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•ORIGINAL RESEARCH ARTICLE•

Comparison of Olanzapine versus Other Second-Generation Antipsychotics in the Improvement of Insight and Medication Discontinuation Rate in Schizophrenia

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Background: In the last decade, olanzapine became widely used in mental health service worldwide even after being criticized for its metabolic side effects. Patients with schizophrenia on olanzapine were usually found to stay on their medications longer than the other second-generation antipsychotics (SGAs) except clozapine. The reason for this is unknown.

objective: This prospective study compared the influences of olanzapine and other SGAs except clozapine on improving insight and medication discontinuation rate in schizophrenia.

Methods: A total of 148 patients with schizophrenia medically indicated for initiation of treatment with olanzapine or other SGAs were evaluated for symptoms, insight, attitudes toward medication, side effects, body weight and fasting lipid and glucose parameters at admission and before discharge, and follow-up calls one-year after discharge documented whether they were regularly taking prescribed psychotropic medication or not.

Results: After an average of 72.8 days of inpatient treatment, the olanzapine and other SGAs group exhibited similar levels of symptom improvement with an average reduction of 28.7 in the Positive and Negative Syndrome Scale (PANSS) total score. The Olanzapine group exhibited better improvement in insight assessed using the G12 item of PANSS and Insight and Treatment Attitudes Questionnaire (ITAQ), more metabolic side effects indexed with total cholesterol, triglycerides levels and weight gain, and a lower medication discontinuation rate than the other SGAs group.

Conclusion: Although general symptom improvement was similar, olanzapine significantly improved insight and presented less medication discontinuation compared to other SGAs, which might partially explain why patients on olanzapine stayed longer on their medications.

Key words: insight, medication discontinuation rate, olanzapine, second-generation antipsychotics, schizophrenia

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1. Introduction

Market approval of olanzapine was issued by both the American Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 1996. In the last decade, olanzapine became widely used in mental health service worldwide even after being criticized for its metabolic side effects. Newest data in the United States (US) reported that olanzapine accounted for 17% of prescriptions for antipsychotic monotherapy in the treatment of first episode schizophrenia.[1] In China, the third national survey on the use of psychotropic medications revealed that olanzapine was one of the most commonly used antipsychotic drugs, prescribed for 15.1% of inpatients with schizophrenia nationwide.[2]

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, the largest randomized clinical trial for schizophrenia sponsored by the US government to evaluate efficacy of different second generation antipsychotics (SGAs) and first generation antipsychotics (FGAs), revealed that olanzapine was the most effective one in terms of the study primary outcome which is the time to the discontinuation of treatment for any cause.[3] While in the multiple secondary analysis, olanzapine did not exhibit better benefits compared to other SGAs in terms of clinical symptoms, quality of life, family burden, instead olanzapine was found to be associated with more metabolic side effects.[4,5] The following open randomized clinical trial involved 50 sites in 14 counties and again found that although symptom reduction was virtually the same, olanzapine showed superiority in the primary study outcome of all cause treatment discontinuation.[6] A recent meta-analysis compared the effectiveness of olanzapine and other antipsychotics in schizophrenia treatment with definition of effectiveness as time to all-cause medication discontinuation and found that olanzapine appeared to be more effective in both observational studies and randomized clinical trials.[7, 8] The reason why patients on olanzapine stayed on their medications longer is still elusive. It was suggested that poor response/symptom worsening was the primary reason for discontinuation.[7] Multiple clinical trials including CATIE have shown that olanzapine did not exhibit clear superiority in symptom reduction.[4,6,9]

The study of schizophrenia in different cultures has revealed that 50-80% of patients with acute or chronic schizophrenia partially or totally lacked insight into their mental disorder.[10] Extensive studies have found that poor insight in schizophrenia was associated with poor medication compliance[11-15] and higher risk of relapse and readmission[16, 17] while good insight was closely correlated with better treatment compliance.[18-20] Poor insight in schizophrenia has been considered the primary cause of treatment noncompliance[21] and one of the major treatment compliance issues was drug discontinuation, which has been reported in a previous study.[22] Negative attitudes towards medication were shown to predict discontinuation of initiated treatment in a subsample of 228 patients who participated in the European First-Episode Schizophrenia Trial (EUFEST).[20] Poor insight and attitudes toward medication might cause many individuals with schizophrenia to refuse to be admitted when in need of hospitalization and to discontinue their prescribed medications. Therefore, it was presumed that better improvement in insight and more positive attitude towards medications might help the patients stay longer with their medications with less drug discontinuation.

Previous studies focused more on the correlates and consequences of poor insight, and only a few studies evaluated the potential differences of the therapeutic effectiveness in insight among different antipsychotics in patients with schizophrenia.[21] Thus it is not well documented if different antipsychotics showed different therapeutic effectiveness in insight improvement, and the potential correlations between insight and the medication discontinuation rate among different antipsychotics (especially why patients on olanzapine stayed longer on their medication). Thus, in this prospective observational study, we compared the general symptom control, insight, attitude towards medication, metabolic side effects and the one-year medication discontinuation rate of olanzapine and other SGAs in a sample of patients with schizophrenia in a large psychiatric hospital in China to evaluate the therapeutic effectiveness of olanzapine and other SGAs except clozapine on insight, which may help us further understand why patients on olanzapine stayed on their medications longer.

