 12.

Administration of probiotics concurrently with olanzapine slowed the increases in fasting insulin and IRI, and significant between-group differences were observed. Patients receiving olanzapine plus probiotics showed an increase in the fasting insulin level of 2.39 μIU/mL at week 12 (SD = 2.08; $p < .001$) compared with an increase of 5.98 μIU/mL (SD = 5.32; $p < .001$) in the olanzapine monotherapy group. Similarly, the IRI increased by 0.62 (SD = 0.59; $p < .001$) in the olanzapine plus probiotics group at week 12, which was smaller than the increase of 1.27 (SD = 1.11; $p < .001$) in the olanzapine monotherapy group. Compared with the olanzapine monotherapy group, there were significant improvements with the olanzapine plus probiotics group in insulin (estimated mean difference −3.64, [95% CI, −5.71 to −1.58]; $p < .001$) and IRI (estimated mean difference −0.65, [95% CI, −1.10 to −0.20]; $p = .005$) at week 12. The treatment effects on the main outcomes in Study 1 are summarized in table 2, table S1, and fig. S2.

There were no significant differences in the fasting glucose and lipid profiles between the groups after 12 weeks (table 2). The higher LDL-C and total cholesterol levels in the olanzapine plus probiotics group at baseline demonstrated that the interventional effects of the probiotics on the secondary outcomes were not overestimated. The psychopathological symptoms improved for both groups after 12 weeks with no significant differences.

Adverse events (≥grade 3) were reported for ≥5% of the evaluable patients. The most common adverse events were hypoactivity (26–30%), somnolence (26–27%), and abnormal liver function (15–16%), and these events were not significantly different between the groups. In total, 10% of the patients in the olanzapine plus probiotics group experienced diarrhea compared to 3% of patients in the olanzapine monotherapy group ($p = .174$). In contrast, 3% of patients in the olanzapine plus probiotics group and 14% of patients in the olanzapine monotherapy group experienced constipation ($p = .077$).

Study 2

In Study 1, we assessed the effect of probiotics alone on weight gain in drug-naïve first-episode schizophrenia patients being treated concurrently with antipsychotics and found that probiotics did not alleviate weight gain but affected the IRI. Moreover, the preliminary experiment with dietary fiber alone did not show good improvement in weight gain. Eight patients receiving olanzapine and dietary fiber gained 6.93 kg (SD = 2.34; $p < .001$) after 12 weeks (Supplemental material 1). Therefore, in Study 2, we evaluated the effects of probiotics plus dietary fiber on olanzapine-induced weight gain and metabolic disturbances.

Table 2. Treatment Effects of Olanzapine Plus Probiotics vs Olanzapine Monotherapy at Week 4/8/12 in Study 1

	Week 4		Week 8		Week 12	
	Mean difference olanzapine plus probiotics vs olanzapine alone	*p* value	Mean difference olanzapine plus probiotics vs olanzapine alone	*p* value	Mean difference olanzapine plus probiotics vs olanzapine alone	*p* value
Primary outcomes						
Weight, kg	−0.82 (−2.38, 0.73)	.293	−1.45 (−3.02, 0.13)	.072	−1.74 (−3.79, 0.31)	.095
Body mass index, kg/m^2	−0.40 (−0.83, 0.03)	.064	−0.43 (−1.06, 0.20)	.179	−0.45 (−1.29, 0.38)	.284
Secondary outcomes						
Fasting insulin, μIU/mL	−0.70 (−1.35, −0.04)	.037	−2.26 (−3.48, −1.04)	<.001	−3.64 (−5.71, −1.58)	<.001
IRI	−0.18 (−0.34, 0.02)	.031	−0.51 (−0.77, −0.24)	<.001	−0.65 (−1.10, −0.20)	.005
Fasting glucose, μIU/mL	−0.14 (−0.33, 0.04)	.123	−0.10 (−0.27,0.08)	.269	0.13 (−0.04, 0.31)	.133
Triglyceride, mmol/L	−0.10 (−0.20, 0.00)	.059	0.11 (−0.25, 0.03)	.128	−0.11 (−0.29, 0.07)	.222
Cholesterol, mmol/L	0.24 (0.06, 0.42)	.009	0.08 (−0.14, 0.31)	.465	−0.10 (−0.39, 0.19)	.496
HDL-C, mmol/L	0.02 (−0.05, 0.09)	.522	0.05 (−0.04, 0.13)	.266	0.04 (−0.06,0.15)	.425
LDL-C, mmol/L	0.14 (0.00, 0.29)	.046	0.07 (−0.16, 0.30)	.538	0.09 (−0.20, 0.37)	.550

The estimated differences are based on the estimated marginal means. *P* values represented the differences in characteristics at different time points between the olanzapine plus probiotics group and the olanzapine alone group.
IRI, insulin resistance index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. BMI was calculated as weight in kilograms divided by height in meters squared; IRI was calculated as insulin level (mIU/L) × fasting glucose(mmol/L)/22.5. Data were presented with estimated mean difference and 95% confidence interval.

