



Efficacy and safety of aripiprazole in Chinese Han schizophrenia subjects: A randomized, double-blind, active parallel-controlled, multicenter clinical trial



Huafang Li^a, Jianfeng Luo^b, Chuanyue Wang^c, Shiping Xie^d, Xiufeng Xu^e, Xiaoping Wang^f, Wenjuan Yu^a, Niufan Gu^a, John M. Kane^{g,*}

^a Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai Key Laboratory of Disorders, Shanghai 200030, China

^b Department of Health Statistics and Social Medicine, School of Public Health, Fudan University, Shanghai 200032, China

^c Beijing Anding Hospital, Beijing 100088, China

^d Nanjing Brain Hospital, Nanjing 210029, China

^e First Affiliated Hospital of Kunming Medical University, Kunming 650032, China

^f Renmin Hospital of Wuhan University, Wuhan 430060, China

^g Zucker Hillside Hospital and The Hofstra North Shore-LIJ School of Medicine, Glen Oaks, NY 11004-1100, USA

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ABSTRACT

Objective: Antipsychotics, such as aripiprazole and risperidone, are often used to treat individuals with schizophrenia. The efficacy as well as safety of aripiprazole in Western populations has been described. The objective of this study is to investigate the efficacy, safety, and tolerability of aripiprazole and risperidone in Chinese Han schizophrenia subjects in mainland China.

Method: The 6-week, double-blind, randomized, parallel study was conducted in 5 medical centers in mainland China from November 2007 to March 2011. A total of 279 subjects with a primary DSM-IV diagnosis of schizophrenia were randomly assigned (with a randomization ratio of 1:1) to aripiprazole ($n = 139$) or risperidone ($n = 140$). Efficacy measurements included the Positive and Negative Syndrome Scale (PANSS) total, positive, negative and general psychopathology subscale scores, and Clinical Global Impressions-Severity of Illness (CGI-S), and Improvement scale scores. Extrapyramidal symptoms (EPS), weight gain, serum prolactin level, QTc interval, and self-reported adverse events were also assessed as measures of safety and tolerability.

Results: Both the aripiprazole and risperidone groups showed statistically significant improvement of PANSS total, positive, negative, general psychopathology subscale scores, and CGI-S scores from baseline to the endpoint (all $p < 0.01$). Significant improvement was noted in the first week for both treatment groups. There were no significant differences in efficacy measurements between the two treatment groups. Mean change of PANSS total scores from baseline to the endpoint was -26.8 ± 18.1 for aripiprazole and -30.0 ± 17.7 for risperidone, ($p = 0.1475$). The responder rate was 71% ($n = 99$) and 76% ($n = 107$) for aripiprazole and risperidone, respectively, ($p = 0.323$). The incidences of EPS were similar in the aripiprazole (25%, $n = 35$) and risperidone groups (24%, $n = 34$), respectively ($p = 0.757$). No clinically meaningful effects on QTc interval, QRS duration, or PR interval were observed in either treatment groups. However, the incidence of clinically significant weight gain ($p = 0.0118$) and hyperprolactinemia ($p < 0.001$) in the aripiprazole group was significantly lower than in the risperidone group.

Conclusion: The study demonstrated that aripiprazole, as well as risperidone, had rapid and persistent efficacy for psychotic symptoms from the first week of therapy. There may be poor efficacy for aripiprazole compared with risperidone for overall improvement, but there were no significant differences in this study. Aripiprazole showed good tolerability with less weight gain and hyperprolactinemia compared with risperidone. The overall efficacy and safety of aripiprazole in Chinese Han schizophrenia subjects were similar to that reported in Western populations.

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1. Introduction

Schizophrenia is a devastating, chronic mental illness that affects approximately 1% of the general population worldwide (Compton et al., 1991). In mainland China, schizophrenia is also a serious public-health

* Corresponding author.

E-mail address: psychiatry@nshs.edu (J.M. Kane).

problem. It is estimated that there are more than 4 million people in mainland China with schizophrenia on the basis of the adjusted point prevalence of 4.70 per 1000 aged 15 years or older, according to the national psychiatric epidemiology study in 1993 (Zhang et al., 1998).

