Metabolic Effects of 7 Antipsychotics on Patients With Schizophrenia:

A Short-Term, Randomized, Open-Label, Multicenter, Pharmacologic Trial

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ABSTRACT

Objective: To compare longitudinal metabolic effects of 7 antipsychotics, including body mass index (BMI), waist circumference (WC), blood pressure (BP), glucose, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C); to investigate risk factors for metabolic syndrome (MetS); and to make recommendations on frequency and timing of monitoring metabolic measurements.

Methods: This randomized, open-label, pharmacologic trial was conducted among patients with schizophrenia (*DSM-IV*) in 32 hospitals across China. Patients were randomly assigned to 7 groups and assessed at baseline, 2, 4, and 6 weeks. Linear mixed-effect models were used to assess changes of metabolic measures over time. Multivariable logistic regression analysis was performed to investigate the risk factors for MetS.

Results: In total, 2,550 (718 drug-naïve) of 2,774 patients finished the study between July 6, 2010, and November 30, 2011. We found significant ($P < .05$) changes for BMI, WC, TG, and LDL-C, with TG and LDL-C reaching a plateau. Interactions between baseline metabolic condition and changes over time were observed for BMI ($\chi^2 = 43.11$, $P < .001$), WC ($\chi^2 = 36.34$, $P < .001$), systolic BP ($\chi^2 = 11.92$, $P = .002$), glucose ($\chi^2 = 6.09$, $P = .01$), and TG ($\chi^2 = 6.01$, $P = .01$). Antipsychotics generally had greater adverse effects on patients who were initially screened as metabolically normal. After controlling for other associated factors, we found that antipsychotics resulted in differing risk for incident MetS, with a similar pattern to findings in other populations: olanzapine (odds ratio [OR] = 3.36, $P < .001$) > quetiapine (OR = 3.29, $P < .001$) > perphenazine (OR = 2.73, $P = .007$) > risperidone (OR = 2.21, $P = .02$) > aripiprazole (OR = 1.74, $P = .15$) ≈ haloperidol (OR = 1.75, $P = .22$) ≈ ziprasidone (OR = 1, reference).

Conclusions: Metabolic traits should be monitored frequently in early stages of antipsychotic treatment due to rapid and substantial changes. Clinicians should not assume low risk for patients with normal metabolic parameters at baseline.

Trial Registration: Chinese Clinical Trial Registry identifier: ChiCTR-TRC-10000934

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Patients with schizophrenia have reduced life expectancy by 15–20 years, with cardiovascular disease (CVD) a major cause.[1] To identify people at high risk of CVD in the general population, metabolic syndrome (MetS) was introduced as a diagnostic tool.[2] MetS has higher prevalence among patients with schizophrenia compared with that of the general population.[3] Drug-treated patients have significantly higher prevalence than both first-episode and drug-naïve patients,[3,4] indicating that antipsychotic medication contributes to risk of MetS.

Differing risks of MetS liability have been reported for different antipsychotics.[5,6] Previous retrospective studies have demonstrated these differences, although some did not directly measure MetS.[7] Subsequent prospective studies have generally included small samples or compared only a

Clinical Points

- No agreement exists for when monitoring the physical health of patients treated with antipsychotics should be started because no previous study has intensely investigated metabolic changes that occur shortly after initializating antipsychotic treatment.
- We found rapid and substantial metabolic changes during the first 6 weeks of treatment, indicating that metabolic health should be monitored frequently in the early stages of antipsychotic treatment.

limited number of antipsychotics (Supplementary Table 1). Most of these studies included limited measures, and only 4 specifically diagnosed MetS. Further prospective studies with comprehensive measurements are needed to compare risks from multiple antipsychotics.

Regular monitoring of metabolic measurements after initializing antipsychotic treatment to detect MetS in advance was recommended as secondary prevention.[8] Switching to lower-risk antipsychotics is shown to be an effective solution for some patients.[9] However, frequency of monitoring for MetS is not clearly recommended in current guidelines. A systematic review[10] of 18 clinical guidelines worldwide reported large variation in recommended timing of monitoring. For example, assessment of BP is variously recommended at 4, 6, 8, 12, or 24 weeks after baseline, which reflects the lack of a rigorous evidence base for these guidelines.[11] In addition, all previous studies have focused on long-term effects of antipsychotics and did not start data collection prior to 4 weeks (Supplementary Table 1). This later start time limits the ability of clinicians to draw conclusions on early precursors of MetS and to intervene in the early stages to prevent MetS.

Through an investigation of how metabolic measures change during early stages of different antipsychotic monotherapy, we can provide evidence on when to monitor metabolic parameters for patients with schizophrenia. The aims of our study were to (1) compare metabolic effects of 7 antipsychotics over time, including body mass index (BMI), waist circumference (WC), blood pressure (BP), glucose, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C); (2) investigate risk factors for MetS among Chinese participants; and (3) make recommendations for guidelines on frequency and timing of measurements during early stages of treatment.

METHODS

Patients

Eligible patients aged 18–45 years with *DSM-IV* schizophrenia who were drug-naïve (never received antipsychotics) or recently relapsing without medication for at least a week were recruited from inpatient departments of 32 hospitals across China by the Chinese Antipsychotics Pharmacogenomics Consortium. Details of inclusion and exclusion criteria can be found in Supplementary Appendix 1. Briefly, we excluded patients with (1) *DSM-IV* diagnosis other than schizophrenia; (2) severe unstable physical disease, such as diabetes, hypertension, or cardiac disease; and (3) contraindication to any drug to which they might be assigned. To focus on the effects of antipsychotics, we additionally excluded individuals with (1) poor treatment adherence (actual dosage < 90% of the prescribed dosage as reported by the carer) and (2) mood stabilizer or antidepressant prescribed during the study.

The study was approved by the institutional review board at each site and was conducted in accordance with Good Clinical Practice guidelines and the Helsinki Declaration. Written informed consent to participate was obtained both from the patients and their legal guardians. Chinese Clinical Trials number: ChiCTR-TRC-10000934.

Treatment

Participants were randomly assigned (1:1:1:1:1:1:1/2:1/2) to 5 atypical antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone) and 2 typical antipsychotics (perphenazine and haloperidol) using random allocation sequence generated by computer. The random allocation was unmasked only to patients and their psychiatrists, but not to the researchers, following baseline assessment. Antipsychotic doses were titrated up during the first 2 weeks and remained unchanged throughout the study. Doses of antipsychotics were converted to chlorpromazine equivalents.[12] Further details can be found in Supplementary Table 2 and in our previous study[13] on antipsychotic efficacy.

Assessments

Demographic information (age, sex, educational level, marital status, and living conditions) and clinical characteristics (severity of illness, family history of mental illness, duration of illness [DOI], and psychiatric medication history) were collected by trained researchers at baseline. Severity of illness was evaluated biweekly (ie, every 2 weeks) using the Positive and Negative Syndrome Scale.[14] DOI (months) was defined as the period between onset of psychosis and pretrial clinical interview.

BP was measured biweekly with patients in a sitting position. Anthropometric measures, including body height, body weight, WC, and BMI, which was calculated as weight divided by height squared (kg/m^2), were assessed biweekly with individuals' wearing light clothing without shoes. WC was taken at the end of normal expiration, measuring the minimum circumference to the nearest 0.5 cm at the level of umbilicus.

Overnight fasting blood samples (≥ 8 hours) were collected at baseline and 4 and 6 weeks. Samples were analyzed in the local laboratory using the same standard methods. TG, HDL-C, LDL-C, glucose, alanine aminotransferase (ALT), and white blood cell count (WBC) were examined.

