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Therapeutic Response Is Associated With Antipsychotic-Induced Weight Gain in Drug-Naive First-Episode Patients With Schizophrenia:

An 8-Week Prospective Study

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ABSTRACT

Background: Some previous studies have shown that weight gain is associated with greater improvement in psychopathology during antipsychotic treatment in patients with chronic schizophrenia. However, the results are mixed due to many confounding factors. The current study aimed to investigate whether weight gain was associated with antipsychotic response in patients with antipsychotic-naive and first-episode (ANFE) *DSM-IV*–diagnosed schizophrenia.

Methods: 526 ANFE patients and 313 healthy controls were enrolled in this study, which was conducted from January 2012 to December 2018. Treatment outcome was measured by the Positive and Negative Syndrome Scale (PANSS) at baseline and follow-up. Weight was measured at baseline and at the end of 8 weeks.

Results: After treatment, PANSS scores were significantly reduced as follows: positive symptoms (−10.40; 95% CI, −9.31 to −10.60), negative symptoms (−5.01; 95% CI, −4.43 to −5.54), general psychopathology (−13.01; 95% CI, −12.01 to −14.01), and PANSS total score (−28.53; 95% CI, −26.73 to −30.33). In addition, the average weight of ANFE patients increased by 2.89 kg (95% CI, 2.55 to 3.22), although it was still lower than the average weight of healthy controls. The proportion of patients with weight gain ≥ 7% after treatment was 38.2%. Weight gain was positively associated with decrease of PANSS positive symptoms, general psychopathology, and total score (all $P < .05$). Multiple linear regression analysis showed that baseline weight, decrease of PANSS total score, and sex were significantly associated with weight gain after treatment.

Conclusions: Our findings suggest that there is a significant association between weight gain and improvement of clinical symptoms after 8 weeks of antipsychotic treatment in patients with ANFE schizophrenia.

Trial Registration: ClinicalTrials.gov identifier: NCT04076371

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Antipsychotics are the most commonly used drugs for patients with schizophrenia across the world.[1] However, the side effects of antipsychotics, such as weight gain and metabolic dysfunction, are concerning.[2,3] Antipsychotic-induced weight gain is associated with obesity, dyslipidemia, impaired glucose tolerance, and metabolic syndrome, which ultimately leads to decreased quality of life, increased risk of mortality, and noncompliance with treatment.[3,4]

Although a number of randomized controlled clinical trials have found that antipsychotics are effective in reducing the acute symptoms of schizophrenia,[5–8] it is well established that antipsychotics can produce clinical severe side effects. Most antipsychotics are associated with weight gain induced by complex peripheral and central mechanisms.[9,10] About 16% of individuals with schizophrenia develop obesity, and the prevalence of metabolic syndrome is as high as 69% in chronic schizophrenia patients.[11] Even though weight gain is related to the risk of metabolic syndrome and other undesirable consequences,[12] a growing number of studies have emerged to identify the link between weight gain caused by antipsychotics and therapeutic efficacy in patients with schizophrenia.[13–16] For example, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial in schizophrenia revealed that percentage change in body mass index (BMI) was positively correlated with decrease in Positive and Negative Syndrome Scale (PANSS) total score after treatment with risperidone, olanzapine, quetiapine, perphenazine, and ziprasidone in an 18-week randomized, double-blind trial.[17] Similarly, another study of 107 adolescents with schizophrenia showed that greater reductions in psychiatric symptoms were significantly associated with weight gain in a 6-week, double-blind, placebo-controlled trial comparing olanzapine with placebo.[18] In particular, clozapine has been evaluated in a large number of clinical studies to validate this link, showing that clozapine treatment for 14 weeks, 6 months, and 5 years is correlated with improvement in psychosis in patients with chronic schizophrenia.[13,14,19,20] Interestingly, a study demonstrated that the initial treatment response to

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Clinical Points

- Our study found that 8 weeks of antipsychotic treatment significantly improved symptoms and increased weight in patients with first-episode and drug-naive schizophrenia.
- A significant correlation was found between antipsychotic-induced weight gain and improvement of clinical symptoms.
- The clinical benefits of antipsychotic treatment and the effects of weight gain must therefore be evaluated carefully in the early stages of schizophrenia.

clozapine was associated with long-term weight gain over 8 years.[16] Overall, there appears to be a close relationship between weight gain and clinical efficacy.