Antipsychotic medications are often prescribed in the treatment of schizophrenias. All currently available antipsychotics exert their therapeutic efforts mainly through dopamine D2 receptor antagonism in the brain. The blockade of dopamine receptors is thought to be associated with improving not only the psychotic symptoms, but also the unwanted adverse effects. The pathophysiology of schizophrenia is proposed to be associated with dysfunctional regulation of dopaminergic neurotransmission in the brain. Namely, too much dopamine activity is in some regions but too little in others (Potkin et al., 2003).

Dopamine receptor partial agonism has been proposed as a more rational strategy for antipsychotic therapy. The mechanism of action of partial dopamine agonists is different from other antipsychotics, allowing them to act either as functional agonists or antagonists to counterbalance abnormalities in the dopamine transmission at different endogenous levels (Hirose et al., 2004; Lieberman, 2004).

Aripiprazole is the first drug with dopamine partial agonist activity approved by the U.S. Food and Drug Administration. It has only about 30% intrinsic agonist activity compared with that of endogenous dopamine (Preskorn, 2009). In the preclinical animal studies, it was shown that aripiprazole displayed D2 receptor antagonism effects in hyperdopaminergia and D2 agonist activity in hypodopaminergia (Kikuchi et al., 1995). In addition to its D2 activity, aripiprazole is a partial agonist at 5-HT_{1A} receptors and an antagonist at 5-HT_{2A} receptors (McEvoy et al., 2007). Aripiprazole has been shown to be effective in the treatment of positive and negative symptoms in the acute and long-term treatment of schizophrenia or schizoaffective disorder in adults at doses of 10 to 30 mg/day (Pigott et al., 2003; Potkin et al., 2003; Chan et al., 2007; McEvoy et al., 2007). The therapeutic effect is associated with minimal potential for extrapyramidal symptoms (EPS), weight gain, hyperprolactinemia, sedation and QTc prolongation (McQuade et al., 2004; Chrzanowski et al., 2006). However in different age groups such as children and adolescents, the weight gain caused by aripiprazole may be obvious (Christoph U. Correll et al., 2009), so we should pay attention to the potential weight gain problem, especially to that of patients initially being exposed to this medication.

In order to evaluate the efficacy and safety profile of aripiprazole in the Chinese population, the current described study was designed to evaluate the efficacy, safety, and tolerability of aripiprazole in Han subjects with schizophrenia in mainland China. Risperidone, a widely available atypical antipsychotic, was used as the active control in this study.

2. Materials and methods

The study protocol was reviewed by all appropriate governing ethical committees and was performed under the ethical principles laid down by Good Clinical Practice and the Declaration of Helsinki. After receiving a complete description of the study, all subjects and/or their authorized legal representatives provided written informed consent.

3. Subjects

Male and nonpregnant, nonlactating female subjects 18 to 65 years of age with a DSM-IV diagnosis of schizophrenia, were eligible for the study. Subjects were required to have a total Positive and Negative Syndrome Scale (PANSS) score between 60 and 120 (inclusive) at screening and baseline.

Major exclusion criteria were: current DSM-IV axis I psychiatric diagnosis other than schizophrenia; significant risk of suicidal or violent behavior; history of mental retardation, major depressive episodes, neuroleptic malignant syndrome, tardive dyskinesia, any neurologic disorder, severe head trauma, or any unstable medical condition; history of substance dependence or participation in a drug clinical trial within

3 months before screening; standard treatment with aripiprazole or risperidone within 4 weeks before screening; allergy, hypersensitivity, or history of lack of response to aripiprazole or risperidone; prohibited medications including mood stabilizers, antidepressants, and other psychotropics, within 2 weeks, or drug depot preparation within 4 weeks, or clozapine within 3 months before screening; refractory schizophrenia (treatment resistance to antipsychotics according to prior trials of two different antipsychotics of adequate dose and duration); or clinically significant abnormal vital signs or laboratory values.

Other exclusion criteria included uncontrolled major medical illnesses, ischemic heart disease, history of myocardial infarction, coronary bypass surgery, coronary angioplasty, or clinically relevant electrocardiographic (ECG) abnormalities, or current treatment with any disallowed medications or continuous anticholinergic therapy for EPS.

Subjects were permitted to participate in this study on an outpatient, partial hospitalization, or full inpatient basis at any given time of the study.

4. Study design

The 6-week multicenter, randomized, double-blind, double-dummy, parallel-group clinical study was designed to assess the efficacy, safety, and tolerability of aripiprazole in subjects with schizophrenia. The study was conducted at 5 sites in China from November 2007 to March 2011. Risperidone, a widely available atypical antipsychotic, was used as the active control in this study to measure the study group's response to treatment.