2. Methods

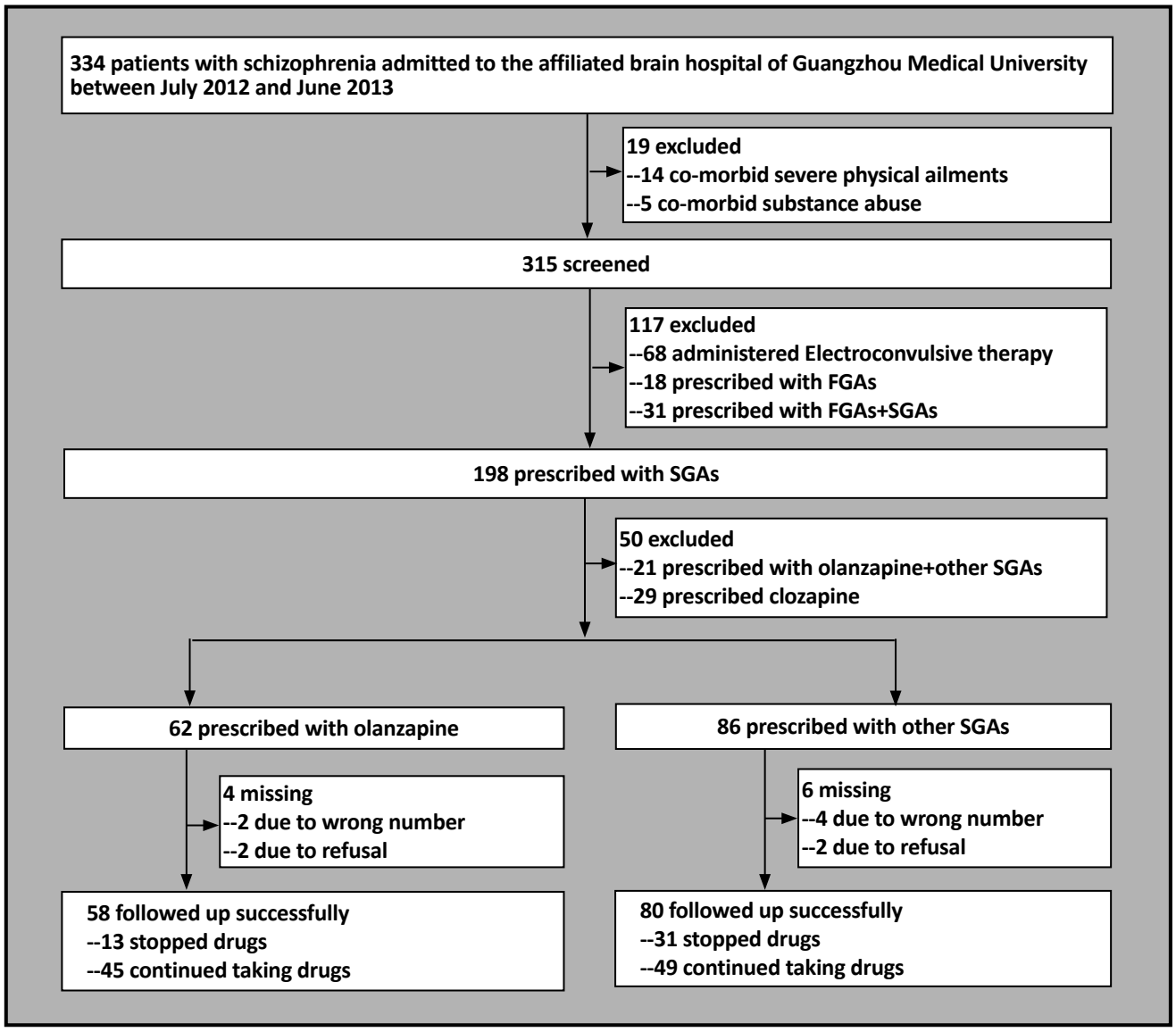
2.1 Patients, study settings and time

This prospective naturalistic observational study was conducted in the affiliated brain hospital of Guangzhou Medical University, the first psychiatric hospital in China (established in 1898), with 1600 psychiatric beds.

Patient enrollment was between July 2012 and June 2013. All participants were not randomly assigned to one of the two treatment groups, and the choices of prescribing which antipsychotics were dependent on the treating psychiatrist's decision, consistent with a "real world" design. All patients began antipsychotic treatment on the day of admission or the next day.

Preliminary diagnoses were established by two senior psychiatrists within one week of admission and the inter-rater reliability was good (Cronbach's α= 0.89). The final diagnoses were based on the Tenth Edition of the International Classification of Diseases (ICD-10) and were independently established by the study personnel, including review of all available information (including psychiatric and general medical records) along with one or more interviews with the participant. Any diagnostic uncertainties were resolved via discussion with one of the senior clinicians in the research group. The study inclusion criteria were as follows: confirmed diagnosis of schizophrenia, age

Figure 1. Flowchart of the study



18-60 years, clinical decision that oral SGAs were appropriate, adequate decision-making capacity and provision for written informed consent. Subjects were excluded if they had been administered first-generation antipsychotics, clozapine or electroconvulsive therapy during this hospitalization. Other exclusionary conditions included co-morbid substance abuse, current significant medical illness, organic brain syndrome, or any history of diabetes, hyperlipidemia, hepatic insufficiency, acute systemic infection, cardiovascular disorder and other severe physical ailments. The study was approved by the hospital ethics committee and all participants provided written informed consent.

