Effectiveness of Antipsychotic Drugs for 24-Month Maintenance Treatment in First-Episode Schizophrenia:

Evidence From a Community-Based "Real-World" Study

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ABSTRACT

Objective: Maintenance treatment of schizophrenia with antipsychotic medications has become a standard for the prevention of psychotic relapse. However, little is known about the effectiveness of antipsychotic drugs for maintenance treatment in "real-world" populations with schizophrenia. We carried out a prospective study to assess the effectiveness of the most frequently prescribed antipsychotic drugs in the maintenance treatment of schizophrenia from 2 community settings.

Methods: This study was conducted from October 2011 to December 2014. All participants were diagnosed with schizophrenia according to *DSM-IV*, were treated with an antipsychotic monotherapy, and were registered in a case management program with monthly monitoring for 24 months. The primary outcome measure, Positive and Negative Syndrome Scale (PANSS), and the Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales were used to evaluate symptom severity and treatment response. The Personal and Social Performance scale (PSP) was used to evaluate the patients' social functioning. The Medication Adherence Rating Scale (MARS) was used to assess medication adherence behavior. On the basis of antipsychotic used at baseline, patients were clustered into 7 groups: aripiprazole (n = 21), clozapine (n = 84), chlorpromazine (n = 61), olanzapine (n = 34), perphenazine (n = 21), quetiapine (n = 27), and risperidone (n = 99).

Results: Of the 347 patients enrolled in the study, 312 completed the 24-month follow-up. There were no significant differences among the treatment groups in the PANSS total and subscale scores or the CGI-S and CGI-I scores over 24 months (all *P* values > .05). There were also no significant differences in interactions between PSP scores and antipsychotic drugs (*P* = .17). The remission rates increased as the follow-time lapsed in all groups, but no significant difference was observed in remission rates at each time point among the 7 groups (*P* values > .05). At the endpoint, MARS total scores were over 6, but did not significantly differ among the studied drugs (*P* = .24).

Conclusions: These findings suggest that antipsychotic drugs can achieve equivalent effectiveness in maintenance treatment of first-episode schizophrenia through a well-organized case management program and family participation.

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Schizophrenia is a debilitating and often lifelong psychiatric disorder, affecting approximately 1% of the population worldwide. It is characterized by typical manifestations including positive symptoms (hallucination, delusions, and disorganized behavior) and negative symptoms (affective blunting, apathy, and social withdrawal).

First-generation antipsychotics (FGAs) are effective against positive symptoms, but second-generation antipsychotics (SGAs) have been widely used for the treatment of schizophrenia in clinical practice due to their lower risk of extrapyramidal symptoms (EPS) and tardive dyskinesia (TD) compared to FGAs.[1] Although SGAs were initially believed to be more efficacious than FGAs,[2] especially for negative symptoms, the results from randomized controlled effectiveness clinical trials such as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)[3] did not support this view. Traditional clinical efficacy trials rely on carefully laid out, treatment-optimizing protocols with strict inclusion and exclusion criteria.[4,5] In addition, most clinical efficacy trials have been conducted in hospital settings.[6] Moreover, randomized placebo-controlled efficacy trials often have short follow-up durations.[7] Therefore, results from the efficacy of short- and long-term trials might not be generalizable to patients in community settings.

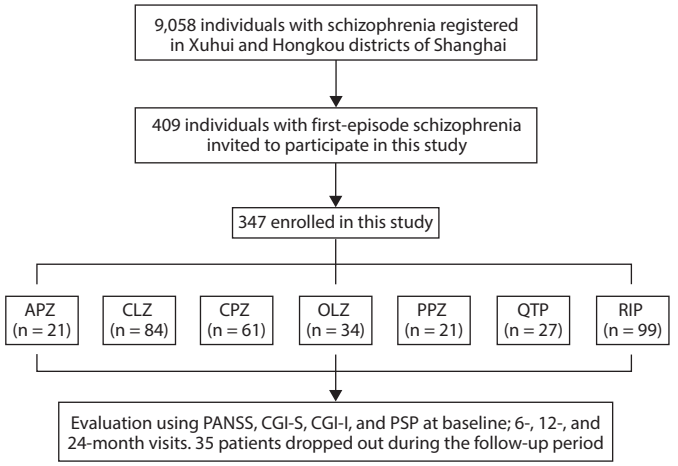
Although various guidelines and algorithms have been developed for maintenance treatment of schizophrenia based on the results of randomized placebo-controlled efficacy trials, recommendations for maintenance treatment have been inconsistent.[8] More importantly, the effectiveness of antipsychotic drugs for maintenance treatment in real-world conditions remains unknown. Because most patients with schizophrenia receive maintenance treatment in communities, there is an urgent need to conduct effectiveness trials of antipsychotics in patients with schizophrenia in community settings.[9]