On the other hand, some studies have argued that weight gain was only a nonspecific response to antipsychotics and, in itself, did not clarify the potential mechanism underlying the relationship. Potential confounding factors including blood lipids, initial body weight, physical comorbidities, and concomitant medications may lead to a false link between weight gain and antipsychotic efficacy.[16,20] For example, Meltzer et al[20] showed that this relationship was not significant in the first 10–12 weeks of treatment but became apparent in most long-term studies of 4–6 months or longer. In particular, there are several lines of evidence indicating a contradictory relationship between body weight gain and treatment outcomes. For example, Procyshyn et al[21] found that in a randomized, double-blinded trial, weight gain was not associated with improvement in psychopathology after risperidone treatment in chronic schizophrenia patients who had a poor treatment response to clozapine. Another study showed that there were no significant correlations between psychopathological improvement and weight gain in schizophrenia patients after treatment with clozapine for 4, 8, and 12 weeks.[22] Other studies with small sample sizes also failed to find a significant association between psychopathological improvement and weight gain.[23,24] Taken together, the findings regarding the relationship between weight gain and treatment response are inconsistent and influenced by a variety of confounding factors, which warrant further investigation for the clinical benefits.

Most of the previous longitudinal studies have been conducted in chronic schizophrenia patients to investigate the relationship between weight gain and psychopathological improvement. Studying first-episode and unmedicated patients has the advantages of minimizing the potential impacts of antipsychotics, long course of disease, and psychiatric and medical comorbidities associated with chronic illness. Therefore, in our study, we recruited antipsychotic-naive first-episode (ANFE) schizophrenia patients. Also, patients stayed in hospital throughout the duration of the study. Thus, potential confounders such as diet, activity levels, and drug compliance were controlled well. Furthermore, all patients were treated with antipsychotic monotherapy. Therefore, this setting provided a favorable environment for investigating the relationship between weight changes and improvement in clinical symptoms after short-term antipsychotic treatment.

In the current study, we investigated the relationship between psychological improvement and weight gain after 8 weeks of treatment with antipsychotics in a large sample of ANFE patients with schizophrenia. We hypothesized that improvement in symptoms shown on the PANSS would be associated with weight gain during antipsychotic treatment.

METHODS

Subjects

The current study was conducted from January 2012 to December 2018. Five hundred twenty-six ANFE patients with schizophrenia were recruited at the First Hospital of Shanxi Medical University and Beijing Huilongguan Hospital. These patients were diagnosed with schizophrenia at admission and reconfirmed after 2 months based on the Chinese version of the Structured Clinical Interview for *DSM-IV* (SCID).[25] Inclusion criteria included (1) diagnosis of schizophrenia by using SCID; (2) able to provide informed consent; (3) aged between 18 and 45 years; (4) course of disease < 5 years; (5) antipsychotic free or cumulative antipsychotic treatment < 14 days; (6) without substance abuse or dependence except tobacco; and (7) without physical diseases (ie, infection, diabetes, hypertension, hyperthyroidism, and eating disorders) that may affect weight. We defined the patients as antipsychotic naive and first-episode based on a previous study by Lieberman et al (2003),[26] in which the duration of illness was capped at 5 years.

Three hundred thirteen unrelated healthy subjects were recruited in the local community. Experienced clinical psychiatrists ruled out potential individuals by using SCID. We excluded those healthy controls who received psychoactive drugs (eg, mood stabilizers, anxiolytics, antidepressants, or antipsychotics) or had physical and mental disorders. Our study was approved by the ethical committee of First Hospital of Shanxi Medical University and Beijing Huilongguan Hospital. All subjects provided signed informed consent before entry into the study. The study was registered at ClinicalTrials.gov (identifier: NCT04076371).