A total of 334 consecutive inpatients with schizophrenia were enrolled in the study. 186 subjects were excluded due to not meeting the inclusion criteria. 148 subjects who were prescribed with olanzapine monotherapy or other SGAs were included in the final analysis. The inclusion and exclusion of patients is shown in Figure 1. Altogether, 62 (41.9%) patients were prescribed with olanzapine, 86 (58.1%) patients were prescribed with other SGAs except clozapine and olanzapine, including 32 with risperidone, 11 with quetiapine, 5 with ziprasidone, 12 with others and 26 with co-prescription of two different atypical antipsychotics. Other co-medication, including benzodiazepines, valproate, and antidepressants were not limited in this study.

2.2 Measures

All patients underwent blood collection, body weight measurements and clinical assessment at two different time points, i.e. one week within admission and one

week before discharge from the hospital. The range of length of stay was 12 to 215 days (mean=72.8[52.3]).

One year after discharge, all patients were contacted by phone and inquiry was made into their current pattern of medication treatment to determine whether patients had discontinued their medication in the previous year and were no longer taking the prescribed medication. 58 in the olanzapine group and 80 in the other SGAs group were followed-up one-year after the discharge successfully, and data from 10 subjects were missing: 6 due to the wrong telephone number, 4 due to refusal.

2.3 Assessment of metabolic effects

At admission, a medical history was collected and a physical examination was performed. Body weight was measured. Blood samples (4 mL) were drawn after 8-12 hours of overnight fasting for the measurement of total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol and fasting plasma glucose, glycosylated serum protein (GSP), and beta-hydroxybutyric acid (β-OHB) levels. Plasma glucose was measured using the glucose oxidase–peroxidase method, TG by standard enzymatic procedures, and TC, LDL, HDL cholesterol by direct assay method. Sample collection, processing and assay analysis were handled by staff from the hospital clinical laboratory department.

2.4 Clinical measures

Two psychiatrists with at least 5 years of clinical experience, who were blind to the study aims and medication status, were responsible for the symptom assessments with the Positive and Negative Syndrome Scale (PANSS), insight assessment with the Insight and Treatment Attitudes Questionnaire (ITAQ) and measure of side effects with the Treatment Emergent Symptoms Scale (TESS). The same rater followed the patients across the duration of the study at the time of admission and discharge from the hospital.

Clinical symptoms were assessed using the PANSS, which ranged from 30 to 210, with higher scores indicating more severe symptoms.[23] It included three sub-scales: positive, negative and general psychopathology symptoms. The Chinese translation of the PANSS has been previously validated using the back translation method.[24] Before patient enrollment, all the raters in this study were systematically trained by an internationally registered PANSS trainer from Peking Medical University. The inter-rater reliability of the clinical rating instruments was conducted on 20 patients with symptomatic schizophrenia. Assessment of inter-rater reliability for raters in this study was in the excellent to good range for all the scales used, with intra-class correlations ranging from 0.90 to 0.96.

Insight was assessed using the ITAQ which included 11 questions: five assessing the first dimension of insight, awareness of mental disorder (first 5 questions, ITAQ 1), and six assessing the second dimension of insight, awareness of the need for treatment (last 6 questions, ITAQ 2). Responses to each question are scored as 0 = no insight, 1 = partial insight, and 2 = good insight, giving a possible range between 0 and 22. The Chinese translation of the ITAQ has also been previously validated by the back translation method[25] and was widely used in China as well.

Therapeutic side effects were assessed using the TESS, which consisted of 34 items including symptoms and laboratory tests, with each item rating from 0-4 (higher scores indicating more serious therapeutic side effects). These 34 specific side effects were classified into 6 groups: toxic symptoms, abnormal tests, nervous system, vegetative nervous system, cardiovascular and others (including skin allergy, weight gain, weight reduction, anorexia, headache and tardive dyskinesia).

Attitudes toward medication were assessed by the Drug Attitude Inventory (DAI),[26] a 10 item true-false scale, on which higher numbers indicated more positive views toward medication. The instrument focused on unpleasant and negative subjective responses that were common adverse effects of antipsychotic medications. The Chinese translation of the DAI has also been previously validated by the back translation method.[27]

2.5 Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 17.0. Differences between the two groups in terms of sociodemographic and clinical characteristics were compared with independent two samples t-tests for continuous variables and Chi-square tests for categorical variables. Repeated measures analysis of variance was used to compare the changes of PANSS, ITAQ, DAI, TESS scores and serum lipids, fasting plasma glucose, body weight over time between patients with schizophrenia who took olanzapine and other SGAs. The significance level was set at 0.05 (two-sided).

2.6 Ethical considerations

This study was conducted with the approval of the affiliated brain hospital of Guangzhou Medical University ethics committee (Approval No. 2014–047).

3. Results

3.1 Patient characteristics

The mean (SD) age of the subjects was 35.6 (12.1) years old, and the mean (SD) duration of illness was 8.1(9.5) years. Demographic and clinical data showed no differences among the two group subjects, which suggested that they were homogeneous for age, gender, marital status, number of previous admissions, duration of illness, length of hospital stay and drug combination. The mean chlorpromazine equivalent dosage in

olanzapine and other SGAs group was 599.3mg and 577.6mg daily, respectively, and were not statistically different (Table 1).