The enrolled subjects were tapered off their current antipsychotic medication 12 h prior to randomization. Subjects were randomly assigned in a double-blind manner to either aripiprazole or risperidone with a double-dummy design. Allocation numbers were assigned sequentially in ascending order. Study drugs were administered orally, once daily (QD), after the evening meal. Aripiprazole was initiated at 10 mg/day, and could be titrated to 30 mg/day during the first two weeks. The dosage was 10–30 mg/day from the third week and at that dose throughout the remainder of the study. Risperidone was started at 1 mg/day, with planned increases to 2 or 3 mg/day on day 3 or 4 and to a maximum of 6 mg/day at the end of week 2. A dosage between 2 and 6 mg/day was maintained from the third week until the end of the study.

Measurements of psychiatric efficacy, safety, and tolerability were performed at screening, baseline, and the end of weeks 1, 2, 4, and 6.

5. Efficacy assessments

Treatment efficacy was assessed with the PANSS and Clinical Global Impressions (CGI) Scale.

The primary efficacy measurement was the change of PANSS total score from baseline to the endpoint. The secondary efficacy measurement included change of total PANSS score from baseline to weeks 1, 2 and 4. The secondary measures also included the mean change of the PANSS positive, negative, general psychopathology subscale scores, CGI-S score from baseline to the endpoint, and the number and the percentage of responders (subjects with at least a 30% decrease of PANSS total score at end point compared with baseline).

6. Safety and tolerability assessments

Adverse events (AEs) were monitored from baseline to the end of the study at every visit. Extrapyramidal symptoms were monitored at each scheduled visit by the Simpson–Angus Scale for Parkinsonism and Barnes Rating Scale for akathisia. Fasting clinical laboratory testing (including hematology, serum chemistry, prolactin levels and urinalysis), body weight, vital sign, electrocardiograms, and physical examination were also assessed at screening and end of the study.

7. Concomitant medication

The use of psychotropic drugs other than those prescribed by the study protocol was prohibited during the study, with the exception of lorazepam, up to 4 mg/day, for agitation (anxiolytic) or sedative purposes. Anticholinergic treatment was allowed for EPS during the treatment with the maximum dose equivalent to 6 mg/day of benztropine, if necessary, at any time during the study. Treatment with lorazepam within 4 h or anticholinergic agents within 12 h before efficacy ratings or administration of movement scales was prohibited. Furthermore, prophylactic treatment with anticholinergic drugs was not permitted.

8. Statistical analyses

The safety analysis set (SS) consisted of all randomized subjects who received at least one dose of study medication. The full analysis set (FAS) included the subjects who received at least one dose of study medication and had at least one post-baseline measure of the primary efficacy parameter (PANSS total score). The last-observation-carried-forward (LOCF) method was used to estimate the missing data. The per-protocol (PP) population included subjects in the intention-to-treat population who had no major protocol violations or deviations, had no prohibitory medication, had good compliance (compliance within 80%–120% according to the pill counts), and had filled in a Case Report Form (CRF).

The primary endpoint was the reduction of the PANSS total score from the baseline to the end of the treatment (end of week 6). Continuous efficacy data (e.g., change from baseline) were analyzed by analysis of covariance (ANCOVA), with treatment and center as fixed factors and baseline total PANSS score as covariate. Categorical efficacy data (e.g., CGI-I score) were analyzed using the Cochran–Mantel–Haenszel (CMH) chi-square test with pooled center as strata, when appropriate, or Fisher's exact test. The least-squares means derived from this model were used for comparing risperidone with aripiprazole treatment. The tests were two-sided and evaluated at the 0.05 significance level.

9. Results

9.1. Subject characteristics and disposition

A total of 279 subjects were eligible and randomized to 2 treatment groups for 6 weeks with aripiprazole ($n = 139$) or risperidone

($n = 140$) (Fig. 1). Baseline demographic and clinical characteristics were similar between two treatment groups (Table 1).

Among the 279 subjects, 238 (85%) completed the 6-week study. Forty one subjects (15%) withdrew from the trial, 24 in the aripiprazole group, and 17 in the risperidone group (nonsignificant difference between two groups, $p = 0.2269$). Seventeen (6% of total) subjects withdrew for lack of efficacy, nine (3%) withdrew their consents, two (1%) withdrew for noncompliance, seven (3%) was lost to follow-up, and five (2%) withdrew for other reasons (Table 2).