Study Design

This was a longitudinal clinical study. ANFE patients were treated with a flexible dose of antipsychotic for 8 weeks after admission. In this study, all patients received monotherapy with an antipsychotic, including risperidone, olanzapine, ziprasidone, quetiapine, aripiprazole, and haloperidol. During 8 weeks of treatment, the dose of antipsychotic could be changed according to clinical efficacy and side effects, but the type of antipsychotic drug itself was not allowed to be changed. In this 8-week observational study, all patients were hospitalized, and nurses monitored adherence to the antipsychotic medications. Anticholinergic drugs could be used for extrapyramidal side effects, and benzodiazepines could be used for sleep disorders. Thirty percent of patients

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Table 1. Demographic Characteristics and Clinical Data in Healthy Controls and Antipsychotic-Naive First-Episode Patients With Schizophrenia at Baseline[a]

Variable	Patients (n = 526)	Controls (n = 313)	*F* or χ^2 (*P* value)	Weight gain (n = 206)	Non–weight gain (n = 223)	*F* or χ^2 (*P* value)
Sex, male/female, n	267/259	164/149	0.21 (.65)	76/130	88/135	0.30 (.58)
Age, y	27.1 ± 9.1	28.4 ± 6.8	0.14 (.70)	25.3 ± 8.5	28.6 ± 9.3	3.8 (.06)
Education, y	8.5 ± 3.8	10.0 ± 3.0	25.6 (< .001)	8.4 ± 3.8	10.2 ± 3.8	25.8 (< .001)
Smokers/nonsmokers, n	149/377	99/214	1.0 (.31)	44/162	43/180	0.3 (.59)
Weight, kg	58.6 ± 10.6	65.8 ± 14.7	49.2 (< .001)	54.9 ± 8.0	61.3 ± 11.5	30.8 (< .001)
BMI, kg/m^2	21.4 ± 3.1	23.3 ± 4.3	36.0 (< .001)	20.2 ± 2.2	22.2 ± 3.4	41.5 (< .001)
Waist circumference, cm	76.4 ± 8.5	80.3 ± 12.4	33.3 (< .001)	70.4 ± 6.4	74.1 ± 10.2	4.1 (.05)
Hip circumference, cm	88.8 ± 5.9	93.9 ± 8.7	61.6 (< .001)	85.7 ± 5.0	89.1 ± 6.8	7.5 (.01)
Age at onset, y	26.3 ± 8.9	…	…	23.7 ± 7.0	26.4 ± 9.1	9.4 (.002)
Duration of illness, mo	25.9 ± 18.3	…	…	19.3 ± 21.2	27.3 ± 28.1	4.7 (.03)

[a]Values expressed as mean ± SD unless otherwise noted.
Abbreviation: BMI = body mass index.

were also taking anticholinergic medications in addition to antipsychotics.

Height, waist circumference, and hip circumference were measured at enrollment, and body weight and BMI were collected after an overnight fast at baseline and at the end of 8 weeks. Throughout the study, the same scales and the same height measurement device were used. Body weight was measured in light clothing without shoes after pockets were emptied. All measurements were repeated twice for each patient, and the average values were reported. If the patient gained equal to or more than 7% of their baseline weight, we defined the patient as weight gain (WG); we defined the other patients as non–weight gain (non-WG). The percentage of weight gain was calculated as ($weight_{follow\ up} - weight_{baseline}$)/$weight_{baseline}$. The cutoff of 7% was selected based on the generally accepted threshold for clinically significant weight changes for weight management and psychiatric treatments.[27]

Assessments of Psychotic Symptoms of the Patients

Six experienced psychiatrists assessed patients through PANSS.[28] They received a training course before the study began. After training, the interobserver correlation coefficient for PANSS total score was maintained at > 0.8 during repeated assessments. The clinical symptoms of patients were assessed by PANSS at baseline and after treatment.