Presence of MetS was assessed at baseline and endpoint using China-specific criteria published by the International

Table 1. Characteristics of Subjects by Treatment at Baseline[a]

Characteristic	Overall (N = 2,774)	Ziprasidone (n = 475)	Aripiprazole (n = 455)	Olanzapine (n = 464)	Quetiapine (n = 464)	Risperidone (n = 458)	Haloperidol (n = 224)	Perphenazine (n = 234)
Male, n (%)	1,380 (49.7)	231 (48.6)	215 (47.3)	228 (49.1)	224 (48.3)	249 (54.4)	118 (52.7)	112 (47.9)
Age, y	31.55 ± 7.88	31.01 ± 8.00	31.93 ± 7.86	31.08 ± 7.88	31.61 ± 7.72	31.43 ± 7.90	32.56 ± 7.85	32.06 ± 7.93
Drug-naïve, n (%)	809 (29.2)	143 (30.1)	127 (27.9)	135 (29.1)	128 (27.6)	147 (32.1)	69 (30.8)	60 (25.6)
DOI, mo	74.72 ± 69.30	72.32 ± 68.93	76.26 ± 69.17	74.46 ± 67.19	76.68 ± 71.93	68.90 ± 66.00	76.16 ± 69.37	82.65 ± 75.00
PANSS (total score)	89.40 ± 15.37	90.11 ± 15.22	89.54 ± 15.67	87.89 ± 15.75	90.59 ± 14.69	88.27 ± 15.12	89.35 ± 15.22	90.56 ± 16.05
BMI	22.07 ± 3.46	22.04 ± 3.39	22.01 ± 3.64	22.18 ± 3.48	22.24 ± 3.35	22.14 ± 3.50	21.45 ± 3.34	22.12 ± 3.39
WC	79.27 ± 10.33	78.96 ± 10.15	78.60 ± 9.90	79.77 ± 10.13	79.87 ± 10.47	79.99 ± 10.70	77.82 ± 10.08	79.00 ± 11.03
Systolic BP	114.46 ± 10.38	114.52 ± 10.45	114.68 ± 10.31	115.14 ± 10.56	113.73 ± 10.08	114.39 ± 11.01	114.24 ± 10.06	114.35 ± 9.63
Diastolic BP	74.27 ± 7.05	74.00 ± 6.85	74.62 ± 7.10	74.73 ± 7.20	74.01 ± 6.91	73.76 ± 7.22	74.49 ± 6.87	74.62 ± 7.13
Glucose	4.83 ± 0.76	4.80 ± 0.72	4.91 ± 0.79	4.82 ± 0.76	4.81 ± 0.72	4.83 ± 0.79	4.72 ± 0.74	4.97 ± 0.75
Triglycerides	1.23 ± 0.72	1.21 ± 0.69	1.25 ± 0.76	1.21 ± 0.70	1.25 ± 0.79	1.21 ± 0.69	1.21 ± 0.69	1.24 ± 0.73
HDL-C	1.32 ± 0.35	1.33 ± 0.35	1.33 ± 0.37	1.31 ± 0.36	1.30 ± 0.34	1.32 ± 0.34	1.32 ± 0.37	1.31 ± 0.36
LDL-C	2.32 ± 0.80	2.27 ± 0.77	2.36 ± 0.86	2.32 ± 0.79	2.32 ± 0.81	2.32 ± 0.81	2.25 ± 0.77	2.38 ± 0.81

[a]All values are mean ± SD unless otherwise noted. N (%) and mean ± SD are presented for categorical and continuous variables, respectively.
Abbreviations: BMI = body mass index, BP = blood pressure, DOI = duration of illness, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, PANSS = Positive and Negative Syndrome Scale, WC = waist circumference.

Diabetes Federation.[15] Presence of any 3 of the following 5 conditions confirmed MetS: (1) WC ≥ 85 cm in men and ≥ 80 cm in women, (2) TG ≥ 1.7 mmol/L, (3) HDL-C < 1.0 mmol/L in men and < 1.3 mmol/L in women, (4) systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 85 mm Hg, and (5) fasting glucose ≥ 5.6 mmol/L. For each item, drug treatment was an alternative indicator.

Statistical Analysis

Subjects who dropped out were compared with those who finished the study using a 2-sample *t* test for continuous variables and χ^2 tests for categorical variables, followed by multivariable logistic regression including significant variables.

Repeated measurement analysis of variance was used to compare change of metabolic measures over time. Pearson correlation was performed to investigate the relationship between 2-week change and 6-week change within and between each measure. We then employed linear mixed-effect models to assess changes of metabolic measures over time ("lme4" package in R software version 3.3.2; The R Foundation for Statistical Computing, Vienna, Austria). Time (categorical variable), baseline value of the dependent variable, antipsychotics, total dosage of antipsychotics, and significant predictors of MetS identified in the regression model described later were included as fixed terms. Terms representing treatment-by-time and baseline-by-time interactions were included. Random subject effect and random time effect were also included.

We conducted analysis of covariance (ANCOVA) for change of each metabolic measure over 6 weeks, adjusting for significant covariates in the linear mixed-effect model. For metabolic measures with significant baseline-by-time interaction, ANCOVA was performed for normal and abnormal groups, respectively, where BMI ≥ 24 was adopted as the definition for overweight for Chinese.[16] Least squares adjusted means of changes were calculated ("LSmean" package in R). To further distinguish effects of baseline values from effects of prior drug treatment, we repeated ANCOVA in drug-naïve patients.

Multivariable logistic regression analysis was performed for baseline MetS and incident MetS (diagnosed with MetS only following 6-week treatment). Backward stepwise selection based on Akaike information criterion was carried out to select independent variables from demographic variables, clinical characteristics, and general health related variables (ALT, WBC, and number of previous hospital admissions). For incident MetS, antipsychotics, total dosage of antipsychotics, and whether adjuvant drugs such as hypnotics and antiparkinsonian were prescribed were added for selection (using ziprasidone as the reference due to mild metabolic effects in previous studies[17]). Last observation carried forward (LOCF) analysis was carried out for patients who dropped out after the fourth week. Two regression models were built with and without LOCF, respectively.