In the past decade, the Shanghai Center for Disease Control and Prevention (SCDC) of China has developed a 3-tier monitoring system in community settings for patients with severe psychiatric disorders, in which patients can receive regular monthly follow-up visits without any charge.[10] This system provides a unique opportunity to conduct effectiveness studies in patients with schizophrenia. In the present study, the effectiveness of commonly prescribed antipsychotics was assessed in

Clinical Points

- Maintenance treatment of schizophrenia with antipsychotic medications has become a standard for the prevention of psychotic relapse. However, little is known about the effectiveness of antipsychotic drugs for maintenance treatment in "real-world" populations with schizophrenia.
- For maintenance treatment of first-episode schizophrenia, antipsychotic drugs can achieve similar effectiveness through a well-organized case management program and family participation.

Figure 1. Flowchart of the Study



Abbreviations: APZ = aripiprazole, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, CLZ = clozapine, CPZ = chlorpromazine, OLZ = olanzapine, PANSS = Positive and Negative Syndrome Scale, PPZ = perphenazine, PSP = Personal and Social Performance scale, QTP = quetiapine, RIP = risperidone.

patients with schizophrenia who were stabilized and discharged from the hospital for 24 months.

METHODS

Participants

The study protocol was reviewed and approved by the ethics committee of the Shanghai Mental Health Center. Patients with schizophrenia registered in the community-based case management program for schizophrenia in Xuhui and Hongkou Districts of Shanghai city were recruited from October 2011 to January 2012. The last patient completed the study in December 2014. All participants provided written informed consent prior to the inclusion in this project and were treated in accordance with the Declaration of Helsinki.

The study inclusion criteria have been reported previously.[11] Briefly, each patient was required to meet the following 5 conditions: (1) the patient was in the first-episode of schizophrenia diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) (corresponding to the *International Classification of Diseases*, 10th Revision [*ICD-10*] item F20), diagnoses were made using modified sections of the Structured Clinical Interview for *DSM-IV* disorders by at least 2 trained research psychiatrists, and all relevant diagnostic information for each patient was reviewed; (2) the patient had a stable psychiatric condition with a PANSS total score less than 60; (3) the patient had no previous discharge after hospitalization due to schizophrenia-like psychosis; (4) the patient was 18–45 years old; and (5) the patient was diagnosed with no physical disease or psychiatric disorder other than schizophrenia.

Evaluation

Demographic and treatment course–related variables were extracted from a standard documentation system in SCDC. To evaluate symptom severity and the level of antipsychotic response, the Positive and Negative Syndrome Scale for schizophrenia (PANSS)[12] was employed as the primary outcome instrument. Overall symptomatic status was assessed using the expanded version of the Clinical Global Impressions (CGI) scale[13] including the CGI-Severity of Illness scale (CGI-S) and the CGI-Improvement scale (CGI-I). A CGI-S score equal to or lower than 3 was considered as remission for this study.[14,15] The patients' social functioning was examined by the Chinese version of the Personal and Social Performance scale (PSP).[16] The ratings were based on the assessment of 4 objective indicators: (*a*) socially useful activities, (*b*) personal and social relationships, (*c*) self-care, and (*d*) disturbing and aggressive behaviors. The Chinese version of the PSP had good reliability, validity, and sensitivity.[16] The 10-item Medication Adherence Rating Scale (MARS), a reliable and valid measure for assessing medication adherence behavior in psychosis,[17,18] was used to measure adherence in this study.

Study Design

All participants were on antipsychotic monotherapy and registered in the case management program. The details of this program were described previously.[10] Briefly, the participants who were discharged from the hospital after stabilization for acute psychosis received regular monitoring every month by research psychiatrists during the 24-month follow-up period. The patients were evaluated with the PANSS, the CGI-I, and the CGI-S at baseline and 6-, 12-, and 24-month visits. At the endpoint, the MARS was used to evaluate patients' adherence to prescribed medications. Ratings for this measure were obtained by trained clinicians. All raters were trained to use all scales, and a median intraclass correlation coefficient of 0.80 or higher across all items of the scales was established.