Statistical Analysis

Subjects who dropped out were compared with those who finished the study using an analysis of variance (ANOVA) for continuous variables and χ^2 test for categorical variables, followed by multivariable regression analysis including significant variables.

ANOVA and χ^2 test were performed to examine whether there were differences in demographic characteristics, clinical data, weight, and BMI between patients and controls at baseline, as well as between the WG and non-WG groups. Whereas there was a significant difference between WG and non-WG groups, further analysis of covariance (ANCOVA) was conducted after adjusting for those potentially confounding covariates. Then, in the patients, we carried out Pearson correlation analysis to examine the relationship between weight or BMI and PANSS scores at baseline and, further, the relationship between weight gain and decrease in PANSS scores from baseline to week 8 of antipsychotic treatment. Further regression analysis was performed to assess the association between the decrease of PANSS scores and changes in weight after 8 weeks of antipsychotic monotherapy while adjusting for various potential confounding variables, such as age, sex, baseline weight, age at onset, and antipsychotic type and dose.

SPSS version 20.0 was used to run all statistical analyses. Statistical significance was defined as $P < .05$.

Table 2. Demographic Characteristics and Clinical Data of Dropouts and Completers[a]

Variable	Finished (n = 429)	Dropouts (n = 97)	*F* or χ^2 (*P* value)
Sex, male/female, n	206/223	61/36	7.0 (.01)
Age, y	27.3 ± 8.7	26.2 ± 8.6	1.3 (.26)
Education, y	8.9 ± 3.9	6.4 ± 3.1	25.6 (< .001)
Weight, kg	58.8 ± 10.7	57.4 ± 10.0	1.3 (.25)
BMI, kg/m^2	21.4 ± 3.1	21.1 ± 3.0	0.8 (.41)
Age at onset, y	25.3 ± 8.4	25.6 ± 9.0	0.06 (.81)
Duration of illness, mo	22.9 ± 17.5	25.4 ± 18.3	0.8 (.40)
Positive	23.8 ± 6.5	21.3 ± 5.7	11.6 (.001)
Negative	20.0 ± 6.7	20.0 ± 7.1	0.01 (.92)
General	40.5 ± 12.2	36.4 ± 8.5	9.0 (.003)
Total	84.2 ± 19.8	78.0 ± 15.6	7.5 (.007)

[a]Values expressed as mean ± SD unless otherwise noted.
Abbreviation: BMI = body mass index.

RESULTS

Demographic and clinical data of patients and healthy controls are shown in Table 1. At baseline, the patients had an average weight of 58.6 kg (95% CI, 54.8 to 60.9), height of 165 cm (95% CI, 163.7 to 166.2), and BMI of 21.4 kg/m^2 (95% CI, 21.2 to 22.2). Compared to controls, ANFE patients had lower weight, BMI, and waist and hip circumferences (all $P < .01$, Bonferroni-corrected all $P < .05$).

For ANFE patients at baseline, Pearson correlation analysis showed a significant association between weight and general psychopathology ($P < .05$). In addition, the WG group had more severe clinical symptoms than the non-WG

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Table 3. Reduction of Symptoms and Weight Gain After 8 Weeks of Antipsychotic Treatment in WG and Non-WG Subgroups[a]