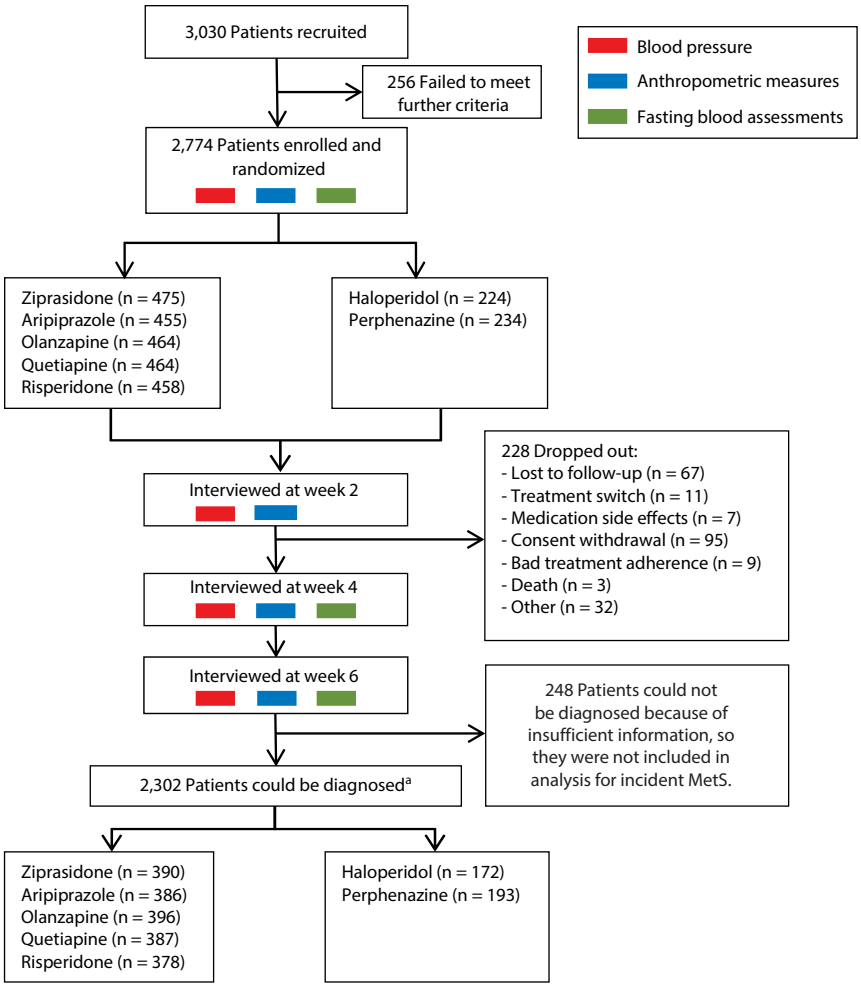
Frequency of MetS and pathological proportion for some measures at baseline and endpoint were compared using McNemar test (matched pairs). Endpoint prevalence was assessed both with and without LOCF. Extreme outlying data were winsorized at level 1% or 99% for metabolic assessments. Significance level was set at $P < .05$ (2-sided). All statistical analyses were performed with R 3.3.2 (https://www.R-project.org/).

RESULTS

Between July 6, 2010, and November 30, 2011, 2,774 patients with schizophrenia were recruited; 809 (29.2%) were drug-naïve. Characteristics of subjects are described in Table 1. Patients who dropped out before the fourth week (n = 224, 8.1%) tended to be younger, drug-naïve, have higher educational level, shorter DOI, milder symptoms and lower glucose (Supplementary Table 3). No significant differences were found between treatment groups. In multivariable analysis, only higher educational level, drug-naïve, and milder clinical symptoms were significant.

In total, 2,550 patients finished the study and 2,302 (90.3%) patients had sufficient information for a diagnosis of MetS at baseline and sixth week without LOCF. The study sample is shown in Figure 1.

Figure 1. Trial Profile



[a]These patients had sufficient information for diagnosis of MetS. Because any 3 of 5 conditions confirm MetS, we can diagnose some patient with missing values: (1) patients who had 3 conditions can be diagnosed as having MetS even though they may have 0–2 parameters missing, (2) patients with 1 missing parameter and < 2 conditions can be diagnosed as non-MetS, (3) patients with 2 missing parameters and < 1 condition can be diagnosed as non-MetS.
Abbreviation: MetS = metabolic syndrome.

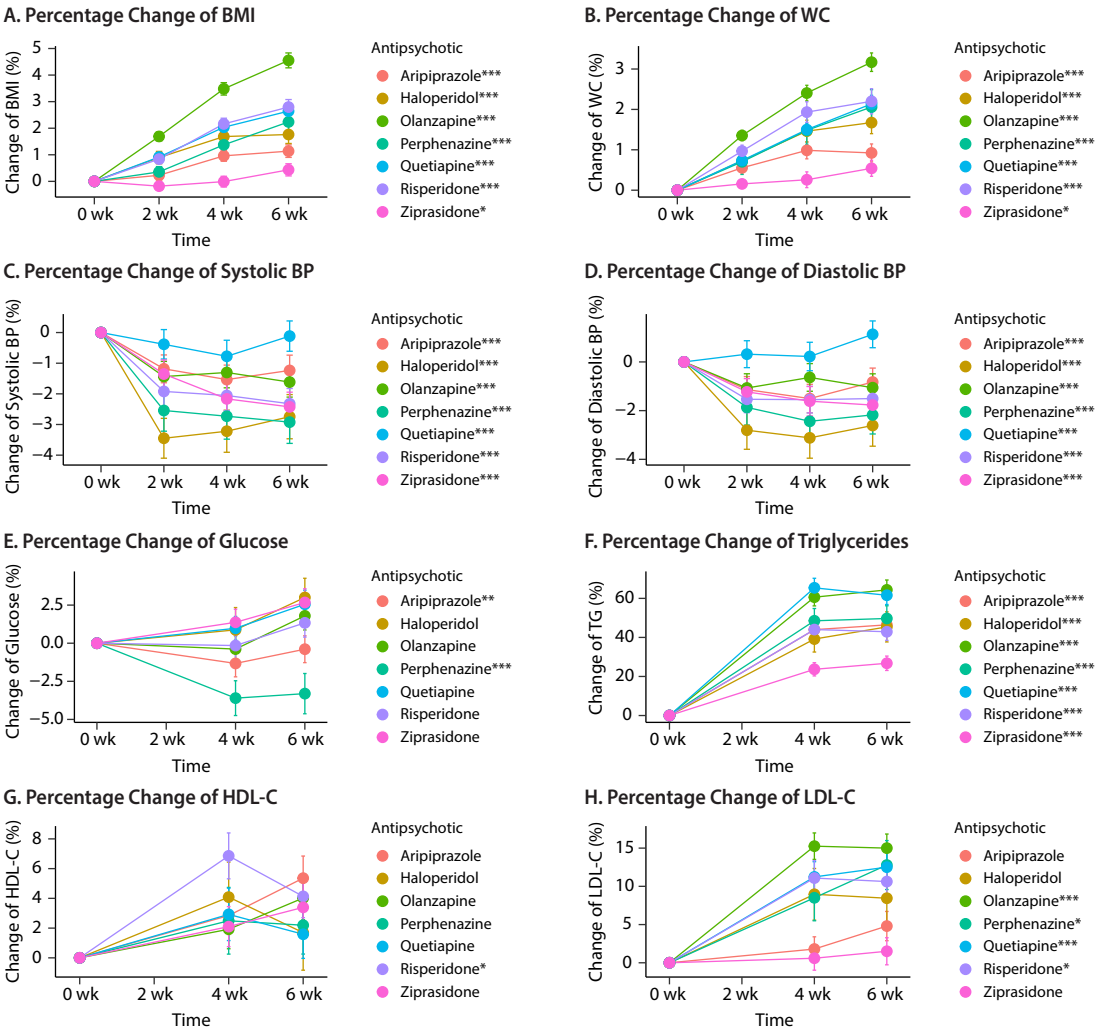
Change of Metabolic Measures Over Time

Interactions between baseline metabolic condition and changes over time were observed for BMI ($\chi^2 = 43.11$, $P < .001$), WC ($\chi^2 = 36.34$, $P < .001$), systolic BP ($\chi^2 = 11.92$, $P = .002$), glucose ($\chi^2 = 6.09$, $P = .01$), and TG ($\chi^2 = 6.01$, $P = .01$). BMI increased significantly for all antipsychotics after 6 weeks (Figure 2A). Drug-naïve patients tended to gain more weight, but the difference was not significant (Supplementary Figure 1A). For individual drugs, time course was similar except for ziprasidone, where BMI decreased at first and then returned to baseline after 6 weeks in drug-naïve patients (Supplementary Figure 1B and 1C). A significant baseline-by-time interaction was found (Supplementary Table 4). For patients with BMI < 24 (n = 1,763), all antipsychotics caused significant BMI change, while only olanzapine, quetiapine, and risperidone resulted in significant BMI change for those with BMI ≥ 24 (n = 651; Figure 3A and 3B). Olanzapine induced significantly higher BMI change than all other antipsychotics in both groups. The same interaction was observed in drug-naïve patients (n = 718; Supplementary Figure 2).