A total of 60 participants were assigned to either the olanzapine and probiotics plus dietary fiber group or the olanzapine monotherapy group (figure S3). The mean age was 24.4 years (SD = 6.95), the illness duration was approximately 8.6 months (SD = 5.14), and the total PANSS score was approximately 84.5 points (SD = 15.09). The average olanzapine dosage in this study was 18.3 mg/day (SD = 3.42). During the study, two patients from the olanzapine monotherapy group withdrew their consent. This left 58 participants (28 in the olanzapine monotherapy group and 30 in the olanzapine and probiotics plus dietary fiber group), who were evaluated at least once during the follow-up visit. Finally, 86.2% of the patients completed the 12-week treatment. The basic characteristics of the participants in the two groups are summarized in table 3. The baseline characteristics and outcomes were not different between the groups ($p > .05$), except for a slight difference in glucose ($p = .048$) and triglyceride ($p = .045$).

Using random-effects modeling, after adjusting for baseline weight, there was a significant main effect for time-by-group interaction in weight ($F = 9.62$, $df = 3,55$, $p = .003$). A random-effects model that adjusted for baseline BMI revealed a significant main effect for time-by-group interaction ($F = 8.61$, $df = 3,55$, $p = .005$). Patients in the olanzapine and probiotics plus dietary fiber group gained 5.14 kg (SD = 3.52; $p < .001$) after 12 weeks and patients in the olanzapine monotherapy group gained 9.20 kg (SD = 3.79; $p < .001$) after 12 weeks. Significant group differences in weight (estimated mean difference −3.45 kg, [95% CI −5.91 to −1.00]; $p = .007$) and BMI (estimated mean difference −1.26, [95% CI −2.28 to −0.24]; $p = .016$) were found after 12 weeks.

For the secondary outcomes, significant increases in the fasting insulin (mean 6.96 µIU/mL, SD = 4.89, $p < .001$) and IRI (mean 1.74, SD = 1.11, $p < .001$) were observed in the olanzapine monotherapy group, but not in the olanzapine plus probiotics and dietary fiber group after 12 weeks [insulin (mean 1.33 µIU/mL, SD = 10.82, $p = .600$) and IRI (mean 0.47, SD = 2.16, $p = .355$), respectively]. There were significant group differences in insulin (estimated mean difference −3.79 µIU/mL, [95% CI −7.37 to −0.22]; $p = .038$) and IRI (estimated mean difference −0.95, [95% CI −1.77 to −0.14]; $p = .022$) at week 12. The fasting glucose levels and lipid metabolism (except for HDL-C) were not significantly different between the groups after 12 weeks. A significant difference in HDL-C was observed between the two groups at week 12 (estimated mean difference 0.26 mmol/L, [95% CI 0.07 to 0.44]; $p = .008$). The psychopathological symptoms improved in both groups after 12 weeks, but no significant differences were found between the groups ($p > .05$). The treatment effects on the outcomes in Study 2 are summarized in table 4, table S2, and fig. S4.

We examined whether the effect of probiotics plus dietary fiber on weight gain was associated with insulin resistance attenuation using ancillary analysis. After adjusting for the insulin resistance status, the weight remained significantly lower in the olanzapine and probiotics plus dietary fiber group than in the olanzapine monotherapy group after 12 weeks, suggesting that the

Table 3. Baseline Characteristics of the Patients by Treatment Groups in Study 2

	Olanzapine and probiotics plus dietary fibers ($N = 30$)				Olanzapine alone ($N = 28$)
	Mean	SD	Mean	SD	Normal range
Age, y	24.60	8.65	24.21	4.65	
Duration of illness, mo	6.57	5.59	10.82	3.55	
Dose of olanzapine, mg	17.67	4.30	18.93	1.98	
Weight, kg	52.49	8.23	55.61	7.52	
Body mass index, kg/m^2	20.04	2.84	21.12	1.56	18.50–23.90 kg/m^2
Fasting glucose, mmol/L*	4.33	0.50	4.40	0.36	3.90–6.10 mmol/L
Fasting insulin, µIU/mL	9.55	8.19	7.79	1.65	6.40–15.00 uIU/mL
IRI	1.83	1.59	1.53	0.35	<2.67
Triglyceride, mmol/L*	1.21	1.08	0.67	0.24	<1.71 mmol/L
Total cholesterol, mmol/L	3.98	0.78	3.78	0.50	2.90–5.20 mmol/L
HDL-C, mmol/L	1.30	0.27	1.22	0.15	>1.04 mmol/L
LDL-C, mmol/L	2.29	0.63	2.10	0.36	<3.12 mmol/L
Total score of PANSS	88.70	19.00	80.07	7.30	
	N	%	*N*	%	
Female	23	76.7	21	75.0	
Male	7	23.3	7	25.0	

Med, median; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
*$p < .05$, compared between the two treatment groups.