3.2 Comparison of clinical measurement

At admission, with a mean (SD) total PANSS score of 91.6(15.5), the samples showed severe psychotic symptoms according to a recently published set of severity standards.[29] There were no significant differences between these two groups on the PANSS subscale score (w/o insight item), ITAQ, DAI or TESS scores.

The results of the treatment with olanzapine and other SGAs in the two groups of patients are shown in Table 2. After inpatient treatment, the olanzapine group and other SGAs group exhibited similar levels of symptom improvement with mean (SD) reduction of 28.7(6.4) in PANSS total score. The repeated measurement analysis of variance for the scores of the PANSS subscales, G12 (insight item), ITAQ and DAI all showed a dramatic improvement over time, and ITAQ1, ITAQ2 and G12 item showed significant time by-group interaction, indicating that greater improvement in insight in the olanzapine group than in the other SGAs group, but PANSS subscales or DAI showed no

Table 1. Comparison of socio-demographic and clinical characteristics between patients on olanzapine and other atypical antipsychotics[1]

Variables	Olanzapine (n=62)		Other SGAs[1] (n=86)		Statistics	
	n	%	n	%	X^2	*p*-value
Gender (male)	44	71.0	51	59.3	2.13	0.144
Employment status(working)	18	29.0	20	23.3	0.63	0.427
Marital status					4.36	0.113
Unmarried	29	46.8	48	55.8		
Married	23	37.1	33	38.4		
Divorced/widowed	10	16.1	5	5.8		
Alcohol abuse	11	17.7	12	14.0	0.39	0.530
Cigarette abuse	18	29.0	23	26.7	0.09	0.759
Number of previous admissions					2.56	0.464
0	18	29.0	32	37.2		
1	11	17.7	19	22.1		
2	13	21.0	16	18.6		
≥3	20	23.3	19	22.1		
Combined with other than antipsychotics						
Antidepressants	8	12.9	17	19.8	1.21	0.271
Mood stabilizers	15	24.2	25	29.1	0.43	0.510
Benzodiazepines	18	29.0	28	32.6	0.21	0.647
	Mean	***SD***	***Mean***	***SD***	***t-value***	***p***
Age (year)	35.8	12.1	35.4	12.2	0.19	0.850
Education (year)	11.3	3.0	11.4	3.5	-0.60	0.548
Duration of disorder(year)	9.3	8.5	7.2	10.2	0.52	0.607
Length of stay(day)	74.4	44.2	71.6	57.6	0.31	0.754
Antipsychotics dose (mg/d)[2]	599.3	170.1	577.6	215.4	0.66	0.512

[1]Other atypical antipsychotics: Of the patients, 32 with risperidone, 11 quetiapine, 5 ziprasidone, 12 others and 26 used two different atypical antipsychotic medications.
[2]Chlorpromazine equivalent dose.
SGAs=second-generation antipsychotics

differences by group and no significant time by-group interaction effects.

According to TESS, the results of the repeated measurement analysis of variance showed that there was a significant deterioration over time in toxic symptoms, abnormal test and other domains including skin allergy, weight gain, weight reduction, anorexia, headache and tardive dyskinesia, and indicated significant time by-group interaction effects on abnormal tests and other domains (Table 2).

3.3 Comparison of metabolic indices and body weight

No significant statistical differences were found in biochemical parameters and body weight at admission between the olanzapine and other SGAs groups. Table 3 showed that TC, TG, HDL, GLU, β-OHB and body weight in the two groups were increased at discharge, but TC, TG and body weight showed significant time by-group interaction effects indicating a more significant increase in the olanzapine group than the other SGAs group.

There were 21% (n=13) and 56.5% (n=35) of subjects in the olanzapine group ending up with TC and TG levels higher than 5.72 mmol/L and 1.71 mmol/L respectively, which were the upper limits for the normal range in China. The other SGAs group had 7.0% (n=6) and 39.5% (n=34) of the subjects with TC and TG levels beyond the upper limits.

3.4 Comparison of the antipsychotic medication discontinuation rate

Of the 148 subjects at baseline, 138 (58 in olanzapine group and 80 in other SGAs group) were successfully followed-up one-year after the discharge, and 10 subjects were missing: 6 due to the wrong telephone number, 4 due to refusal. The medication discontinuation rate was significantly different between the two groups with the olanzapine group less likely to stop their medication (22.4%, n=13 vs. 38.8%, n=31, X^2=4.13, p=0.042).

4. Discussion

4.1 Main findings

The primary objective of this study was to explore if olanzapine could exhibit better benefits in insight and

Table 2. Comparison of PANSS, ITAQ, DAI and TESS scores between patients on olanzapine and other SGAs[1] with analysis of variance of repeated measures