	Baseline		8 Weeks		Changes in PANSS score and weight		
	WG (n = 164)	Non-WG (n = 265)	WG (n = 164)	Non-WG (n = 265)	WG (95% CI)	Non-WG (95% CI)	*F* (*P* value)[b]
PANSS score							
Positive	24.5 ± 6.9	23.4 ± 6.1	12.7 ± 4.9	13.0 ± 5.7	−11.6 (−11.0 to −12.7)	−9.8 (−9.0 to −10.5)	9.2 (.003)
Negative	20.3 ± 7.0	19.8 ± 6.4	14.9 ± 5.6	15.2 ± 5.8	−5.7 (−4.9 to −6.6)	−4.5 (−3.7 to −5.2)	3.7 (.054)
General	43.7 ± 13.8	38.5 ± 10.6	27.7 ± 8.4	27.5 ± 8.0	−16.1 (−14.4 to −18.0)	−11.2 (−9.9 to −12.2)	23.0 (< .001)
Total	88.4 ± 22.2	81.6 ± 17.6	55.2 ± 14.8	56.2 ± 16.3	−32.6 (−30.0 to −35.1)	−25.4 (−23.1 to −27.6)	19.8 (< .001)
Weight, kg	54.9 ± 7.9	61.3 ± 11.5	62.3 ± 11.8	60.9 ± 8.2	6.0 (5.5 to 6.5)	0.8 (0.6 to 1.2)	18.0 (< .001)
BMI, kg/m^2	20.2 ± 2.3	22.2 ± 3.4	22.5 ± 2.4	22.5 ± 3.4	2.2 (2.0 to 2.4)	0.3 (0.23 to 0.42)	16.4 (< .001)

[a]Values expressed as mean ± SD unless otherwise noted.
[b]Comparison of the changes after antipsychotic treatment between WG and non-WG subgroups.
Abbreviations: BMI = body mass index, PANSS = Positive and Negative Syndrome Scale, WG = weight gain.

Table 4. Weight and BMI Mean and Standard Deviation Values[a]

	Baseline		Follow-up		Gain	
	Weight, kg	BMI, kg/m^2	Weight, kg	BMI, kg/m^2	Weight, kg	BMI, kg/m^2
Ziprasidone (n = 27)	59.3 ± 8.8	21.3 ± 2.4	60.2 ± 8.1	21.9 ± 2.5	1.0 ± 2.6	0.3 ± 0.9
Risperidone (n = 245)	59.1 ± 11.5	21.4 ± 3.4	61.9 ± 11.2	22.4 ± 3.2	2.7 ± 3.6	1.0 ± 1.3
Quetiapine (n = 24)	62.0 ± 9.4	22.1 ± 3.0	64.4 ± 8.3	23.2 ± 3.4	3.1 ± 4.2	1.2 ± 1.6
Olanzapine (n = 92)	57.8 ± 9.5	21.5 ± 2.7	61.6 ± 9.9	23.2 ± 2.8	4.1 ± 3.1	1.7 ± 2.0
Aripiprazole (n = 21)	55.5 ± 9.0	20.6 ± 2.7	55.4 ± 8.3	20.5 ± 2.3	0.3 ± 1.2	0.09 ± 0.5
Typical antipsychotic (n = 20)	59.8 ± 9.9	21.6 ± 3.0	61.5 ± 9.8	21.9 ± 3.0	0.8 ± 1.6	0.25 ± 0.7

[a]Values expressed as mean ± SD unless otherwise noted.
Abbreviation: BMI = body mass index.

group in terms of PANSS general psychopathology ($F = 17.5$, $P < .01$) and total scores ($F = 11.2$, $P < .01$) at baseline.

Of the 526 patients in the initial study, 441 completed 8 weeks of treatment and were included in further analysis. Eighty-five patients dropped out of this study due to withdrawal of consent (n = 21), switching treatment (n = 11), discharge from the hospital in violation of doctor's order (n = 46), and unknown reasons (n = 7). Twelve patients had missing clinical data, so a total of 429 patients had complete data. There were no differences in the proportion of dropouts between the antipsychotic treatment groups (olanzapine vs risperidone vs other atypical antipsychotics vs typical antipsychotics) ($\chi^2 = 0.64$, $df = 3$, $P > .05$), suggesting that dropouts may be random, independent of specific antipsychotic treatment. Comparison of demographic characteristics and clinical data between dropouts and completers is shown in Table 2. There were significant differences in sex, education, and symptom severity between dropouts and completers (all $P < .05$).