Statistical Analysis

Comparisons for clinical correlates and baseline characteristics were carried out with the Fisher exact test for categorical variables and the Kruskal-Wallis test or the analysis of variance *F* test for metric variables, depending on the assumption of normality. The treatment effectiveness was defined by the ability of

Table 1. Baseline Demographic and Clinical Characteristics of Participants

Characteristic	APZ (n = 21) n (%)	CLZ (n = 84) n (%)	CPZ (n = 61) n (%)	OLZ (n = 34) n (%)	PPZ (n = 21) n (%)	QTP (n = 27) n (%)	RIP (n = 99) n (%)	χ^2	*P*
Demographic									
Male	5 (23.8)	46 (54.8)	26 (42.6)	16 (47.1)	7 (33.3)	6 (22.2)	53 (53.5)	16.83	.01
Married	6 (28.6)	17 (20.2)	25 (41.0)	9 (26.5)	8 (38.1)	5 (18.5)	21 (21.2)	12.13	.06
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*F*	*P*
Age, y	26.2 (6.3)	31.7 (7.4)	32.9 (7.5)	26.4 (6.6)	30.3 (7.8)	28.9 (7.5)	29.7 (8.2)	4.53	< .001
Education, y	12.0 (3.6)	11.5 (5.2)	11.0 (3.5)	12.1 (2.1)	11.5 (2.8)	11.6 (2.8)	11.4 (3.0)	0.40	.88
Duration of illness, mo[a]	8.5 (10.0)	18.5 (13.7)	15.3 (12.5)	10.7 (7.8)	14.7 (14.5)	12.9 (14.8)	11.8 (10.7)	3.78	.001
Clinical									
PANSS positive factor[b]	8.0 (1.7)	8.0 (2.0)	7.2 (1.4)	7.7 (1.0)	7.5 (1.8)	8.3 (1.9)	7.5 (1.6)	2.01	.06
PANSS negative factor[b]	14.2 (2.8)	14.1 (3.5)	13.4 (2.9)	13.6 (1.9)	13.5 (3.2)	14.7 (3.4)	13.2 (2.8)	1.28	.26
PANSS disorganized/ concrete factor[b]	7.6 (1.6)	7.5 (1.9)	7.3 (1.5)	7.2 (1.1)	7.1 (1.7)	7.8 (1.8)	7.0 (1.6)	1.14	.34
PANSS excited factor[b]	8.9 (1.8)	8.9 (2.2)	8.3 (1.6)	8.4 (1.2)	8.4 (1.9)	9.2 (2.2)	8.2 (1.8)	1.67	.12
PANSS depressive factor[b]	5.7 (1.3)	5.7 (1.5)	5.3 (1.1)	5.5 (0.8)	5.5 (1.4)	5.9 (1.4)	5.4 (1.2)	1.61	.15
PANSS total score[b]	44.3 (9.2)	44.3 (11.0)	41.6 (7.9)	42.4 (5.9)	42.1 (9.8)	45.9 (10.6)	41.3 (8.8)	1.38	.22
CGI-S[b]	3.4 (0.5)	3.5 (0.8)	3.2 (0.8)	3.5 (0.8)	3.4 (0.7)	3.5 (0.6)	3.4 (0.7)	1.81	.10
CGI-I[b]	3.3 (0.7)	3.4 (0.7)	3.5 (0.6)	3.3 (0.8)	3.6 (0.8)	3.4 (0.9)	3.5 (0.7)	1.01	.42
PSP[b]	70.4 (11.6)	71.3 (13.5)	69.4 (12.0)	70.2 (13.6)	65.9 (17.7)	66.1 (17.8)	67.8 (13.6)	1.34	.24

[a]Duration of illness prior to admission.
[b]The *P* values were controlled by age, sex, and duration of illness prior to admission, which were included as covariates.
Abbreviations: APZ = aripiprazole, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, CLZ = clozapine, CPZ = chlorpromazine, OLZ = olanzapine, PANSS = Positive and Negative Syndrome Scale, PPZ = perphenazine, PSP = Personal and Social Performance scale, QTP = quetiapine, RIP = risperidone, SD = standard deviation.