Variables	Admission		Discharge		Time effect		Group effect		Time×Group	
	Olanzapine (n=62)	Other SGAs[1] (n=86)	Olanzapine (n=62)	Other SGAs[1] (n=86)	*F*	*p*	*F*	*p*	*F*	*p*
PANSS positive	24.4(6.5)	22.5(6.3)	11.8(4.0)	11.9(3.9)	26.13	<0.001	0.06	0.804	3.55	0.061
PANSS negative	23.5(8.1)	24.9(8.8)	18.0(7.0)	19.5(7.8)	106.16	<0.001	1.53	0.218	0.01	0.967
PANSS general (no insight item)	38.2(7.7)	38.8(8.7)	26.0(6.5)	27.5(7.5)	363.73	<0.001	0.85	0.358	0.60	0.439
G12 (insight item)	5.4(1.2)	5.4(1.2)	3.2(1.0)	4.0(1.2)	220.65	<0.001	9.11	0.003	8.68	0.004
ITAQ 1	2.0(2.2)	1.7(1.9)	6.2(3.0)	4.8(3.1)	278.83	<0.001	5.99	0.016	6.56	0.011
ITAQ 2	3.1(3.2)	3.1(2.9)	7.5(3.2)	6.1(3.2)	180.90	<0.001	2.53	0.113	6.70	0.011
DAI	0.6(5.0)	2.0(4.9)	4.6(3.6)	4.3(4.0)	46.00	<0.001	0.81	0.370	3.75	0.055
TESS										
Toxic symptom	0.37(0.70)	0.18(0.59)	1.23(1.14)	0.90(1.02)	65.88	<0.001	1.44	0.232	0.49	0.485
Abnormal test	0.20(0.31)	0.33(0.64)	0.63(0.97)	0.41(0.81)	8.54	0.004	0.28	0.601	4.23	0.041
Nervous system	0.30(0.84)	0.60(1.14)	0.46(0.89)	0.34(0.73)	0.26	0.613	0.55	0.461	4.67	0.032
Vegetative nervous system	0.46(0.86)	0.34(0.67)	0.32(0.73)	0.23(0.66)	2.72	0.101	1.30	0.255	0.05	0.816
Cardiovascular	0.10(0.25)	0.17(0.62)	0.30(0.63)	0.24(0.74)	3.52	0.063	0.74	0.392	0.74	0.382
Others†	0.46(0.62)	0.34(0.46)	0.30(1.08)	0.60(0.84)	25.49	<0.001	4.49	0.036	3.95	0.049

[1]See Table 1

Abbreviations: PANSS: Positive and Negative Syndrome Scale; ITAQ: Insight and Treatment Attitudes Questionnaire; DAI: Drug Attitude Inventory; TESS: Treatment Emergent Symptoms Scale.

†, include 6 items (skin allergy, weight gain, weight reduction, anorexia, headache and tardive dyskinesia).

SGAs=second-generation antipsychotics

Table 3. Comparison of metabolism indexes between patients on olanzapine and other SGAs[1] with analysis of variance of repeated measures.

Variables	Admission		Discharge		Time effect		Group effect		Time×Group	
	Olanzapine (n=62)	Other SGAs[1] (n=86)	Olanzapine (n=62)	Other SGAs[1] (n=86)	*F*	*p*	*F*	*p*	*F*	*p*
TC (mmol/L)	4.33(0.92)	4.21(0.91)	4.87(1.11)	4.30(0.99)	11.07	0.001	7.20	0.008	5.66	0.019
TG (mmol/L)	1.18(1.05)	1.27(0.70)	2.60(1.63)	1.74 (0.94)	69.02	<0.001	8.41	0.004	17.32	<0.001
HDL (mmol/L)	1.53(0.28)	1.47(0.31)	1.40(0.26)	1.42 (0.34)	12.63	0.001	0.16	0.688	2.12	0.147
LDL (mmol/L)	2.94(0.87)	2.89(0.80)	3.10(0.84)	2.88 (0.82)	0.93	0.336	1.33	0.25	1.18	0.278
GLU (mmol/L)	4.75(1.15)	4.70(0.71)	5.14(1.04)	5.01(1.17)	11.91	0.001	0.49	0.485	0.16	0.686
GSP (mmol/L)	1.71(0.22)	1.679(0.23)	1.84(0.38)	3.68 (17.28)	0.95	0.331	0.67	0.414	0.73	0.394
β-OHB (**mmol/L)**	0.10(0.13)	0.08(0.05)	0.17(0.20)	0.15(0.20)	16.90	<0.001	1.71	0.301	0.02	0.893
Body weight (kg)	60.4(9.5)	62.1(13.6)	64.4(8.4)	63.1(12.9)	126.60	<0.001	0.01	0.972	20.71	<0.001

[1]See Table 1

Abbreviations: TC: Total Cholesterol; TG: Triglycerides; HDL: High Density Lipoprotein Cholesterol; LDL: Low Density Lipoprotein Cholesterol; GLU: Glucose; GSP: glycosylated serum protein; β-OHB: Beta-hydroxybutyric Acid.

medication discontinuation rate which may shed light on why patients on olanzapine stay on their medications longer. This prospective study naturally observed inpatients who were treated with olanzapine or other SGAs except clozapine in a large psychiatric hospital in China and found that in general symptom control as evaluated with PANSS total score and subscale scores, olanzapine and other SGAs were similarly effective, while in the recovery of insight evaluated with PANSS item of G12, ITAQ total and subscale scores, the olanzapine group showed better improvement. Similarly olanzapine also showed a lower medication discontinuation rate in the year after discharge.

Although olanzapine has been found to be associated with a significantly longer treatment period and lower rates of discontinuation than other SGAs [3, 6-8], a more in-depth explanation of this phenomenon has not been provided in previous research. The superiority of one antipsychotic over another is the topic of much discussion, but some prescription guidelines strongly suggested the early use of olanzapine.[29] Although some clinical trials showed more advantages in symptom reduction for olanzapine versus other SGAs,[30, 31] more studies did not find significant differences.[4, 6, 9] Our study first reported that olanzapine-treated patients showed a better improvement in ITAQ and G12 of PANSS compared to other SGAs-treated patients during inpatient treatment. Previous studies have shown that insight was highly correlated with treatment compliance[18-21] which in turn was closely related with drug discontinuation.[20, 22] Thus, our data suggested that it was the advantageous effect of olanzapine in the improvement of insight that might contribute to the longer treatment time and lower rates of discontinuation.