The time course of WC change (Figure 2B) was similar to BMI. We also found significant baseline-by-time interaction (Supplementary Table 4). For patients with normal WC (n = 1,606), olanzapine resulted in largest WC increase; however, this increase was not significantly larger than that for quetiapine, risperidone, or perphenazine (Figure 3C and 3D). For patients with abnormal baseline WC (n = 804), only olanzapine, quetiapine, and risperidone caused significant WC increase.

Except for quetiapine, all antipsychotics reduced BP, especially during the first 2 weeks (Figure 2C and 2D). Time was not significant in a mixed-effect model (Supplementary Table 4), indicating that BP did not show significant further changes beyond week 2. Baseline-by-time interaction was significant for systolic BP. Patients with abnormal systolic

Figure 2. Percentage Change of Metabolic Measures in Each Treatment Group[a]



[a]Bars denote standard error.
*P < .05, **P < .01, ***P < .001 in the repeated measurement ANOVA.
Abbreviations: BMI = body mass index, BP = blood pressure, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglycerides, WC = waist circumference.

BP (n = 265) showed greater BP reduction compared with those with normal systolic BP (n = 2,153; Figure 3E and 3F).

Changes of glucose were generally not observable (Figure 2E), but changes occurring in opposite directions were found when comparing patients with normal and abnormal baseline glucose separately (Figure 3G and 3H). Glucose increased for patients with glucose < 5.6 mmol/L (n = 1,865), but decreased among the remaining patients (n = 345).

TG significantly increased in all treatment groups, especially during the first 4 weeks (Figure 2F). Time was not significant in a mixed-effects model (Supplementary Table 4), indicating that compared with week 4, change at week 6 was not significantly different. Significant baseline-by-time interaction was found, and all antipsychotics increased TG levels of patients with TG < 1.7 mmol/L (n = 1,801). For those with TG ≥ 1.7 mmol/L (n = 388), ziprasidone and aripiprazole slightly decreased TG levels. (Figure 3I and 3J).

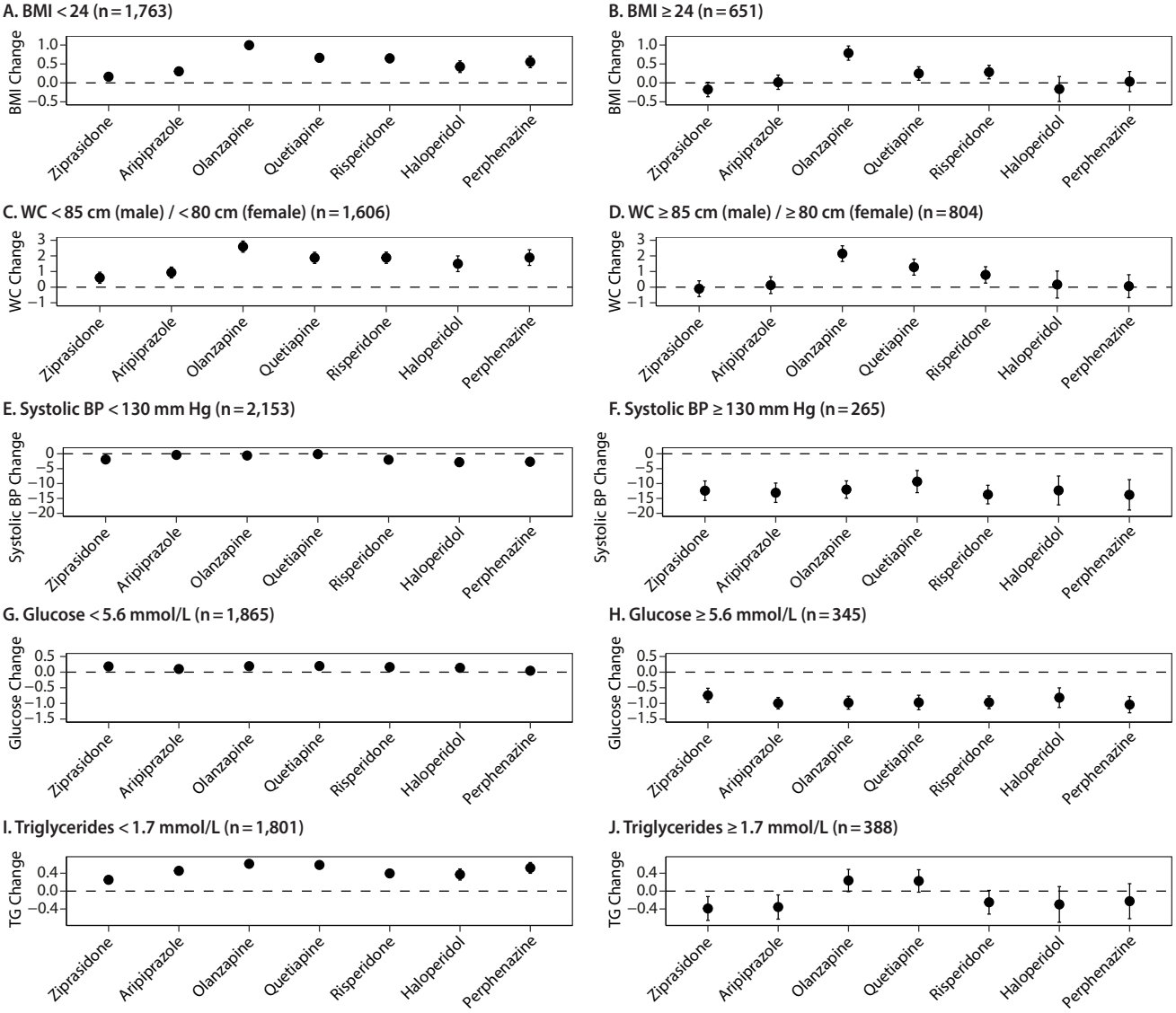
HDL-C showed an increasing trend during the first 4 weeks, but began to decrease after 4 weeks for some antipsychotics (Figure 2G). Change of LDL-C was more observable than HDL-C, with significant effects observed for olanzapine, quetiapine, risperidone, and perphenazine (Figure 2H). Time was not significant in a mixed-effects model, and there was no baseline-by-time interaction(Supplementary Table 4).

Changes at 2 or 4 weeks correlated well with longer term (6-week) change for each measure, with r ranging from 0.43 for LDL-C to 0.64 for BMI. However, the correlations between different measures were low (Supplementary Table 5).

Change of MetS Prevalence

Overall, prevalence of MetS significantly increased from 11.1% to 13.2% ($\chi^2 = 7.67$, $P = .006$) following 6-week treatment. The increase was significant in olanzapine and

Figure 3. Least Squares Adjusted Mean of Metabolic Changes in Patients With Different Baseline Conditions[a]



[a]Bars denote 95% confidence interval. One patient that may have some metabolic parameters missing at endpoint can still be diagnosed, so the sample size for each group may not add up to 2,302, which is the number of patients that had sufficient information for a diagnosis of MetSs.
Abbreviations: BMI = body mass index, BP = blood pressure, TG = triglycerides, WC = waist circumference.

quetiapine groups, with a trend of increase shown in drug-naïve patients. Because almost all antipsychotics resulted in decreased BP, we grouped subjects with reduced BP who would otherwise meet MetS criteria at the endpoint (n = 60) into the MetS group. Prevalence change was additionally found for aripiprazole, risperidone, and perphenazine (Supplementary Table 6). When we applied LOCF, the results were similar (details are available on request). For single metabolic measures, the increased proportion of subjects reaching pathological thresholds was significant for BMI and blood lipids (Supplementary Table 7).