the antipsychotic drugs to reduce symptoms and improve general function.[19] The follow-up data were all repeated measures. The time course and treatment differences for the change in PANSS, CGI-I, CGI-S, and PSP scores among the antipsychotic treatments were assessed by means of a mixed-effects model for repeated-measures analyses with effects of treatment, time, and treatment × time interaction, adjusted by age, sex, and duration of illness. The model included treatment and time as fixed effects and subject as a random effect. Comparison of medication adherence (MARS scores) for antipsychotic drugs was performed with analysis of covariance. Variables that possibly affected medication adherence were included as covariates. To test for the effect of antipsychotic medication on remission, a log-linear analysis was performed with 3 categorical variables: treatment, time, and remission. For all models, a 2-sided *P* value of less than .05 was considered statistically significant. Statistical analyses were carried out using SPSS 17.0 (SPSS Inc, Chicago, Illinois).

RESULTS

Patient Disposition

There were 409 patients screened. Three hundred forty-seven patients consented to the study and received baseline assessments. In total, 35 patients prematurely discontinued the study for various reasons, and 312 patients completed the study (Figure 1). According to the medication that patients were taking at baseline, they were divided into 7 groups: aripiprazole (n = 21), clozapine (n = 84), chlorpromazine (n = 61), olanzapine (n = 34), perphenazine (n = 21), quetiapine (n = 27), and risperidone (n = 99).

Demographic and Baseline Clinical Correlates

As shown in Table 1, there were no significant differences in demographic characteristics among the 7 groups with the exception of sex ($P = .01$), age ($P < .001$), and the duration of illness prior to admission ($P = .001$). There were also no significant differences among the groups in baseline severity as measured with the PANSS, CGI-S, CGI-I, or PSP.

Primary Outcome Measures

There was an overall significant interaction of all maintenance treatments with the reduction in psychotic symptoms and global symptom severity (PANSS positive factor: $F_6 = 2.85$, $P = .009$; PANSS negative factor: $F_{6, 1,288} = 3.22$, $P = .004$; PANSS disorganized/concrete factor: $F_{6, 1,288} = 2.95$, $P = .007$; PANSS excited factor: $F_{6, 1,288} = 3.35$, $P = .003$; PANSS depressive factor: $F_{6, 1,288} = 3.27$, $P = .003$; PANSS total score: $F_{6, 1,288} = 3.22$, $P = .004$; CGI-S: $F_{6, 1,288} = 2.16$, $P = .04$; CGI-I: $F_{6, 1,288} = 2.53$, $P = .02$; PSP: $F_{6, 1,288} = 3.13$, $P = .005$). Similarly, there was a significant interaction of time with improvement in symptom severity during all maintenance treatments over the 24-month period (PANSS positive factor: $F_{3, 1,319} = 28.53$, $P < .001$; PANSS negative factor: $F_{3, 1,319} = 27.92$, $P < .001$; PANSS disorganized/concrete factor: $F_{3, 1,319} = 26.14$, $P < .001$; PANSS excited factor: $F_{3, 1,319} = 29.61$, $P < .001$; PANSS depressive factor: $F_{3, 1,319} = 23.14$, $P < .001$; PANSS total score: $F_{3, 1,319} = 28.44$, $P < .001$; CGI-S: $F_{3, 1,319} = 36.22$, $P < .001$; CGI-I: $F_{3, 1,319} = 20.46$, $P < .001$; PSP: $F_{3, 1,319} = 18.75$, $P < .001$). However, there were no significant differences in changes from baseline to each visit in PANSS, CGI, or PSP scores among the different treatment groups (Table 2).

Remission

The results of log-linear analyses are presented in Table 3. The remission rates were generally increased with all maintenance treatments over time. However, there was no significant difference in remission rates among the different treatment groups ($\chi^2_{18} = 2.43$, $P = 1.00$).