Currently few studies have evaluated the effects on level of insight among different antipsychotics. One study with 55 subjects reported that SGAs, including olanzapine, aripiprazole and ziprasidone had the same efficacy in the recovery of insight for patients with schizophrenia in the 6 month follow up.[32] This is an outpatient follow up different from out study regiment which measured the acute changes of insight during inpatient stay with a comparatively larger sample. Another fact is that level of insight in patients in China with acute schizophrenia was found to be more severe than in patients in the US.[33] Although the reason for this is unknown, this comparatively lower level of insight at baseline potentially gives patients more potential to exhibit better improvement, which may not exist in some other studies.

It is not completely clear how the SGAs could affect insight in schizophrenia. Some research indicated that improvement of insight with SGAs could be, at least partially, due to the psychopathological improvement rather than a specific effect of these drugs on insight itself,[32] because there was a relatively strong correlation between insight and the severity of psychopathology which was found during the acute phase of the disease.[34] However, the fact that olanzapine and other SGAs showed a similar efficacy on all domains of symptoms suggests a possible independence between the two domains. Therefore other mechanisms of action of olanzapine may be involved in the observed insight improvement, likely involving specific brain regions related to insight, which sustained the hypothesis that insight could be considered a specific psychopathological dimension of schizophrenia, which was not entirely associated with symptoms.[35]

On the other hand, both acute and chronic use of olanzapine has been associated with multiple metabolic side effects especially weight gain[36] and hyperlipidemia.[37] In our study, after an average of nine weeks inpatient treatment, patients on olanzapine were found to have significantly higher weight gain than other SGAs. And for the elevations of plasma, total cholesterol (TC) and total triglycerides (TG) levels, as much as 21% of olanzapine-treated subjects displayed hyperlipidemia with total TC and/or TG levels beyond the upper limits of normal ranges, and 7.0% for patients on other SGAs. Our results suggest that even with short term use of olanzapine, the weight and plasma lipids levels need to be closely monitored.

4.2 Limitations

The results should be viewed with caution due to a couple of limitations. This study was carried out in an inpatient setting in China where patients often display severe psychosis and low levels of insight at admission. Therefore, these results are not universal to all patients with schizophrenia. Second, due to the nature of observational study, the lack of random assignment and some bias factors such as treating physicians' individual prescribing preference, drug prices, and treatment history, clinicians choice between olanzapine or other SGAs may have been impacted. Third, lack of the waistline, hips, body mass index data may constrain comparison with other studies.

4.3 Implications

Despite the above-mentioned limitations, our study first showed that olanzapine may provide better benefits in insight and a lower medication discontinuation rate in the one year after discharge in patients with schizophrenia. This may be one of the main reasons why patients on olanzapine stayed on their medications longer, even with more metabolic side effects. Future studies are warranted to further evaluate the differences in insight among different antipsychotics under different clinical settings.

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Conflicts of interest statement

The authors declare no conflicts of interest.

Ethical approval

This study was conducted with the approval of the affiliated Brain Hospital of Guangzhou Medical University ethics committee (Approval No. 2014–047).

Authors' contributions

Drs. He, Zhou and Luo designed the study together and Dr. He wrote the study protocol. Drs. Zhou and Yang collected the data, undertook the statistical analysis. Drs. He and Li wrote the first draft of the manuscript. Dr. Zhou worked with Dr. Luo on the final preparation. All authors contributed to and have approved the final manuscript.

比较奥氮平与其他二代抗精神病药物对改善精神分裂症患者自知力和药物中断率的影响

何红波，周燕玲，杨铭哲，李雄雄，项玉涛，罗建东

背景：在过去 10 年中，奥氮平即使被指出具有代谢副作用但依然被广泛应用于精神卫生服务中。服用奥氮平的精神分裂症患者通常服药时间比除了氯氮平外的其他二代抗精神病药物（SGAs）更长，而原因不明。

目的：该前瞻性研究旨在比较奥氮平与其他除氯氮平以外的二代抗精神病药物（SGAs）治疗对改善精神分裂症患者自知力和药物停药率的影响。

方法：共有 148 例精神分裂症患者起始治疗就采用奥氮平或其他 SGAs，对他们进行评估入院前和出院前的症状、自知力、用药态度、副作用、体重和空腹血脂和血糖参数。出院后一年的随访电话包括是否定期服用精神药物。

结果：平均 72.8 天的住院治疗后，奥氮平和其他 SGA 组表现的症状改善水平相似，阳性和阴性症状量表（PANSS）总分平均减少 28.7。采用 PANSS 的 G12 项目和自知力及治疗态度问卷（ITAQ）评估后奥氮平组自知力方面有了更好的改善，总胆固醇、甘油三酯水平、和体重增加引起的代谢副作用更多，而药物停药率比其他二代抗精神病药物组低。

结论：虽然奥氮平和其他二代抗精神病药物对一般症状的改善相差不大，但是奥氮平比其他 SGAs 明显改善了自知力并且停药率也较低，这可能部分解释了为什么患者服用奥氮平的时间会更长。