Table 4. Treatment Effects of Olanzapine and Probiotics Plus Dietary Fiber vs Olanzapine Monotherapy at Week 4/8/12 in Study 2.

	Week 4		Week 8		Week 12	
	Mean difference Olanzapine and probiotics plus dietary fiber vs olanzapine alone	*p* value	Mean difference Olanzapine and probiotics plus dietary fiber vs olanzapine alone	*p* value	Mean difference Olanzapine and probiotics plus dietary fiber vs olanzapine alone	*p* value
Primary outcomes						
Weight, kg	0.78 (−0.64, 2.21)	0.275	−0.64 (−2.83, 1.56)	0.561	−3.45 (−5.91, −1.00)	0.007
Body mass index, kg/m^2	−0.32 (−0.24, 0.88)	0.258	−0.24 (−1.20, 0.73)	0.621	−1.26 (−2.28, −0.24)	0.016
Secondary outcomes						
Fasting insulin, μIU/mL	4.29 (−1.80, 10.39)	0.162	0.63 (−2.45, 3.72)	0.679	−3.79 (−7.37, −0.22)	0.038
IRI	0.87 (−0.44, 2.17)	0.187	−0.12 (−0.73, 0.49)	0.695	−0.95 (−1.77, −0.14)	0.022
Fasting glucose, μIU/mL	0.33 (−0.13, 0.79)	0.159	0.23 (−0.10, 0.57)	0.167	−0.16 (−0.39, 0.07)	0.161
Triglyceride, mmol/L	−0.14 (−0.55, 1.27)	0.489	0.16 (−0.27, 0.59)	0.448	0.06 (−0.35, 0.47)	0.760
Cholesterol, mmol/L	0.65 (0.33, 0.97)	<0.001	0.35 (−0.11, 0.80)	0.136	0.20 (−0.27, 0.67)	0.401
HDL-C, mmol/L	0.21 (0.09, 0.34)	0.002	0.18 (0.02, 0.35)	0.028	0.26 (0.07, 0.44)	0.008
LDL-C, mmol/L	0.37 (0.10, 0.640)	0.008	0.20 (−0.22, 0.62)	0.339	0.11 (−0.31, 0.53)	0.616

The estimated differences are based on the estimated marginal means. *P* values represented the differences in characteristics at different time points between the olanzapine plus probiotics and dietary fiber group and the olanzapine alone group.
IRI, insulin resistance index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. BMI was calculated as weight in kilograms divided by height in meters squared; IRI was calculated as insulin level (mIU/L) × fasting glucose(mmol/L)/22.5. Data were presented with estimated mean difference and 95% confidence interval.

impact of the treatment was primarily independent of insulin resistance.

Adverse events (≥grade 3) were reported for ≥5% of the evaluable patients. The most common adverse events were hypoactivity (25–28%), somnolence (24–32%), and abnormal liver function (13–15%), and these events were not significantly different between groups.

We further combined the two control groups and compared the effects on weight, BMI, and other metabolic related index in three groups. Consistent results were found on weight, BMI, and other metabolic related index after combination (Supplemental material 2).

Discussion

To the best of our knowledge, this is the first study to assess the effects of probiotics plus dietary fiber supplementation on olanzapine-induced weight gain and metabolic disturbances in drug-naïve patients with first-episode schizophrenia. The main findings of our study were that probiotics plus dietary fiber supplementation was effective for attenuating olanzapine-induced weight gain while retaining the desired psychopathological effects; probiotics alone was not useful for preventing weight gain induced by olanzapine. Probiotics and dietary fiber are safe dietary substances that alter the gut microbiota of the host.[19] However, the effect of probiotics or dietary fiber on schizophrenia is uncertain and controversial.[17,20] The administration of dietary fiber selectively promotes the growth of some colonic microbes or probiotics and elicited beneficial impacts on metabolic functions.[23] Our results using probiotics plus dietary fiber supplementation resulted in a significant benefit on weight gain for drug-naïve first-episode schizophrenia patients. In the future, probiotics and dietary fiber may be tested for efficacy for weight loss in patients with antipsychotic-induced weight gain.