Table 2. Outcome Measures of Effectiveness in Each Treatment Group During the 24-Month Follow-Up Period

	Treatment Group, Mean (SD)							Analysis[a]					
								Treatment		Time		Treatment ×Time	
Assessment	APZ (n=21)	CLZ (n=84)	CPZ (n=61)	OLZ (n=34)	PPZ (n=21)	QTP (n=27)	RIP (n=99)	*F*	*P*[b]	*F*	*P*[b]	*F*	*P*[b]
PANSS positive factor[c]								2.85	.009	28.53	<.001	0.97	.49
Baseline	8.0 (1.7)	8.0 (2.0)	7.2 (1.4)	7.7 (1.0)	7.5 (1.8)	8.3 (1.9)	7.5 (1.6)						
6-month	7.3 (1.2)	7.1 (1.1)	7.0 (1.1)	7.7 (1.3)	7.1 (1.5)	7.4 (1.4)	7.0 (1.3)						
12-month	6.9 (0.9)	6.7 (1.0)	6.8 (0.9)	7.1 (0.9)	6.9 (1.2)	6.8 (1.0)	6.7 (1.1)						
24-month	6.9 (1.2)	6.6 (1.0)	6.6 (0.9)	6.8 (1.1)	6.9 (1.2)	6.7 (1.1)	6.6 (1.1)						
PANSS negative factor[c]								3.22	.004	27.92	<.001	0.80	.70
Baseline	14.2 (2.8)	14.1 (3.5)	13.4 (2.9)	13.6 (1.9)	13.5 (3.2)	14.7 (3.4)	13.2 (2.8)						
6-month	13.2 (2.3)	12.7 (2.0)	12.5 (1.6)	13.6 (2.2)	12.7 (2.5)	13.1 (2.3)	12.4 (2.1)						
12-month	12.3 (1.6)	12.1 (1.7)	12.0 (1.4)	12.8 (1.6)	12.3 (2.2)	12.3 (1.8)	11.9 (1.8)						
24-month	12.4 (2.3)	11.8 (1.9)	11.9 (1.9)	12.4 (1.7)	12.0 (2.1)	12.3 (1.8)	11.8 (1.8)						
PANSS disorganized/concrete factor[c]								2.95	.007	26.14	<.001	0.75	.76
Baseline	7.6 (1.6)	7.5 (1.9)	7.3 (1.5)	7.2 (1.1)	7.1 (1.7)	7.8 (1.8)	7.0 (1.6)						
6-month	7.1 (1.3)	6.7 (1.1)	6.5 (0.9)	7.2 (1.4)	6.7 (1.5)	6.9 (1.2)	6.6 (1.3)						
12-month	6.6 (1.0)	6.4 (1.0)	6.2 (0.9)	6.8 (1.0)	6.5 (1.3)	6.5 (1.0)	6.3 (1.1)						
24-month	6.6 (1.4)	6.2 (1.1)	6.2 (0.8)	6.5 (0.9)	6.3 (1.3)	6.4 (1.0)	6.2 (1.1)						
PANSS excited factor[c]								3.35	.003	29.61	<.001	0.98	.48
Baseline	8.9 (1.8)	8.9 (2.2)	8.3 (1.6)	8.4 (1.2)	8.4 (1.9)	9.2 (2.2)	8.2 (1.8)						
6-month	8.2 (1.5)	7.9 (1.3)	7.8 (1.1)	8.5 (1.5)	7.9 (1.6)	8.3 (1.5)	7.7 (1.4)						
12-month	7.7 (1.1)	7.5 (1.1)	7.4 (1.0)	7.9 (1.0)	7.7 (1.4)	7.7 (1.1)	7.4 (1.2)						
24-month	7.6 (1.4)	7.4 (1.2)	7.3 (1.0)	7.7 (1.1)	7.5 (1.5)	7.5 (1.2)	7.4 (1.2)						