The patients were assigned to receive one of the antipsychotics according to the decision of the psychiatrists, who provided clinical treatment and services to these patients in this study. Antipsychotic drugs the patients received consisted of monotherapy with risperidone (n = 245; mean dose = 4.9 mg/d), olanzapine (n = 92; mean dose = 16.20 mg/d), ziprasidone (n = 27; mean dose = 100 mg/d), quetiapine (n = 24; mean dose = 385 mg/d), aripiprazole (n = 21; mean dose = 18.4 mg/d), and haloperidol (n = 20; mean dose = 5.1 mg/d).

After 8 weeks of antipsychotic treatment, PANSS total and subscale scores were significantly lower than the baseline scores (all $P < .01$, Bonferroni corrected all $P < .05$, Table 3). The average reduction of PANSS scores was as follows: PANSS positive symptom 10.40 (95% CI, 9.31 to 10.60), negative symptom 5.01 (95% CI, 4.43 to 5.54), general psychopathology 13.01 (95% CI, 12.01 to 14.01), and total score 28.53 (95% CI, 26.73 to 30.33).

Moreover, after treatment, the weight of patients was significantly increased (58.8 ± 10.7 kg vs 61.8 ± 10.5 kg, $P < .01$, after Bonferroni corrections), with an average weight gain of 2.89 kg (95% CI, 2.55 to 3.22). Table 4 shows weight gain after 6 types of antipsychotics. We found a significant association between weight gain and age at onset, course of disease, and education, which were adjusted in the next analysis. Then, we divided patients into WG and non-WG groups according to the definition of weight gain. Twelve patients were missing weight data at follow-up, and 429 patients had weight data at baseline and follow-up. The weight gain rate in ANFE patients after treatment was 164/429 (38.2%). Further, we compared the decrease of PANSS scores between the WG and non-WG groups and found that there were significant differences in the decrease of positive symptom subscore ($F = 9.2$, $P = .003$), general psychopathology subscore ($F = 23.0$, $P < .001$), and PANSS total score ($F = 19.8$, $P < .001$). When sex, age at onset, course of disease, and antipsychotic type and dose were added as confounding factors in the model, the difference in symptoms between WG and non-WG groups remained significant (all $P < .05$).

Furthermore, weight gain was significantly positively associated with the decrease in PANSS positive subscore ($r = 0.14$, $df = 429$, $P = .004$), general psychopathology subscore ($r = 0.19$, $df = 429$, $P < .001$), and total score

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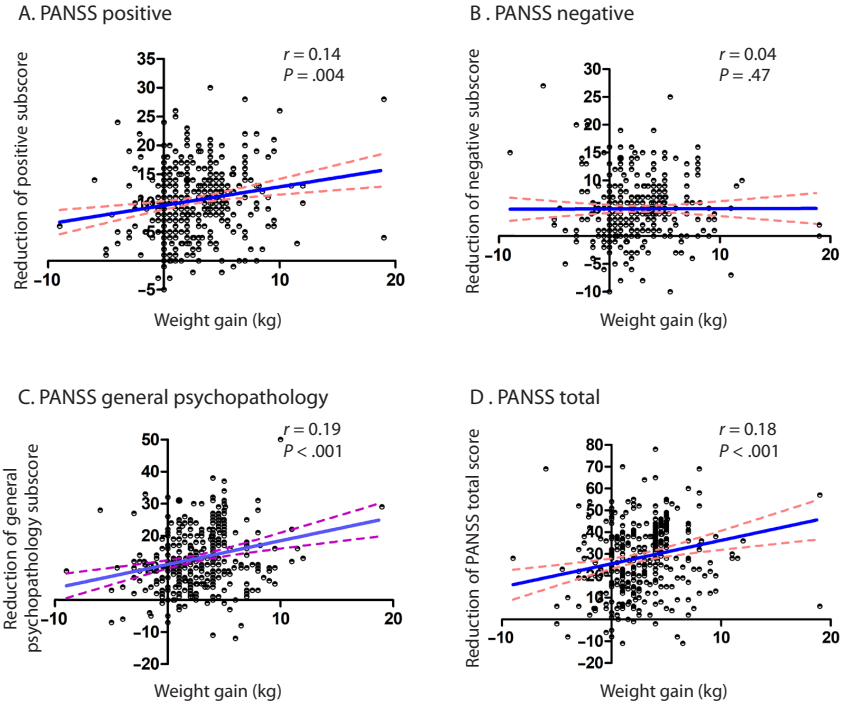
Figure 1. Significant Associations Between Weight Gain and Decrease in PANSS Positive Symptom Subscore, General Psychopathology Subscore, and Total Score in Patients ($P < .05$)[a]