Risk Factors for MetS

For baseline MetS, older age, higher educational level, psychiatric medication history, elevated WBC count, and higher ALT were significant risk factors (Supplementary Table 8). DOI was not included in the model, possibly due to the collinearity between DOI and age. For incident MetS, female sex, living with spouse before hospital admission, antipsychotics, and adjuvant drugs were risk factors, as were psychiatric medication history, elevated WBC, and ALT. Compared with those receiving ziprasidone, patients receiving olanzapine (OR = 3.36, $P < .001$), quetiapine (OR = 3.29, $P < .001$), perphenazine (OR = 2.73, $P = .007$), and risperidone (OR = 2.21, $P = .02$) were at significantly higher risk of developing MetS (Table 2). Application of LOCF did not change the results (details are available on request).

DISCUSSION

In this large, pharmacologic trial of 7 antipsychotics, BMI and WC progressively increased during the first 6 weeks,

Table 2. Multivariable Analysis of Factors Associated With Incident Metabolic Syndrome After 6-Week Treatment of Antipsychotics

Characteristic	OR (95% CI)	*P* Value
Sex		.02
Male	1 (ref)	
Female	1.53 (1.07–2.20)	
Age	1.02 (0.99–1.04)	.20
Living conditions		
Lives with spouse	1 (ref)	
Lives with other relatives	0.55 (0.37–0.81)	.002
Lives alone	0.57 (0.26–0.81)	.14
Other	0.64 (0.26–1.15)	.41
Clinical characteristics		
Medication history		.02
Medicated	1 (ref)	
Drug-naïve	0.61 (0.40–0.92)	
General health condition		
ALT	1.02 (1.01–1.03)	.0002
WBC	1.16 (1.07–1.25)	.0001
Antipsychotic		
Ziprasidone	1 (ref)	
Aripiprazole	1.74 (0.83–3.74)	.15
Olanzapine	3.36 (1.73–6.85)	.0003
Quetiapine	3.29 (1.76–6.49)	.0005
Risperidone	2.21 (1.16–4.43)	.02
Haloperidol	1.75 (0.37–4.29)	.22
Perphenazine	2.73 (1.31–5.79)	.007
Total dosage	1.00 (1.00–1.00)	.09
Adjuvant drugs	1.54 (1.11–2.17)	.01

Abbreviations: ALT = alanine aminotransferase, CI = confidence interval, OR = odds ratio, WBC = white blood cell.

BP decreased mainly during the first 2 weeks, and TG and LDL-C increased mainly during the first 4 weeks. In addition, we identified significant baseline-by-time interactions for BMI, WC, systolic BP, glucose, and TG. In general, antipsychotics had stronger adverse effects on patients with normal baseline metabolic parameters. For incident MetS, we found that different antipsychotics had differing ORs when compared with ziprasidone, with olanzapine > quetiapine > perphenazine > risperidone > aripiprazole ≈ haloperidol ≈ ziprasidone.

Although 6-week and long-term antipsychotic-induced weight gain have been demonstrated,[18] we report here how 2-week increases in BMI and WC are predictive of 6-week changes. The majority of current guidelines[10] recommend that BMI should be determined every 4 weeks, or even quarterly. Our findings provide evidence for the value of a maximum interval of 2 weeks for the initial monitoring of weight gain. Such assessment in the early stages can provide information to indicate whether to intervene, for example, by switching to another drug. More frequent initial monitoring may be valuable; the latest British guidelines[19] recommend weekly assessment for the first 4–6 weeks of antipsychotic treatment.

We found that BP decreased significantly during the first 2 weeks. However, some studies[17,20] find no change of BP after several months. A possible explanation is that cumulative weight gain can induce an increase in BP after a long period of antipsychotic treatment, while antagonism at α_1-adrenergic receptors can decrease BP within a short time.[21] Haloperidol showed the largest BP decrease in our sample. At clinical dosage, haloperidol primarily exhibits selective dopamine D_2 receptor antagonism.[22] In rats, administration of haloperidol reduced BP significantly after 2 weeks, interpreted as being associated with the consequences of disruption of the D_1/D_2 receptor complex.[23]

TG increased rapidly during the first 4 weeks and reached a plateau. A significant increase of TG after 1 month of antipsychotic medication has been reported.[24] However, most guidelines[8,10] for the management of schizophrenia recommend examining blood lipids after 3 months. Our findings indicate the value of determining TG before 4 weeks of antipsychotic medication. We did not observe significant changes of HDL-C. In a previous study[24] that assessed HDL-C at 1, 3, 6, and 12 months, significant decrease was observed after 6 months. Another study[25] of drug-naïve patients did not observe variation in HDL-C after 1-year antipsychotic treatment. However, a significant increase of LDL-C was observed for 4 antipsychotics in our study. These indicate that HDL-C is not a sensitive index for antipsychotic-induced blood lipid disturbance in comparison with TG and LDL-C. Furthermore, the lack of a reduction in HDL-C, which is included in MetS diagnostic criteria, can be misleading because CVD risk is presumably elevated along with TG and LDL-C.

Baseline-by-time interactions were observed. Patients with normal baseline BMI and WC showed greater increases. BP and glucose decreased dramatically in patients with abnormal baseline conditions. TG and glucose increased only in patients with normal baseline lipid and glucose metabolism. Similar interactions were also reported for 3-month and 18-month WC gain in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE).[17] It is important that olanzapine, quetiapine, and risperidone can further increase BMI and WC of patients with abnormally elevated measurements at baseline. Clinicians should be cautious when prescribing these antipsychotics to patients with high BMI and WC. Whether antipsychotics and insulin have synergistic effects on glucose levels has not, to our knowledge, been studied. We recommend that clinicians should remind patients who are taking insulin to correctly adjust the dosage after prescription of antipsychotics.

Guidelines[8,10] indicate a consensus that closer attention should be paid to patients with metabolic problems at baseline and that they should be monitored more frequently. However, our results suggest that patients with normal baseline metabolic parameters experienced more significant detrimental changes in all metabolic measures. Our findings indicate that equivalent care of metabolic health should be provided to all patients, not just those whose initial tests appear abnormal.

Differing effects of antipsychotics have been found for both incident MetS and individual measures. The 6-week BMI change with different drugs observed in our study was in the same rank order as the proportion of ≥7% weight gain over 18 months in CATIE.[26] This finding suggests that the short-term change may predict long-term change and

that antipsychotics have similar metabolic effects on Chinese patients as those of different ethnicity. Similarly, switching to ziprasidone[27] or aripiprazole,[9] which is proven to be effective in other populations, may be applicable to Chinese patients.

Consistent with previous findings,[5] olanzapine resulted in the largest gain in BMI, WC, and TG. Quetiapine showed similar effects on TG to olanzapine while BMI and WC changes were closer to risperidone. This marked adverse lipid signal of quetiapine, disproportionate to its effects on other metabolic measures, has been repeatedly reported.[28,29] We therefore recommend monitoring lipids frequently when prescribing quetiapine.

Typical antipsychotics did not demonstrate lower risk for MetS than did the second generation atypical antipsychotics. We found that perphenazine significantly increased MetS risk compared to ziprasidone with an OR similar to risperidone, while haloperidol is not significantly different from ziprasidone. These findings emphasize that there is no class effect of atypical versus typical antipsychotic drugs on the emergence of MetS, while there remain substantial differences between drugs within each group.