Recently, several studies have found that the gut microbiota composition in obese individuals was significantly different from that of lean individuals, and the modifications of gut microbiota composition were associated with weight changes.[24] However, the use of probiotics to prevent obesity remained debated as the effect of probiotics on weight gain was strain and population specific. Microbiota species including *Bifidobacterium* and *Lactobacillus* genera were effective and the effects of probiotics on weight gain were distinguished in obesity vs. obesity with pregnancy or adolescent vs. adult studies. A randomized clinical trial studied the effects of probiotic bacterium *Lactobacillus salivarius* Ls-33 in obese adolescents, and found altered fecal microbiota with no effect on metabolic syndrome.[25] Another study assessed the effect of probiotics in patients with BMI >25 kg/m^2 and did not find significant weight reduction difference between the probiotics and control groups.[26] Probiotics also improved the gastrointestinal functioning in schizophrenia patients based on the findings of Dickerson et al.[27] In our study, the addition of probiotics was not sufficient to attenuate weight gain in patients although we used probiotics including *Bifidobacterium* and *Lactobacillus.* Thus, the effect may be population specific and be related to the continuous olanzapine administration as olanzapine may modulate the composition of gut microbiota.[7,8]

We also found that the addition of probiotics plus dietary fiber or probiotics alone had a significant benefit for insulin resistance. Kijmanawat et al.[28] found that daily probiotics supplementation for four consecutive weeks improved the plasma fasting insulin and IRI levels in women diagnosed with gestational diabetes mellitus at 24–28 weeks. Kobyliak et al.[29] found that supplementation with concentrated biomass of 14 probiotic bacteria genera for 8 weeks was associated with a reduction of IRI values in individuals with type 2 diabetes. Both trials used probiotics containing *Bifidobacterium* and *Lactobacillus,* as was used in our study. Our findings evaluated the effects of probiotics in schizophrenia patients, and revealed significant IRI improvement by probiotics alone or in combination with dietary fiber. Insulin resistance plays a crucial role in olanzapine-induced dyslipidemia.[30] Although we observed attenuated IRI increases in the probiotics and/or dietary fiber groups, we did not find significant differences in the lipid profiles between the groups. This limited effect could be due to the short treatment duration.[30]

To date, several pharmacological or non-pharmacological interventions have been investigated to prevent weight gain in patients with first-episode schizophrenia. Metformin was the most widely studied pharmacological strategy for treating antipsychotic-induced weight gain. In our previous studies, we found metformin addition attenuated antipsychotics-induced weight gain in first-episode schizophrenia patients.[31,32] The mean difference between metformin and placebo was −3.27 kg (95% CI, −4.49 to −2.06) according to a recent meta-analysis in 2019.[33] Topiramate also showed good effects on reducing weight as well as a greater clinical improvement evaluated by PANSS.[34] However, its interaction with antipsychotics and other drugs may affect treatment efficacy or cause-related side effects.[35] Liraglutide showed obvious advantages in decreasing weight compared with other pharmacological interventions, but patients had to accept daily subcutaneous injection and had relatively high rates of adverse events.[33,36] Non-pharmacological interventions such as lifestyle or nutritional counseling, cognitive-behavioral therapy are preferentially recommended for controlling weight gain, especially in the early stages of antipsychotic treatment. Previous studies reported that non-pharmacological interventions improved psychological symptoms.[37–39] However, their treatment effects varied between studies and further research is needed to fully determine the efficacy of these interventions. In our study, the mean difference between probiotics plus dietary fiber and control was −3.45 kg (95%

CI, −5.91 to −1.00). Prevention of antipsychotic-induced weight gain with probiotics plus dietary fiber can be an effective, cost-efficient, and acceptable option.

This study had some limitations. First, an olanzapine plus dietary fiber group was not included in this trial. The independent role of dietary fiber and the individual effects of each intervention component need to be clarified in a larger sample group. Second, in a study limited to a 12-week duration, it is unknown whether the attenuation of weight gain is sustainable after the probiotics and dietary fiber treatments end. Future studies are required to evaluate the metabolic markers not only at the beginning and end of the intervention, but also after its discontinuation. Third, the female/male ratios differed in two studies, more female patients were involved in Study 2. This may be associated with different researchers for participant recruitment in two studies and the relatively small number of patients in two studies. In addition, certain biochemical indicators, such as adiposity and leptin levels, and other measures of metabolites or inflammation, were not monitored. Baseline dietary intake structure and exercise habits were not evaluated. We did not examine the microbiome, which could help to reveal the underlying mechanism of the treatment response. Finally, this was a single-center trial, which allowed for homogenous samples, but it prevented us from addressing regional variability. Therefore, our results may not be generalizable beyond the population in south-central China.

In conclusion, our results provide the first evidence that probiotic plus dietary fiber supplementation is useful and safe for attenuating antipsychotic-induced insulin resistance and weight gain. It has some clinical implications, as probiotics plus dietary fiber supplementation can be recommended to attenuate weight gain in drug-naïve first-episode schizophrenia patients. Further research is needed to assess the long-term effects of probiotics plus dietary fiber supplementation on antipsychotic-induced weight gain and its potentially synergistic effect on the antipsychotic response.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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