All the 279 enrolled subjects were included in both efficacy and safety analyses.

9.2. Efficacy

9.2.1. Primary efficacy

Through the course of the 6-week study, the psychotic symptoms of subjects were reduced and the primary parameters were significantly improved compared with baseline (all p values < 0.01) in both the aripiprazole and risperidone treatment groups (Fig. 2A). Rapid onset of efficacy with statistically significant improvement as early as week 1 (p values < 0.01 against baseline) (Fig. 2A) was observed. There were no significant differences in the change of PANSS total scores between the aripiprazole and risperidone groups throughout the scheduled visits after randomization (Fig. 2A).

PANSS total scores decreased by 26.8 (SD 18.1) points for aripiprazole and by 30.0 (SD 17.7) points for risperidone from baseline to the end of the study with FAS data. The difference was -3.11 points (95% CI -7.34 to 1.11). There was no statistically significant difference ($p = 0.1475$) between the two treated groups (Table 3; Fig. 2A).

In analysis restricted to the PP population, the change of PANSS total scores between baseline and the end of week 6 was 29.6 (SD 16.1) points for aripiprazole ($n = 113$) and 33.6 (SD 15.5) points for risperidone ($n = 119$). The difference was -3.98 points (95% CI -8.06 to 0.11). There was no statistically significant difference ($p = 0.0566$) between the two treatment groups. Results from PP were consistent with FAS analysis.

9.2.2. Secondary efficacy

All secondary efficacy parameters were significantly improved at the end of week 6 compared with baseline (all p values < 0.01); however, no significant differences in PANSS positive or negative or general

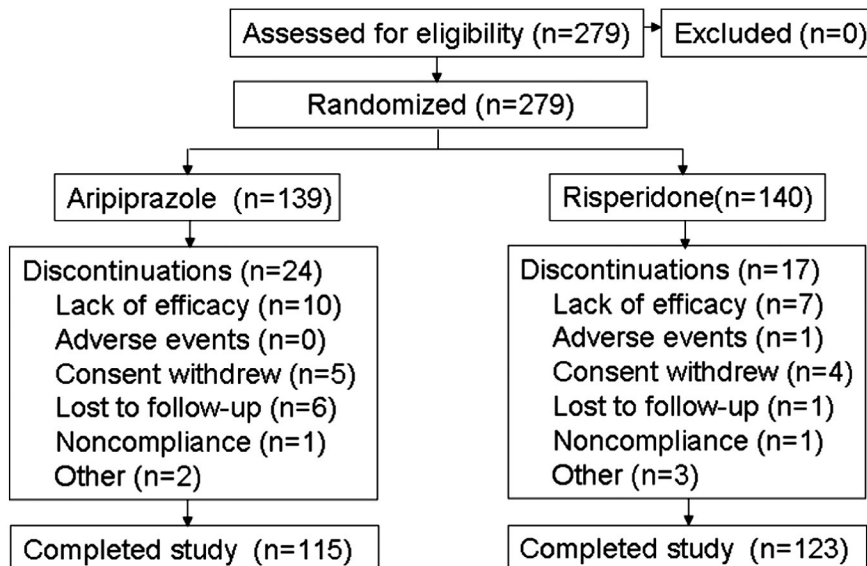


Fig. 1. Summary of subject flow in the randomized clinical trial.

Table 1
The subject characteristics of the two group at baseline.

	Aripiprazole	Risperidone	p value
Total number of subjects	139	140	
Gender			
Male	68	77	0.3095
Female	71	63	
Age (years)	33.6 (10.8)	31.3 (10.6)	0.0707
Height (cm)	165.5 (7.6)	165.8 (7.3)	0.7205
Weight (kg)	60.8 (10.9)	61.2 (11.4)	0.7763
BMI (kg/m ²)	22.1 (3.2)	22.1 (3.4)	0.984
PANSS			
Total	87.7 (12.9)	86.5 (13.7)	0.4582
Positive	23.3 (5.4)	23.5 (6.3)	0.778
Negative	21.3 (7.1)	20.2 (7.0)	0.2086
General psychopathology	43.2 (7.6)	42.8 (7.7)	0.7253
CGI-S	5.3 (0.7)	5.2 (0.9)	0.2525
Disease duration (yr)	8.0 (7.0)	6.5 (6.9)	0.0711