Age,[5,6] previous psychiatric medication,[5] ALT,[30,31] and WBC[32,33] have been consistently associated with MetS in schizophrenia. Conflicting results have been reported for sex, and higher prevalence has been observed for both men[34,35] and women.[36,37] In our study, female sex was associated with incident MetS but not baseline MetS, indicating that women may be more sensitive to this consequence of antipsychotic treatment. However, it is also possible that any sex difference in baseline MetS was neutralized by smoking habits. Smoking, which may increase risk of MetS,[6] is considerably more common among Chinese men with schizophrenia compared with women with schizophrenia (57.5% vs 6.3%).[38] Higher education and living with spouse are risk factors for MetS in our study, which is consistent with previous studies[39] in the general Chinese population, where inverse associations with education, income, and type 2 diabetes are reported. Living with spouse can be a proxy for higher income among Chinese patients.

This study has several limitations. First, we did not collect lifestyle measures associated with MetS, such as diet and smoking,[40] although randomization among a large sample size should have compensated for this. Second, the prevalence of MetS in this study is not entirely representative. We excluded patients diagnosed with hypertension, diabetes, and cardiac disease to minimize medical risk and the influence of their associated treatments. We also excluded the use of other drugs with increased risk for MetS, eg, mood stabilizers and antidepressants.[41] Furthermore, subjects over 45 were excluded. Third, whether the findings are applicable to other populations needs further validation, although we found similarity between Chinese and other populations in BMI changes. Finally, we did not study long-term outcomes of treatment but focused on initial changes. However, these changes are strongly predictive of longer-term consequences in patients receiving antipsychotic treatment.

CONCLUSIONS

Our findings demonstrate that the trajectory of adverse changes among several important contributors to MetS is established within 2–4 weeks, which suggests that most clinical guidelines put insufficient emphasis on ongoing, early-stage monitoring. Guidelines that recommend that frequency of monitoring for MetS should be dependent on the presence of abnormal metabolic parameters observed at baseline require revision. Because of the dramatic changes that can be observed within a relatively short time among patients who are initially screened as metabolically normal, equivalent care should be given to all patients.

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Supplementary Material

Article Title: Metabolic Effects of 7 Antipsychotics on Patients With Schizophrenia: A Short-Term, Randomized, Open-Label, Multicenter, Pharmacological Trial

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List of Supplementary Material for the article

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Supplementary materials

Supplementary Table 1. Summary of prospective studies comparing the different metabolic effects of antipsychotics

Population	Study design	Diagnosis	First-onset/ drug-naïve	Antipsychotics (n)	Timing	Metabolic measures
American[1]	RDBT	schizophrenia or SCD	No	Clozapine; Olanzapine (28); Risperidone (26); Haloperidol (22);	8 and 14 weeks	Glucose level, cholesterol level
Turkish[2]	Non-randomized	schizophrenia	No	Clozapine (14); Risperidone (14); Olanzapine (14); Quetiapine (14); Untreated Control (11)	6 week	Leptin, triglyceride level, BMI
Chinese[3]	ROLT	schizophrenia	First-onset	Clozapine (30); Olanzapine (24); Risperidone (29); Sulpiride (29);	8 week	BMI, waist-to-hip ratio, glucose, insulin, C-peptide, insulin resistance index, cholesterol level, triglyceride
American[4]	RDBT	schizophrenia	No	Olanzapine (74); Perphenazine (52); Quetiapine (67); Risperidone (54); Ziprasidone (31);	3 and 18 months	BMI, waist circumference, blood pressure, HDL-C, triglyceride level, glucose level; MetS
Austrian[5]	Non-randomized	schizophrenia	No	Clozapine (10); AmisuLpride (12);	12 to 16 weeks	BMI, insulin, insulin resistance
Indian[6]	RDBT	schizophrenia	First-onset	Haloperidol (35); Olanzapine (33); Risperidone (31); Healthy control (51)	6 week	Waist circumference, blood pressure, HDL-C, triglyceride level, glucose level; MetS
American[7]	RDBT	schizophrenia	No	Clozapine (34); Olanzapine (31); Haloperidol (28);	12 week	Glucose level, cholesterol level, triglyceride level
Spanish[8]	ROLT	psychosis	drug-naïve	Haloperidol (52); Olanzapine (54); Risperidone (58);	12 months	Glucose level, insulin, insulin resistance index, cholesterol level, triglyceride level, HDL-C, LDL-C
Austrian[9]	Non-randomized	schizophrenia	No	Olanzapine (7); Clozapine (7); Quetiapine (2); Amisulpride (4); Ziprasidone (4); Risperidone (4);	4 week	Body weight, insulin resistance, leptin, cholesterol level, triglyceride level, HDL-C, LDL-C
American[10]	ROLT	schizophrenia	No	Olanzapine (23); Risperidone (21);	2 and 5 months	Glucose level, insulin, C-peptide, glycohemoglobin, OGTT
American[11]	ROLT	schizophrenia	No	Olanzapine (23); Risperidone (23);	2 and 5 months	Body weight, waist circumference, triglyceride, cholesterol, HDL-C, LDL-C, free fatty, leptin
American[12]	ROLT	Schizophrenia, SCD or bipolar disorder	No	Olanzapine (82); Risperidone (78);	1, 3, 6, 12 months	BMI, cholesterol level, triglyceride level, HDL-C
European and African countries[13]	ROLT	schizophrenia	No	Paliperidone (239); Olanzapine (220)	3 and 6 months	BMI, waist circumference, blood pressure, HDL-C, triglyceride level, Glucose level; MetS
Chinese[14]	ROLT	schizophrenia	First-onset	Olanzapine (50); Quetiapine (50); Aripiprazole (50)	8 week	Glucose level, triglyceride level, cholesterol level, HDL-C, LDL-C
French[15]	Non-randomized	schizophrenia	No	Clozapine (19); Olanzapine (30); Risperidone (46); Aripiprazole (39);	12 month	BMI, waist circumference, blood pressure, HDL-C, LDL-C, triglyceride level, Glucose level; MetS
Spanish[16]	randomized clinical trial	non-affective psychosis	Both	Quetiapine (62); Ziprasidone (58); Aripiprazole (78);	12 month	weight, BMI, glucose, insulin, total cholesterol, LDL-C, triglycerides, HDL-C, and the triglyceride/HDL

Abbreviations: BMI= body mass index; HDL-C= high-density lipoprotein cholesterol; LDL-C= low-density lipoprotein cholesterol; OGTT= Oral Glucose Tolerance Test RDBT= Randomized double-blind trial; ROLT= randomized open-label trial; SCD=schizoaffective disorder

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Supplementary Table 2. Dose information for seven antipsychotics

	Antipsychotics	Dose range	Mean dose	Mean dose CPZ Equivalent
Atypical	Ziprasidone	80-160	123.1±29.29	406.27±154.77
	Aripiprazole	10-30	23.64±5.58	647.66±224.05
	Olanzapine	5-20	18.62±3.80	487.67±117.75
	Quetiapine	400-750	656.55±96.20	595.57±111.03
	Risperidone	2-6	4.94±0.96	484.73±324.63
Typical	Haloperidol	6-20	14.75±5.33	661.1±243.39
	Perphenazine	20-60	26.92±9.99	384.98±151.41

All doses are expressed as mg. Abbreviations: CPZ= chlorpromazine.