关键词：自知力、停药率、奥氮平、第二代抗精神病药物、精神分裂症

References

1. Robinson DG, Schooler NR, John M, Correll CU, Marcy P, Addington J, et al. Prescription practices in the treatment of first-episode schizophrenia spectrum disorders: data from the national RAISE-ETP study. *Am J Psychiatry*. 2015; **172**: 237-248. doi: https://doi.org/10.1176/appi.ajp.2014.13101355
2. Li Q, Xiang YT, Su YA, Liang S, Xin Y, Helen C, et al. Antipsychotic polypharmacy in schizophrenia patients in China and its association with treatment satisfaction and quality of life: findings of the third national survey on use of psychotropic medications in China. *Aust N Z J Psychiatry*. 2015; **49**: 129-36. doi: https://doi.org/10.1177/0004867414536931
3. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005; **353**: 1209-1223. doi: https://doi.org/10.1056/NEJMoa051688
4. McEvoy JP, Lieberman JA, Perkins DO, Hamer RM, Gu H, Lazarus A, et al. Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. *Am J Psychiatry*. 2007; **164**: 1050-1060. doi: https://doi.org/10.1176/ajp.2007.164.7.1050
5. Perlick DA, Rosenheck RA, Kaczynski R, Swartz MS, Canive JM, Lieberman JA. Impact of antipsychotic medication on family burden in schizophrenia: longitudinal results of CATIE trial. *Schizophr Res*. 2010; **116**: 118-125. doi: https://doi.org/10.1016/j.schres.2009.09.026
6. Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IPM, et al. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet*. 2008; **371**: 1085-1097. doi: https://doi.org/10.1016/S0140-6736(08)60486-9
7. Kinon BJ, Liu-Seifert H, Adams DH, Citrome L. Differential rates of treatment discontinuation in clinical trials as a measure of treatment effectiveness for olanzapine and comparator atypical antipsychotics for schizophrenia. *J Clin Psychopharmacol*. 2006; **26**: 632-637. doi: https://doi.org/10.1097/01.jcp.0000245563.06660.0f
8. Soares-Weiser K, Bechard-Evans L, Lawson AH, Davis J, Ascher-Svanum H. Time to all-cause treatment discontinuation of olanzapine compared to other antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. *Eur Neuropsychopharmacol*. 2013; **23**: 118-125. doi: https://doi.org/10.1016/j.euroneuro.2012.05.001
9. Strom BL, Eng SM, Faich G, Reynolds RF, D'Agostino RB, Ruskin J, et al. Comparative mortality associated with ziprasidone and olanzapine in real-world use among 18,154 patients with schizophrenia: The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC). *Am J Psychiatry*. 2011; **168**: 193-201. doi: https://doi.org/10.1176/appi.ajp.2010.08040484
10. Carpenter WT SJS, Bartko JJ. Flexible system for the diagnosis of schizophrenia: Report from the WHO International Pilot Study of Schizophrenia. *Science*. 1973; **182**: 1275–1278. doi: https://doi.org/10.1126/science.182.4118.1275
11. Acosta FJ, Hernández JL, Pereira J, Herrera J, Rodríguez CJ. Medication adherence in schizophrenia. *World J Psychiatry*. 2012; **2**(5): 74. doi: https://doi.org/10.5498/wjp.v2.i5.74
12. Laurent B, Michel C, Daniel D, Jessica F, Mohamed B, Raphaelle R, et al. Neurocognition, Insight and Medication Nonadherence in Schizophrenia: A Structural Equation Modeling Approach. *PLoS One*. 2012; **7**(10): e47655. doi: https://doi.org/10.1371/journal.pone.0047655
13. Eticha T, Teklu A, Ali D, Solomon G, Alemayehu A. Factors Associated with Medication Adherence among Patients with Schizophrenia in Mekelle, Northern Ethiopia. *PLoS One*. 2015; **10**(3): e0120560. doi: https://doi.org/10.1371/journal.pone.0120560
14. Na E, Yim SJ, Lee J, Kim JM, Hong K, H MH, et al. Relationships among medication adherence, insight, and neurocognition in chronic schizophrenia. *Psychiatry & Clinical Neurosciences*. 2015; **69**(5): 298-304. doi: https://doi.org/ 10.1111/pcn.12272
15. Higashi K, Medic G, Littlewood KJ, Diez T, Granström O, Hert MD. Medication adherence in schizophrenia: factors influencing adherence and consequences of nonadherence, a systematic literature review. *Ther Adv Psychopharmacol*. 2013; **3**(4): 200. doi: https://doi.org/ 10.1177/2045125312474019
16. Schennach R, Obermeier M, Meyer S, Jäger M, Schmauss M, Laux G, et al. Predictors of relapse in the year after hospital discharge among patients with schizophrenia. *Psychiatr Serv*. 2012; **63**(1): 87-90. doi: https://doi.org/10.1176/appi.ps.201100084
17. Xiao J, Mi W, Li L, Shi Y, Zhang H. High relapse rate and poor medication adherence in the Chinese population with schizophrenia: results from an observational survey in the People's Republic of China. *Neuropsychiatric Disease & Treatment*. 2015; **11**: 1161-1167. doi: https://doi.org/10.2147/NDT.S72367
18. Rettenbacher MA, Hofer A, Eder U, Hummer M, Kemmler G, Weiss EM, et al. Compliance in schizophrenia: psychopathology, side effects, and patients' attitudes toward the illness and medication. *J Clin Psychiatry*. 2004; **65**: 1211-1218. doi: https://doi.org/ 10.4088/JCP.v65n0908
19. Mohamed S, Rosenheck R, McEvoy J, Swartz M, Stroup S, Lieberman JA. Cross-sectional and longitudinal relationships between insight and attitudes toward medication and clinical outcomes in chronic schizophrenia. *Schizophr Bull*. 2009; **35**: 336-346. doi: https://doi.org/10.1093/schbul/sbn067
20. Gaebel W, Riesbeck M, von WM, von Wilmsdorff M, Burns T, Derks EM, et al. Drug attitude as predictor for effectiveness in first-episode schizophrenia: Results of an open randomized trial (EUFEST). *Eur Neuropsychopharmacol*. 2010; **20**: 310-316. doi: https://doi.org/10.1016/j.euroneuro.2010.02.001
21. Lysaker PH, Vohs J, Hillis JD, Kukla M, Popolo R, Salvatore G, et al. Poor insight into schizophrenia: contributing factors, consequences and emerging treatment approaches. *Expert Rev Neurother*. 2013; **13**(7): 785-793. doi: https://doi.org/ 10.1586/14737175.2013.811150
22. Lindenmayer JP, Liu-Seifert H, Kulkarni PM, Kinon BJ, Stauffer V, Edwards SE, et al. Medication nonadherence and treatment outcome in patients with schizophrenia or schizoaffective disorder with suboptimal prior response. *J Clin Psychiatry*. 2009; **70**: 990-996. doi: https://doi.org/10.4088/JCP.08m04221.
23. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987; **13**: 261-276.