Descriptive data were expressed as mean ± SD (Standard Deviation).

psychopathology subscale score between the aripiprazole group and risperidone group were found from week 1 to the end of the study (Fig. 2B–D). At the study endpoint, there were no significant differences between the aripiprazole and risperidone groups in change on the PANSS positive score (9.9 ± 6.9 vs 10.9 ± 7.0; *p* = 0.1441), negative score (5.2 ± 5.6 vs 5.5 ± 5.6; *p* = 0.3191), or general psychopathology subscale score (12.5 ± 9.2 vs 14.0 ± 8.9; *p* = 0.1816) (Table 3; Fig. 2B–D).

At the end of the treatment, the secondary efficacy results of CGI-S score (for FAS, aripiprazole vs risperidone, CMH value = 9.71; *p* = 0.0839) and CGI-I score (for FAS, aripiprazole vs risperidone, CMH value = 9.69, *p* = 0.0459) are shown in Tables 4 and 5. There was a statistically significant difference in the CGI-I score between the two groups (risperidone was superior to aripiprazole).

According to the response criteria of more than 30% reduction of PANSS total score at the end of the study, the responder rates were 71% (*n* = 99) and 76% (*n* = 107) in the aripiprazole group and risperidone group, respectively, with no significant difference between them (*p* = 0.323). The reduction rate of PANSS was not statistically significant between the two groups (*p* = 0.095) (Table 6).

9.3. Safety

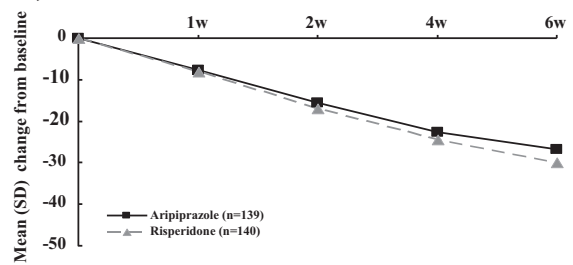
9.3.1. Adverse events

A total of 279 treated subjects were included in the safety evaluation (aripiprazole: *n* = 139; risperidone: *n* = 140). One hundred and five subjects (76%) in the aripiprazole group and 116 subjects (83%) in the risperidone group experienced at least one treatment-emergent adverse event (TEAE). The incidence of TEAEs was similar in the aripiprazole and risperidone treatment groups. The majority of TEAEs were transient and considered to be mild to moderate in severity, and no serious adverse events occurred in either group. No subject discontinued due to adverse events in the aripiprazole group, and only

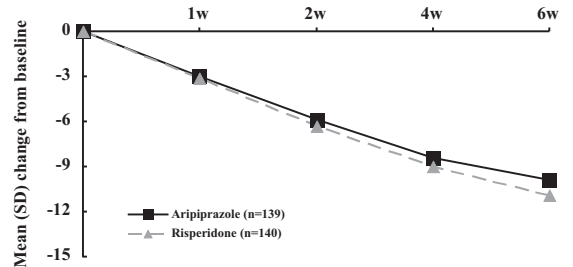
Table 2
Discontinuation in the two groups.

	Aripiprazole	Risperidone
Total number of subjects, <i>n</i>	139	140
Completed the study, <i>n</i> (%)	115 (83)	123 (88)
Withdrew from the study, <i>n</i> (%)	24 (17)	17 (12)
Reason for withdrawal, <i>n</i> (%)		
Lack of efficacy	10 (7)	7 (5)
Adverse events	0 (0)	1 (1)
Consent withdraw	5 (4)	4 (3)
Lost to follow-up	6 (4)	1 (1)
Noncompliance	1 (1)	1 (1)
Other	2 (1)	3 (2)