Supplementary Table 3. Univariable analysis of factors associated with dropout

	Dropped out (n=224)	Finished (n=2 550)	P value
Sex (men %)	109 (48.7)	1268 (49.7)	0.81
Age	30.31±8.04	31.67±7.86	0.01
Education			0.003*
Lower	105 (46.9)	1438 (56.4)	
Intermediate	88 (39.3)	899 (35.3)	
Higher	31 (13.8)	213 (8.4)	
Drug-naïve	91 (40.6)	718 (28.2)	0.0001*
DOI (months)	65.10±69.65	75.51±69.23	0.05
PANSS total score	86.41±13.05	89.66±15.50	0.0008*
PANSS (positive)	24.90±4.14	25.54±4.76	0.03
PANSS (negative)	19.82±6.22	21.95±6.79	<0.0001
BMI	21.74±3.33	22.10±3.47	0.16
WC	78.15±10.48	79.37±10.32	0.13
Systolic BP	114.18±10.52	114.48±10.37	0.68
Diastolic BP	74.26±7.34	74.28±7.03	0.98
Glu	4.72±0.75	4.85±0.76	0.02
TG	1.20±0.71	1.23±0.72	0.65
HDL-C	1.29±0.32	1.32±0.36	0.21
LDL-C	2.27±0.77	2.32±0.81	0.33
Antipsychotics			0.14
Ziprasidone	42 (8.8)	433 (91.2)	
Aripiprazole	29 (6.4)	426 (93.6)	
Olanzapine	30 (6.5)	434 (93.5)	
Quetiapine	40 (8.6)	424 (91.4)	
Risperidone	34 (7.4)	424 (92.6)	
Haloperidol	27 (12.1)	197 (87.9)	
Perphenazine	22 (9.4)	212 (90.6)	

*: significant in multivariable regression analysis. Abbreviations can be found at the end of this file. Educational levels: lower education=years of schooling ≤9; intermediate education=years of schooling ranges from 10 to 15; higher education=years of schooling≥16.

Supplementary Table 4. Linear-mixed model of individual metabolic variable

	BMI (kg/cm^2) β (95%CI)	WC (cm) β (95%CI)	SBP (mm Hg) β (95%CI)	DBP (mm Hg) β (95%CI)	Glu (mmol/L) β (95%CI)	TG (mmol/L) β (95%CI)	HDL-C (mmol/L) β (95%CI)	LDL-C (mmol/L) β (95%CI)
Ziprasidone	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Aripiprazole	0.09 (-0.23-0.41)	0.18 (-0.21-0.58)	0.02 (-1.25-1.28)	0.08 (-0.84-1.00)	-0.08 (-0.17-0.02)	0.20*** (0.08-0.32)	0.02 (-0.03-0.06)	0.02 (-0.07 - 0.11)
Olanzapine	1.02*** (0.70-1.33)	0.91*** (0.52-1.31)	0.05 (-1.20-1.29)	0.09 (-0.82-1.00)	-0.05 (-0.15-0.04)	0.44*** (0.32--0.55)	-0.00 (-0.05-0.04)	0.34*** (0.25 - 0.43)
Quetiapine	0.54*** (0.22-0.86)	0.36 (-0.03-0.76)	0.55 (-0.70-1.81)	0.65 (-0.27-1.56)	-0.01 (-0.11-0.08)	0.47*** (0.35-0.59)	-0.02 (-0.06-0.03)	0.20*** (0.11 - 0.30)
Risperidone	0.54*** (0.22-0.86)	0.56** (0.16-0.95)	-1.07 (-2.32-0.19)	-0.73 (-1.65-0.19)	-0.06 (-0.15-0.04)	0.19*** (0.07-0.31)	0.06* (0.01-0.10)	0.15** (0.06 - 0.25)
Haloperidol	0.52* (0.12-0.92)	0.28 (-0.22-0.78)	-2.58** (-4.17--0.99)	-1.19* (-2.35--0.03)	-0.12 (-0.24-0.00)	0.05 (-0.10-0.20)	0.01 (-0.04-0.07)	0.06 (-0.06 - 0.18)
Perphenazine	0.23 (-0.16-0.62)	0.28 (-0.21-0.76)	-1.64* (-3.19--0.10)	-0.59 (-1.71-0.54)	-0.12 (-0.24-0.00)	0.31*** (0.16-0.45)	0.01 (-0.05-0.06)	0.13* (0.01 - 0.24)
Baseline value	-0.10*** (-0.13--0.07)	-0.04*** (-0.05--0.03)	-0.56*** (-0.60--0.53)	-0.66*** (-0.70--0.62)	-0.64*** (-0.68--0.60)	-0.38*** (-0.42--0.33)	-0.47*** (-0.51--0.43)	-0.40*** (-0.4--0.36)
	χ^2	χ^2	χ^2	χ^2	χ^2	χ^2	χ^2	
Time	368.78***	179.06***	3.56	1.05	21.86***	0.01	0.86	2.03
Treatment by time	107.73***	58.44***	11.32	11.22	4.52	5.20	11.21	8.60
Baseline by time	43.11***	36.34***	11.92**	4.48	6.09*	6.01*	0.07	1.79
Other covariates	\	Age	Age, sex, education, ALT	Age, sex, education, ALT	Age, sex, ALT	Age, sex, WBC	Age, sex, WBC	Age

*: p<0.05; **: p<0.01; ***: p<0.001. Abbreviations can be found at the end of this file.

Supplementary Table 5. Correlation of metabolic changes between the 2nd or 4th week and 6th week

	BMI_6w	WC_6w	SBP_6w	DBP_6w	GLU_6w	TG_6w	HDL-C_6w	LDL-C_6w
BMI_2w	0.64*	0.30*	0.02	0.01	0.04	0.09	0.03	0.10*
WC_2w	0.32*	0.55*	0.03	0.00	0.01	0.03	0.02	0.06
SBP_2w	0.03	0.01	0.61*	0.40*	0.01	-0.03	0.05	0.03
DBP_2w	0.01	-0.01	0.39*	0.59*	-0.00	-0.03	0.02	0.05
GLU_4w	0.03	0.01	0.05	0.06	0.63*	-0.06	0.08*	0.02
TG_4w	0.15*	0.11*	-0.03	0.01	-0.04	0.59*	-0.07	0.05
HDL-C_4w	0.08*	0.05	0.01	0.01	0.05	-0.06	0.62*	0.06
LDL-C_4w	0.16*	0.13*	-0.03	-0.01	0.04	0.04	0.08*	0.43*

*: Bonferroni Correction is used to control multiple tests and p < 0.0008 indicates statistical significance. Abbreviations can be found at the end of this file.

Supplementary Table 6. Prevalence of MetS in subjects with complete metabolic assessments (N=2 302)

	Total (N=2 302)			**Drug naïve (N=619)**			**BP adjusted (N=2 302)[a]**		
	Baseline N (%)	**Endpoint N (%)**	**p value[b]**	**Baseline N (%)**	**Endpoint N (%)**	**p value**	**Baseline N (%)**	**Endpoint N (%)**	**p value**
Ziprasidone (n=390)	43 (11.0)	31 (7.9)	0.08	9 (8.3)	7 (6.4)	0.75	43 (11.0)	40 (10.3)	0.75
Aripiprazole (n=386)	41 (10.6)	48 (12.4)	0.31	4 (4.0)	7 (6.9)	0.37	41 (10.6)	57 (14.8)	0.02
Olanzapine (n=396)	48 (12.0)	68 (17.2)	0.01	7 (6.5)	8 (7.5)	1.00	48 (12.0)	84 (21.2)	<0.0001
Quetiapine (n=387)	43 (11.0)	64 (16.5)	0.007	5 (5.0)	13 (13.0)	0.08	43 (11.0)	70 (18.1)	0.0004
Risperidone (n=378)	41 (10.8)	45 (11.9)	0.68	5 (4.6)	7 (6.4)	0.72	41 (10.8)	56 (14.8)	0.04
Haloperidol (n=172)	19 (11.4)	19 (11.0)	1.00	6 (12.2)	4 (8.2)	0.68	19 (11.4)	24 (14.0)	0.33
Perphenazine (n=193)	21 (10.9)	29 (15.0)	0.19	1 (2.2)	1 (2.2)	1.00	21 (10.9)	33 (17.1)	0.04
Overall	256 (11.1)	304 (13.2)	0.006	37 (6.0)	47 (7.6)	0.23	256 (11.1)	364 (15.8)	<0.0001