PANSS depressive factor[c]								3.27	.003	23.14	<.001	0.73	.79
Baseline	5.7 (1.3)	5.7 (1.5)	5.3 (1.1)	5.5 (0.8)	5.5 (1.4)	5.9 (1.4)	5.4 (1.2)						
6-month	5.4 (1.1)	5.2 (0.9)	5.1 (0.8)	5.5 (1.0)	5.1 (1.1)	5.4 (0.9)	5.0 (0.9)						
12-month	5.1 (0.8)	4.9 (0.8)	4.9 (0.7)	5.2 (0.7)	5.1 (0.9)	5.0 (0.8)	4.8 (0.8)						
24-month	4.9 (1.1)	4.8 (0.8)	4.8 (0.7)	5.1 (0.7)	4.9 (1.0)	4.9 (0.7)	4.8 (0.8)						
PANSS total score[c]								3.22	.004	28.44	<.001	0.85	.64
Baseline	44.3 (9.2)	44.3 (11.0)	41.6 (7.9)	42.4 (5.9)	42.1 (9.8)	45.9 (10.6)	41.3 (8.8)						
6-month	41.2 (7.3)	39.5 (6.3)	38.8 (5.3)	42.5 (7.2)	39.4 (8.0)	41.0 (7.1)	38.8 (6.9)						
12-month	38.4 (5.4)	37.6 (5.3)	37.2 (4.7)	39.7 (5.2)	38.4 (6.9)	38.2 (5.5)	37.1 (5.8)						
24-month	38.4 (7.1)	36.7 (5.9)	36.8 (4.6)	38.7 (5.4)	37.6 (6.9)	37.7 (5.7)	36.6 (5.9)						
CGI-S								2.16	.04	36.22	<.001	0.37	.99
Baseline	3.4 (0.5)	3.5 (0.8)	3.2 (0.8)	3.5 (0.8)	3.4 (0.7)	3.5 (0.6)	3.4 (0.7)						
6-month	3.1 (0.6)	3.1 (0.7)	3.0 (0.5)	3.3 (0.6)	3.1 (0.6)	3.2 (0.9)	3.2 (0.7)						
12-month	2.9 (0.6)	2.9 (0.7)	2.8 (0.5)	3.0 (0.7)	3.0 (0.7)	2.9 (0.8)	3.0 (0.7)						
24-month	2.8 (0.7)	2.9 (0.7)	2.8 (0.5)	2.9 (0.7)	2.9 (0.8)	2.8 (0.7)	2.0 (0.7)						
CGI-I								2.53	.02	20.46	<.001	0.59	.91
Baseline	3.3 (0.7)	3.4 (0.7)	3.5 (0.6)	3.3 (0.8)	3.6 (0.8)	3.4 (0.9)	3.5 (0.7)						
6-month	3.2 (0.7)	3.0 (0.9)	3.3 (0.8)	3.3 (0.8)	3.5 (0.8)	3.2 (1.0)	3.3 (0.8)						
12-month	2.9 (1.0)	2.7 (0.9)	3.0 (1.0)	3.1 (0.9)	3.1 (0.8)	3.0 (1.3)	3.1 (0.9)						
24-month	2.8 (1.0)	2.6 (1.0)	2.9 (1.0)	3.1 (0.9)	3.1 (0.8)	2.9 (1.4)	2.9 (0.9)						
PSP								3.13	.005	18.75	<.001	0.14	1.00
Baseline	70.4 (11.6)	71.3 (13.5)	69.4 (12.0)	70.2 (13.6)	65.9 (17.7)	66.1 (17.8)	67.8 (13.6)						
6-month	73.2 (14.0)	74.6 (12.2)	73.6 (8.0)	72.2 (13.3)	71.9 (10.9)	72.0 (15.1)	71.7 (11.6)						
12-month	76.4 (13.2)	77.7 (9.5)	75.9 (8.7)	75.2 (13.0)	74.5 (11.5)	74.7 (13.5)	75.0 (12.0)						
24-month	76.9 (13.6)	78.2 (10.6)	76.8 (8.8)	75.7 (12.6)	76.4 (10.7)	74.4 (17.4)	76.3 (12.4)						