[a]The blue line represents the trend line, and the dashed pink line is the 95% confidence interval.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Table 5. Multivariable Analysis of Factors Associated With Weight Gain After 8-Week Treatment

Variable	β	95% CI	*t*	*P* value
Demographic characteristics				
Age, y	−0.06	−0.44 to 0.31	−0.34	.73
Female sex	−0.75	−1.44 to −0.05	−2.11	.035
Education, y	0.03	−0.26 to 0.04	0.75	.45
Smoking	−0.04	−1.46 to 1.38	−0.05	.96
Baseline BMI, kg/m^2	−0.29	−0.40 to −0.18	−5.10	<.001
Clinical characteristics				
Age at onset, y	0.04	−0.33 to 0.41	0.19	.85
Atypical class of antipsychotic medication	1.29	−0.66 to 3.24	1.30	.19
Anticholinergic drugs	−0.08	−1.51 to 1.35	−0.12	.91
Reduction of total PANSS score	0.03	0.01 to 0.05	3.17	.002

Abbreviations: BMI = body mass index, PANSS = Positive and Negative Syndrome Scale.

($r = 0.18$, $df = 429$, $P < .001$) (Figure 1). Further linear regression analysis confirmed that decrease in PANSS total score (β = 0.003, $t = 3.17$, $P = .002$), baseline BMI (β = −0.29, $t = -5.10$, $P < .001$), and sex (β = −0.75, $t = -2.11$, $P = .035$) were predictive factors of weight gain (adjusted $R^2 = 0.15$) (Table 5).

Subgroup analysis showed that a significant association between weight gain and clinical symptoms existed only in the atypical antipsychotics group (PANSS positive: $r = 0.13$, $P = .006$; PANSS general psychopathology: $r = 0.17$, $P = .002$, PANSS total: $r = 0.16$, $P = .002$), not in the typical antipsychotics group (all $P > .05$). Moreover, our further ANCOVA analysis showed that there was no interaction between weight group and antipsychotics type ($F = 0.2$, $P = .61$).

DISCUSSION

The main findings of this study were as follows: first, after 8 weeks of antipsychotic monotherapy, the PANSS scores of ANFE patients with schizophrenia were significantly lower compared to baseline. Moreover, the body weight of patients was significantly increased after antipsychotic treatment; however, the weight of patients was still lower than that of controls. Second, there was a significant difference in the decrease of PANSS symptom score between the WG and non-WG groups favoring the WG group. Third, weight gain was positively associated with symptom reduction after controlling for age, sex, course of disease, and antipsychotic type and dose.

The possible relationship between the beneficial effects of antipsychotics and weight gain attracted particular interest in the early studies. In this large clinical schizophrenia study, we found that 8 weeks of treatment with antipsychotics significantly improved psychopathological symptoms as measured by PANSS and increased body weight. Moreover, Pearson correlation analysis showed that weight gain was