[a] In the BP adjusted MetS group, we grouped patients whose BP was higher than the cutoff (systolic BP ⩾130 mm Hg and/or diastolic BP ⩾85 mm Hg) before the medication but dropped below the cutoff, and had two other positive symptoms into MetS group. For example, a patient whose BP changed from 135/75 to 125/70 after medication, and had hyperlipidemia and abnormally high WC were supposed to have MetS;[b] p value of Mc Nemar test

Supplementary Table 7. Diagnostic change of metabolic measures over time

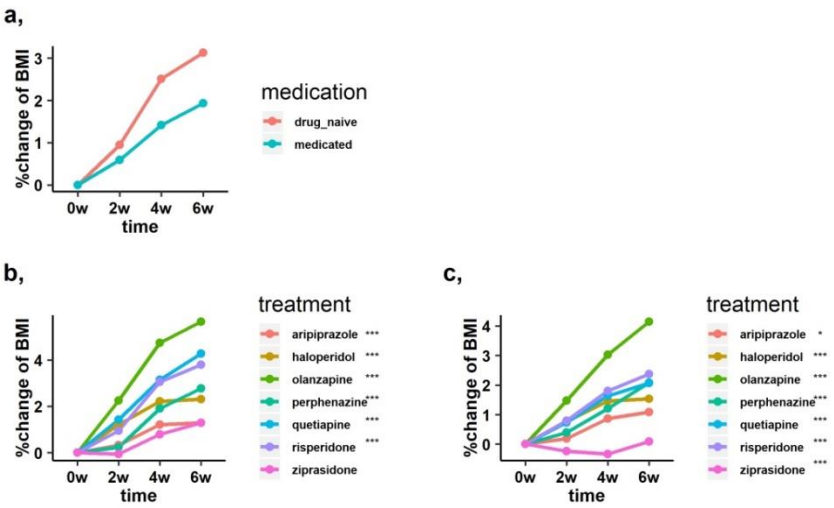
	Overweight (≥24 BMI <28)		Obesity (BMI ≥28)			Hyperlipidemia		
	Baseline N (%)	Endpoint N (%)	Baseline N (%)	Endpoint N (%)	p value	Baseline N (%)	Endpoint N (%)	p value
Ziprasidone	84 (20.4)	83 (20.2)	21 (5.1)	20 (4.9)	NA	86 (25.4)	86 (25.3)	1.00
Aripiprazole	75 (18.5)	84 (20.7)	32 (7.9)	29 (7.1)	0.21	91 (26.1)	112 (32.2)	0.03
Olanzapine	82 (20.0)	98 (23.9)	26 (6.3)	44 (10.3)	<0.001	92 (25.3)	138 (37.9)	<0.001
Quetiapine	96 (23.7)	114 (28.1)	26 (6.4)	30 (7.4)	NA	94 (27.0)	146 (42.0)	<0.001
Risperidone	93 (23.5)	92 (23.2)	27 (6.8)	38 (9.6)	0.007	92 (23.5)	98 (28.1)	0.11
Haloperidol	29 (15.8)	30 (16.3)	6 (3.3)	6 (3.3)	NA	42 (25.9)	57 (32.2)	0.04
Perphenazine	38 (18.85)	43 (21.3)	16 (7.9)	16 (7.9)	NA	43 (25.0)	60 (34.9)	0.02
Overall	497 (20.6)	544 (22.5)	154 (6.4)	183 (7.6)	<0.001	530 (25.5)	697 (33.5)	<0.001

Note: Presence of any 1 of the following 3 conditions confirmed hyperlipidemia: total cholesterol ≥6.2 mmol/L, high-density lipoprotein cholesterol <1.0 mmol/L and triglycerides ≥2.3 mmol/L;

Supplementary Table 8. Multivariable analysis of factors associated with baseline MetS after 6-week treatment

	OR (95%CI)	p value
Demographic characteristics		
Sex		0.34
Men	1 (ref)	
Women	1.13 (0.88-1.47)	
Age	1.05 (1.03-1.07)	<0.0001
Education		
Lower	1 (ref)	
Intermediate	1.47 (1.13-1.91)	0.004
Higher	1.49 (0.96-2.27)	0.07
Clinical characteristics		
Medication history		0.0003
Medicated	1 (ref)	
Drug-naïve	0.55 (0.39-0.76)	
General health condition		
ALT	1.02 (1.02-1.03)	<0.0001
WBC	1.15 (1.08-1.22)	<0.0001

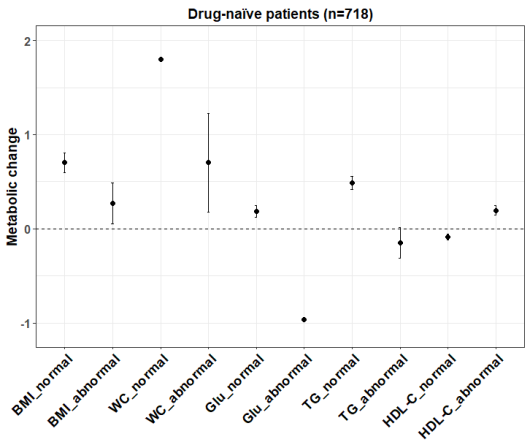
Abbreviations can be found at the end of this file.



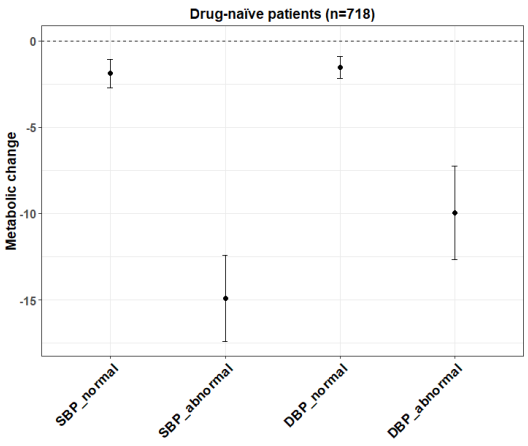
Supplementary Figure 1. Percentage change of BMI in medicated and drug-naive patients

(A) patients with or without medication history; (B) medicated patients treated with different antipsychotics; (C) drug-naïve patients treated with different antipsychotics.

a,



b,



Supplementary Figure 2. Least squares adjusted means of metabolic changes in drug-naïve patients

Note: BP was put in a different plot due to different amplitude of variation.

Abbreviations: ALT= alanine aminotransferase; BMI= body mass index; BP= blood pressure; CI=confidence interval; DBP= diastolic BP; DOI= duration of illness; Glu= glucose; HDL-C= high-density lipoprotein cholesterol; LDL-C= low-density lipoprotein cholesterol; OGTT= Oral Glucose Tolerance Test; OR=odds ratio; PANSS= Positive and Negative Syndrome Scale; SBP= systolic blood pressure; TG= triglycerides; WBC= white blood cell; WC= waist circumference.