[a]Mixed-effects models for repeated measures in unstructured variance matrix were used to model the effects of antipsychotic medication classes on PANSS, CGI-S, CGI-I, and PSP scores over 24-month follow-up visit after baseline.
[b]The *P* values were controlled by age, sex, and duration of illness prior to admission, which were included as covariates.
[c]The *df* values for significance of observed treatment (*df*=6, 1,288), time (*df*=3, 1,319), and treatment×time (*df*=18, 1,318) were the same for all PANSS items.
Abbreviations: APZ=aripiprazole, CGI-I=Clinical Global Impressions-Improvement scale, CGI-S=Clinical Global Impressions-Severity of Illness scale, CLZ=clozapine, CPZ=chlorpromazine, OLZ=olanzapine, PANSS=Positive and Negative Syndrome Scale, PPZ=perphenazine, PSP=Personal and Social Performance scale, QTP=quetiapine, RIP=risperidone, SD=standard deviation.

Medication Adherence

The MARS scores with all antipsychotics were higher than 6 (Figure 2). However, there were no significant differences in MARS scores among the 7 groups when sex, age, duration of illness, and education level were included as covariates ($F_{6, 302}=1.35$, $P=.24$).

DISCUSSION

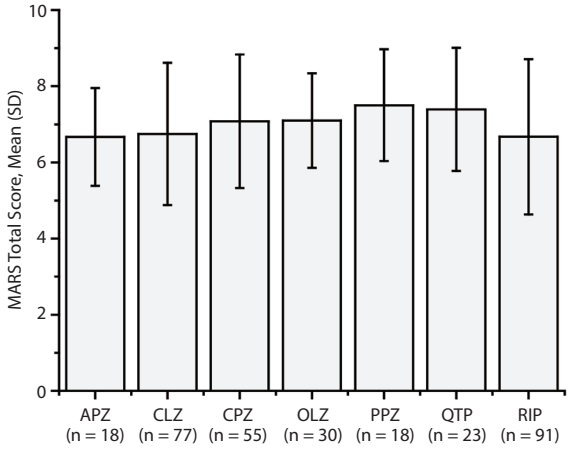
In this prospective antipsychotic monotherapy and long-term treatment study of "real world" patients with schizophrenia, we found that maintenance treatment over 24 months generally improved psychiatric symptoms and social function. However, there were no significant differences among the FGAs (chlorpromazine and perphenazine) and SGAs (clozapine, risperidone, olanzapine, quetiapine, and aripiprazole) in the prevention of psychotic relapse in patients with first-episode schizophrenia. The remission rates of the patients treated with any antipsychotic continued to increase as the follow-up time elapsed. Meanwhile, the adherence to antipsychotics during the 24-month period was high.

Table 3. Log-Linear Analysis of Remission With Each Antipsychotic Medication During the 24-Month Follow-Up Period

	Remission, n (%)				Treatment ×Remission[a]			Time ×Remission[a]			Treatment ×Time[a]		
Treatment	Baseline	6-Month	12-Month	24-Month	χ^2	*df*	*P*	χ^2	*df*	*P*	χ^2	*df*	*P*
APZ (n = 21)	11 (52.4)	15 (71.4)	16 (76.2)	14 (77.8)	27.03	6	<.001	59.80	3	<.001	2.43	18	1.00
CLZ (n = 84)	46 (54.8)	59 (70.2)	67 (79.8)	63 (81.8)									
CPZ (n = 61)	42 (68.9)	51 (85.0)	55 (90.2)	51 (92.7)									
OLZ (n = 34)	16 (47.1)	22 (64.7)	27 (79.4)	25 (83.3)									
PPZ (n = 21)	15 (71.4)	16 (76.2)	18 (85.7)	16 (88.9)									
QTP (n = 27)	15 (55.6)	20 (74.1)	22 (81.5)	19 (82.6)									
RIP (n = 99)	63 (63.6)	77 (77.8)	80 (80.8)	77 (84.6)									

[a]These statistical data reflect comparisons among all treatment groups.
Abbreviations: APZ = aripiprazole, CLZ = clozapine, CPZ = chlorpromazine, OLZ = olanzapine, PPZ = perphenazine, QTP = quetiapine, RIP = risperidone.

Figure 2. Comparison of MARS Scores Among the 7 Treatment Groups at Endpoint



Abbreviations: APZ = aripiprazole, CLZ = clozapine, CPZ = chlorpromazine, MARS = Medication Adherence Rating Scale, OLZ = olanzapine, PPZ = perphenazine, QTP = quetiapine, RIP = risperidone.