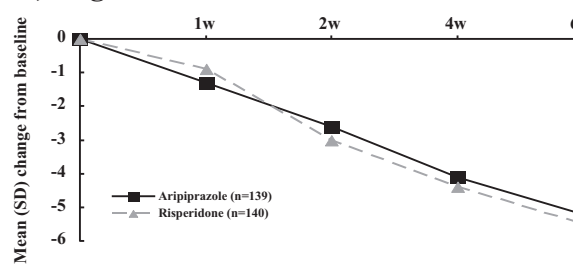
A) Total score



B) Positive score



C) Negative score



D) General psychopathology score

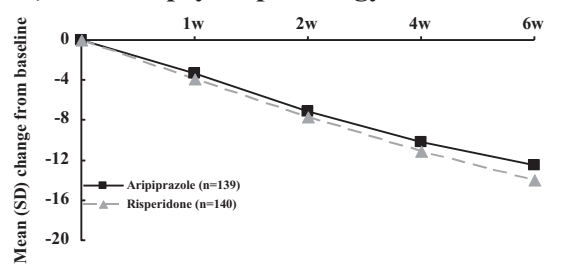


Fig. 2. Mean change from baseline in Positive and Negative Syndrome Scale (PANSS) score over 6 weeks of the treatment with aripiprazole and risperidone. A: Total score; B: Positive score; C: Negative score; D: General psychopathology score. The data were expressed as mean ± SD (Standard Deviation). All *p* > 0.05 between the two groups over 6 weeks.

one subject (1%) discontinued in the risperidone group (Fig. 1). There was no significant withdrawal difference between the two groups.

The common TEAEs that occurred at an incidence of 5% or higher in the two groups are listed in Table 7. The most common TEAEs (>10%) were insomnia (26%), extrapyramidal syndrome (25%), akathisia (23%), and constipation (14%) in the aripiprazole group. In the risperidone group, hyperprolactinemia and upper respiratory infection were most frequently observed in addition to the events mentioned above. The incidences of hyperprolactinemia and upper respiratory infection appeared to be consistently lower in the aripiprazole group than those in the risperidone group. The incidences of these events were 4% and 9% in the aripiprazole group, and 21% and 19% in the risperidone group, respectively. The differences were significant (*p* < 0.01).

Table 3
PANSS total and subscale scores of the two groups.

	Aripiprazole (n = 139)		Risperidone (n = 140)		p value
	Mean	SD	Mean	SD	
PANSS					
Total score					
At week 6	60.1	17.3	56.1	19.3	0.0739
Change	−26.8	18.1	−30.0	17.7	0.1475
Positive subscale score					
At week 6	13.3	5.0	12.5	5.8	0.2231
Change	−9.9	6.9	−10.9	7.0	0.1441
Negative subscale score					
At week 6	16.1	6.8	14.7	6.3	0.0779
Change	−5.2	5.6	−5.5	5.6	0.3191
General psychopathology score					
At week 6	30.6	8.3	28.9	9.6	0.1006
Change	−12.5	9.2	−14.0	8.9	0.1816

Abbreviations: PANSS = Positive and Negative Syndrome Scale.

9.3.2. Extrapyramidal symptoms

The incidence of EPS was similar ($p = 0.757$) for the aripiprazole group ($n = 35, 25\%$) and the risperidone group ($n = 34, 24\%$).

Extrapyramidal symptoms were monitored at each scheduled visit by means of the Simpson–Angus Scale and the Barnes Rating Scale. The results showed that the mean changes of Simpson–Angus scores from baseline were 0.4 ± 0.1 and 0.4 ± 0.2 in the aripiprazole and risperidone groups, respectively (Fig. 3). The mean changes of Barnes Rating Scale scores were 0.8 ± 1.2 and 0.4 ± 1.0 , respectively (Fig. 3). There were no statistically significant differences in either the Simpson–Angus scores or Barnes Rating Scale scores mean changes. Akathisia occurred in 32 subjects (23%) in the aripiprazole group and 31 subjects (22%) in the risperidone group. There were no significant differences in the incidence of akathisia between the two groups ($p = 0.753$). In addition, for the mean changes of both scores, no significant differences between the aripiprazole group and risperidone group were found from week 1 to the end of the study (Fig. 3).

9.4. Body weight

A slight degree of weight gain was observed during the study with a mean of 0.8 ± 2.3 kg for aripiprazole and 1.6 ± 3.8 kg for risperidone. The difference was statistically significant ($p = 0.0406$) between groups. Clinically relevant weight increase, defined as an increase of $\geq 7\%$ in body weight, was experienced by 3% of aripiprazole subjects and 12% of risperidone subjects. The difference was significant between the two groups ($p = 0.0118$).

Table 4
Score of CGI-S at the end of treatment.