24. Phillips MR, Xiong W, Wang RW, Gao YH, Wang XQ, Zhang NP. Reliability and validity of the Chinese versions of the Scales for Assessment of Positive and Negative Symptoms. *Acta Psychiatr Scand*. 1991; **84**(4): 364-370. doi: https://doi.org/10.1111/j.1600-0447.1991.tb03161.x
25. Zhang JX, Li XB, Weng Z, Liu JT, Liu XC, Yuan W, et al. [Clinical trial of insight and treatment attitude questionnaire]. *Shandong Jing Shen Yi Xue*. 1994; **04**: 10-13. Chinese
26. Hogan TP, Awad AG, Eastwood R. A self-report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity. *Psychol Med*. 1983; **13**: 177-183
27. He HB, Zhou YL, Zeng YB, Huang WJ, Liang L, Chen YW, et al. [Clinical factors of length of stay in patients with schizophrenia]. *Zhongguo Shen Jing Jing Shen Ji Bing Za Zhi*. 2014; **6**: 375-378. Chinese
28. Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel RR. What does the PANSS mean. *Schizophr Res*. 2005; **79**: 231-238
29. David Taylor CP, Kapur S. *The Maudsley Prescribing Guidelines in Psychiatry (11 edition)*. New Jersey: John Wiley & Sons Inc; 2014 . p: 26
30. Ye W, Fujikoshi S, Nakahara N, Takahashi M, Ascher-Svanum H, Ohmori T. Improved outcomes following a switch to olanzapine treatment from risperidone treatment in a 1-year naturalistic study of schizophrenia patients in Japan. *Psychiatry & Clinical Neurosciences*. 2012; **66**(4): 313. doi: https://doi.org/10.1111/j.1440-1819.2012.02351.x
31. S. Shafti S, Gilanipoor M. Olanzapine v Risperidone: A Contrast Between Atypical Antipsychotics Concerning Control of Schizophrenia. *Curr Psychopharmacol*. 2016; doi: https://doi.org/ 10.2174/2211556005666160215235251
32. Bianchini O, Porcelli S, Nespeca C, Cannavò D, Trappoli A, Aguglia E, et al. Effects of antipsychotic drugs on insight in schizophrenia. *Psychiatry Res*. 2014; **218**: 20-24. doi: https://doi.org/10.1016/j.psychres.2014.03.022
33. Mohamed S, Rosenheck R, He H, Yuping N. Insight and attitudes towards medication among inpatients with chronic schizophrenia in the US and China. *Soc Psychiatry Psychiatr Epidemiol*. 2014; **49**: 1063-1070. doi: https://doi.org/10.1007/s00127-014-0824-1
34. Zhou Y, Rosenheck R, Mohamed S, Zhang J, Chang Q, Ou Y, et al. Insight in inpatients with schizophrenia: relationship to symptoms and neuropsychological functioning. *Schizophr Res*. 2015; **161**: 376-381. doi: https://doi.org/10.1016/j.schres.2014.12.009
35. Drake RJ, Lewis SW. Insight and neurocognition in schizophrenia. *Schizophr Res*. 2003; **62**: 165-173. doi: https://doi.org/10.1016/S0920-9964(02)00382-1
36. Salviato BM, Cecilio HJE, Arcoverde NE, Homem MM, Triffoni-Melo AT, Ferreira FI, et al. Olanzapine, weight change and metabolic effects: a naturalistic 12-month follow up. *Ther Adv Psychopharmacol*. 2014; **4**: 30-6. doi: https://doi.org/10.1177/2045125313507738
37. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Lobos CA, et al. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. *Schizophr Res*. 2010; **123**: 225-233. doi: https://doi.org/10.1016/j.schres.2010.07.012

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