The finding of similar effectiveness among all studied antipsychotics in the present study supports the speculation that both FGAs and SGAs are effective in preventing psychotic relapse of schizophrenia in "real-world" populations. This finding is also consistent with the results of a meta-analysis[20] of randomized, head-to-head efficacy studies of SGAs versus FGAs in relapse prevention of schizophrenia. This analysis found that none of the individual SGAs outperformed FGAs (mainly haloperidol) in regard to the study-defined relapse with the exception of isolated, single trial–based superiority. A meta-analysis of randomized, placebo-controlled efficacy studies of antipsychotics versus placebo in relapse prevention of schizophrenia also found that FGAs and SGAs did not differ in relapse risk relative to placebo.[21]

The similar effectiveness among FGAs and SGAs in our study was also consistent with the results of acute effectiveness studies on antipsychotics in schizophrenia. In an effectiveness study of haloperidol versus second-generation antipsychotic drugs (amisulpride, olanzapine, quetiapine, and ziprasidone) in patients with first-episode acute schizophrenia, schizophreniform disorder, or schizoaffective disorder (mean PANSS total scores ranged from 80 to 90 at admission), Kahn and colleagues[22] found that symptom reductions were virtually the same in all groups, although the number of patients who discontinued treatment for any cause within 12 months was significantly higher in the haloperidol group than in the other groups. Similarly, in the CATIE study, the effectiveness of perphenazine was similar to that of quetiapine, risperidone, and ziprasidone.[3]

Compared to previous acute and maintenance efficacy and effectiveness studies of antipsychotics in schizophrenia,[3,20–22] the completion rates and adherence to medications in the present study were very high. During the 24-month period, only 35 (10%) of 347 patients dropped out the study prematurely (Figure 1). The MARS total scores over 6 were considered as a good level of adherence,[23] suggesting that patients in the present study were adherent to their treatments. The high rates of completion and the high levels of adherence to treatments in our study might be attributed to our highly organized treatment teams and the participation of patients' families. Subsequently, the high levels of treatment adherence resulted in continuous improvement in psychotic symptoms and function (Tables 2 and 3).

A recent randomized controlled trial[24] showed that antipsychotic maintenance treatment can lead to a substantially lower rate of relapse in patients with first-episode schizophrenia. There is also strong evidence that maintenance treatment with antipsychotics is essential in preventing relapse in patients with multiple episodes of schizophrenia.[20,21] The selection of an antipsychotic agent has a critical impact on prognosis, complications, and treatment compliance.[1] However, there is no consensus on how to select an antipsychotic for preventing relapse after first-episode psychosis in patients with schizophrenia. Therefore, maintenance treatment strategy for patients with schizophrenia has become a focus of psychopharmacology research.

It is well known that nonadherence to antipsychotic treatment is a key factor for relapse, and adherence to antipsychotics is believed to be the most important factor for optimal benefits from antipsychotic treatment.[25] Nonadherence rates in schizophrenia were high regardless of FGAs or SGAs, but some previous studies have shown that

patients receiving FGAs were more likely to have premature discontinuation due to intolerable side effects[26,27] and were less likely to be adherent than those on treatment with SGAs.[28,29] However, our data suggest that both FGAs and SGAs can be well tolerated during long-term maintenance treatment by patients who do not have acute intolerable side effects through vigorous case management and family participation.[10]

This study has a number of limitations. First, the open-label, nonrandomized design of this study was likely to introduce potential selection bias. Although we used a set of demographic and clinical characteristics for statistical adjustments, the bias cannot be completely eliminated. Second, during the follow-up period, a total of 35 patients dropped out of the study, but we did not collect information about the reasons for dropout and could not determine why they dropped out. This small number of patients might not affect the overall study outcome, but it is possible that potential bias was introduced. Third, the sample sizes were still relatively small, especially in the perphenazine, aripiprazole, and quetiapine treatment groups, which limited the statistical power to detect significant differences among the groups. Fourth, only patients in their first episode who received antipsychotic monotherapy and were stabilized during hospitalization were analyzed. Therefore, the results from this study may not be generalizable to other patients with schizophrenia. Fifth, the patients who participated in this study had completed an acute-phase treatment and were in a stable condition with low total PANSS scores. Therefore, this might result in difficulties in observing differences between drugs. Sixth, we used changes from baseline to the end of 24-month visit as the primary endpoint. Although this duration was longer than most of previous studies, maintenance treatment with a longer time period is required for further study.

CONCLUSIONS

In this 24-month follow-up study of antipsychotics in the prevention of relapse in patients with first-episode schizophrenia in China, we found that the effectiveness of the most frequently prescribed FGAs and SGAs was similar in patients who received treatment in community settings. The similar effectiveness, high completion rates, and high levels of adherence among the studied antipsychotics suggest that a highly organized case management program and family participation are essential to prevent relapse in patients with schizophrenia.

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Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), ziprasidone (Geodon and others).

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