		Aripiprazole	Risperidone	Statistics	p value
FAS	Normal	7 (5.0%)	10 (7.1%)	CMH = 9.71	0.0839
	Borderline mentally ill	19 (13.7%)	35 (25.0%)		
	Mildly ill	40 (28.8%)	40 (28.6%)		
	Moderately ill	37 (26.6%)	34 (24.3%)		
	Markedly ill	30 (21.6%)	16 (11.4%)		
	Severely ill	6 (4.3%)	5 (3.6%)		
	Extremely ill	0	0		
PP	Normal	6 (5.3%)	10 (8.4%)	CMH = 8.55	0.1283
	Borderline mentally ill	19 (16.8%)	33 (27.7%)		
	Mildly ill	36 (31.9%)	37 (31.1%)		
	Moderately ill	32 (28.3%)	28 (23.5%)		
	Markedly ill	18 (15.9%)	11 (9.2%)		
	Severely ill	2 (1.8%)	0		
	Extremely ill	0	0		

Abbreviations: CGI-S = Clinical Global Impression-Severity of Illness; CMH = Cochran–Mantel–Haenszel.

Table 5
Score of CGI-I at the end of treatment.

		Aripiprazole	Risperidone	Statistics	p value
FAS	Very much improved	25 (18.0%)	44 (31.9%)	CMH = 9.69	0.0459
	Much improved	55 (39.6%)	50 (36.2%)		
	Minimally improved	37 (26.6%)	29 (21.0%)		
	No change	19 (13.7%)	10 (7.2%)		
	Minimally worse	3 (2.2%)	5 (3.6%)		
	Much worse	0	0		
	Very much worse	0	0		
PP	Very much improved	24 (21.2%)	42 (35.3%)	CMH = 10.	0.0351
	Much improved	46 (40.7%)	47 (39.5%)		
	Minimally improved	29 (25.7%)	21 (17.6%)		
	No change	14 (12.4%)	7 (5.9%)		
	Minimally worse	0	2 (1.7%)		
	Much worse	0	0		
	Very much worse	0	0		

Abbreviations: CGI-I = Clinical Global Impression-Global Improvement; CMH = Cochran–Mantel–Haenszel.

9.5. Vital signs and ECG

There was no clinically relevant change of heart rate or blood pressure during the course of the study for the two groups. ECG measurements included QTc interval, QRS duration, and PR interval. The QTc interval was calculated using Bazett's formula ($QTcB = QT / RR^{1/2}$). At the last visit, the mean changes of QTc intervals were -11.0 ms ($SD = 33.4$) for aripiprazole and -3.5 ms ($SD = 38.1$) for risperidone (Fig. 4). Clinical significance was operationally defined as a QTc of 450 ms or more and a 10% or greater increase from baseline. No subjects experienced a potentially clinically significant increase in QTc intervals. Furthermore, no trends were observed for any potentially clinically significant changes in QRS duration and PR interval.

9.6. Concomitant medications

The incidences of concomitant medication were 115 (83%) and 110 (79%) in the aripiprazole group and risperidone group, respectively. The difference was not significant ($p = 0.3789$). The rate of sedative use was similar in the two treatment groups (aripiprazole, 56%; risperidone, 55%; $p > 0.05$). In addition, the use of concomitant anticholinergic medication was similar in the two treatment groups (aripiprazole, 50%; risperidone, 50%; $p > 0.05$).

10. Discussion

Baseline demographic and clinical characteristics of the two treatment groups were similar, but the aripiprazole subjects were about 2 years older ($p = 0.0707$), and the duration of suffering from psychiatric disorder is 1.5 years longer ($p = 0.0711$); these differences between the two groups were close to the significant level. Age of onset is almost the same in both groups, so the older patients may also have a longer course of disease to some degree, that's to say, the age of the patient is consistent with the years of illness in our study. Therefore, older age and longer course of disease both indicated poor effect. Age and disease duration both would affect the efficacy of assessments about aripiprazole. This supports the result of this study that the efficacy

Table 6
Distribution of PANSS reduction rate in the two groups at endpoint.

Reduction criterion	Aripiprazole (n = 139)	Risperidone (n = 140)	p value
$\geq 80\%$, n (%)	21 (15)	34 (24)	0.095
$\geq 50\%$ and $< 80\%$, n (%)	46 (33)	52 (37)	
$\geq 30\%$ and $< 50\%$, n (%)	32 (23)	21 (15)	
$< 30\%$, n (%)	40 (29)	33 (24)	

The reduction from baseline in total PANSS score.

Table 7

Incidence of treatment-emergent adverse events occurring in $\geq 5\%$ of subjects in both treatment groups (safety sample).