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positively associated with the reduction of clinical symptoms, which was further confirmed by ANCOVA analysis by dividing patients into WG and non-WG subgroups. Our findings were in line with a previous large clinical study by Hermes et al,[17] which demonstrated that in a randomized, double-blind trial, reductions in psychopathology were significantly associated with weight gain after 18 months of treatment with several antipsychotics. There is a noticeable difference that patients were treated with short-term antipsychotics in our study, while in Hermes and colleagues' study, patients took long-term antipsychotic drugs. Also, the inclusion and exclusion criteria used in Hermes et al study were relatively loose, and the clinical treatment was closer to real-world practice. An earlier study involving 1,337 olanzapine- or haloperidol-treated patients with schizophrenia spectrum disorders for 6 weeks, which was similar to our study in treatment duration, showed that weight gain was associated with improvement in the core symptoms of schizophrenia.[29] Our findings also were consistent with most of the studies in drug-naive patients,[18,30–34] suggesting that this relationship is a common phenomenon in schizophrenia. In particular, Chukhin and coauthors[35] did find worsened psychopathology after body weight loss in olanzapine- or clozapine-treated overweight or obese male patients who took orlistat, a weight loss medication. However, we do not know the exact mechanism of the close relationship between therapeutic efficacy and weight gain. Previous studies supported that weight gain may be due to the effects of antipsychotics on the disruption of dopamine, serotonin, and H_1 histamine-related reward pathways and food consumption.[36–39] Dopaminergic, histaminergic, serotoninergic, and muscarinic receptors potentially mediate antipsychotic action. The pathophysiologic basis of weight gain may overlap with the pharmacologic basis of antipsychotics for schizophrenia, thereby influencing neurotransmitters and cytokines related to weight gain and the pathophysiology of schizophrenia.

However, several studies have argued that the relationship between weight gain and the changes in schizophrenia symptoms exist only in olanzapine, with no relationship in any other type of antipsychotic. For example, some clinical studies failed to reveal the relationship between weight gain and decreased PANSS scores after treatment with clozapine, risperidone, and haloperidol.[14,23] We found that the association between weight gain and symptom reduction existed in atypical antipsychotic drugs but not in typical antipsychotics in ANFE patients with schizophrenia. In addition, several drug-naive studies also showed no significant association between weight gain and symptom improvement.[40,41] Therefore, it remains unclear whether this link between weight gain and improvement in clinical symptoms has a causal interrelationship through real pathophysiologic mechanisms, and this question deserves further study.

It is worthy of mention that the average weight of patients was 61.3 kg after 8 weeks of treatment, which was still lower than that of healthy controls (65.8 kg). In this study, the weight of the WG group at baseline was significantly lower than that of the non-WG group, suggesting that patients with lower body weight were more likely to gain weight after 8 weeks of antipsychotic monotherapy. In addition, it is noteworthy that the associations between weight gain and symptom improvement were weak, with a Pearson correlation coefficient of < 0.3. We could not provide a reasonable explanation for this weak association. We speculate that this weak association was due to the fact that most of our patients had lower weight gain in a shorter treatment course.

Several limitations of the study should be noted. First, one of the main limitations is the low r values. The P values are driven by the large sample size, but the correlation coefficients are actually quite small. Second, we did not collect laboratory measures of metabolic functioning, such as fasting glucose, fasting lipids, and related metabolic outcomes. Therefore, our results are preliminary. Further study will be significantly strengthened by their inclusion. Third, 85 patients dropped out of the study, which may bias the results. At least in our linear regression analysis, however, variables that were significantly different between completers and dropouts were controlled. Therefore, it is likely that the dropouts had little effect on the findings of our regression analysis. Fourth, even if we controlled for the differences in sex, education, and symptom severity in the regression model, that did not address the issue of generalizability. The dropouts reflected selection bias. That is, there was some self-selection among the patients who completed the study. Therefore, the sample may not be so representative of all patients who are drug-naive first-episode schizophrenia patients.

In conclusion, this study found that 8 weeks of antipsychotic treatment improved symptoms and increased weight in ANFE patients with schizophrenia. Moreover, there was a significant correlation between antipsychotic-induced weight gain and psychopathological reduction. These results support the notion that there exists a significant relationship between antipsychotic response and weight gain, and thereby the clinical benefits of antipsychotic treatment and weight gain must be evaluated in the early stages of the disease. However, given the weak association in the present study, a further larger sample of a randomized, double-blind trial longitudinal design will be warranted to elucidate the relationship.

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