Adverse event, n (%)	Aripiprazole (n = 139)	Risperidone (n = 140)	p value
Any adverse event	105 (76)	116 (83)	0.1321
Nervous system	90 (65)	86 (61)	0.566
Insomnia	36 (26)	33 (24)	0.652
Extrapyramidal syndrome	35 (25)	34 (24)	0.757
Akathisia	32 (23)	31 (22)	0.753
Tremor	7 (5)	3 (2)	0.194
Hypertonia	3 (2)	8 (6)	0.127
Digestive system	29 (21)	31 (22)	0.795
Constipation	20 (14)	20 (14)	0.981
Endocrine system	5 (4)	31 (22)	<0.001
Hyperprolactinemia	5 (4)	30 (21)	<0.001
Respiratory system	13 (9)	29 (21)	0.008
Upper respiratory infection	12 (9)	27 (19)	0.01
Cardiovascular system	11 (8)	9 (6)	0.631
Other	6 (4)	8 (6)	0.593
Asthenia	3 (2)	7 (5)	0.498
Abnormal liver function	5 (4)	8 (6)	0.402

measurement improved poorly by the numerical value of the aripiprazole group.

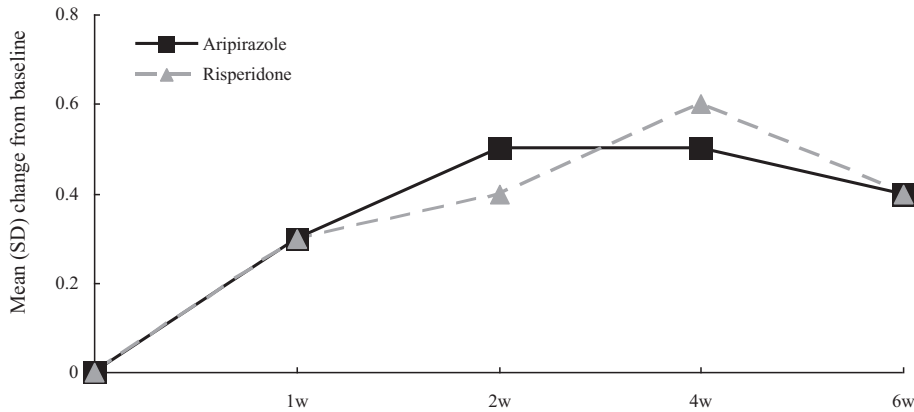
This study was a randomized, double-blind, and active controlled clinical trial to evaluate the efficacy, safety, and tolerability of aripiprazole in Han subjects with schizophrenia in Mainland China. Overall, aripiprazole at doses of 10 to 30 mg/day was an effective, safe,

and well-tolerated treatment for Chinese Han subjects with schizophrenia. Aripiprazole produced statistically significant improvements according to PANSS total scores (the primary efficacy measure) at last assessment, as well as other efficacy scales (i.e., the PANSS positive, negative, and general psychopathology subscale scores, CGI-S score and CGI-I score) compared with those at baseline. Aripiprazole (10–30 mg/day) showed comparable efficacy to risperidone (2–6 mg/day) in the treatment of schizophrenia.

Rapid onset of efficacy was found in both treatment groups, and statistically significant improvements were produced as early as week 1 (the PANSS positive, negative, and general psychopathology subscale scores, CGI-S score and CGI-I score). These significant improvements were sustained throughout the 6-week study.

However, the difference in change of the PANSS total in the PP population was 3.98 points ($p = 0.0566$). This is close to significant. Other comparisons showed weaker but consistent trends in favor of risperidone on efficacy. For example, CGI were near significant. In the FAS sample, 18.7% of patients were normal or borderline ill on aripiprazole at endpoint compared with 32.1% on risperidone. 21.6% of aripiprazole patients were still markedly ill at the end of the study, vs. only 11.4% on risperidone. These seem numerically important though p was 0.0839. In the PP sample, 21.2% were very much improved on aripiprazole vs 35.3% on risperidone, and this time $p = 0.0351$. These data implicated that there may be better efficacy with risperidone over aripiprazole for overall improvement. However, a recent meta-analysis article found that there were no significant differences on global state ($n = 6381$, 80 RCTs, low quality evidence) between aripiprazole and risperidone

A) Simpson-Angus scores



B) Barnes Rating Scale scores

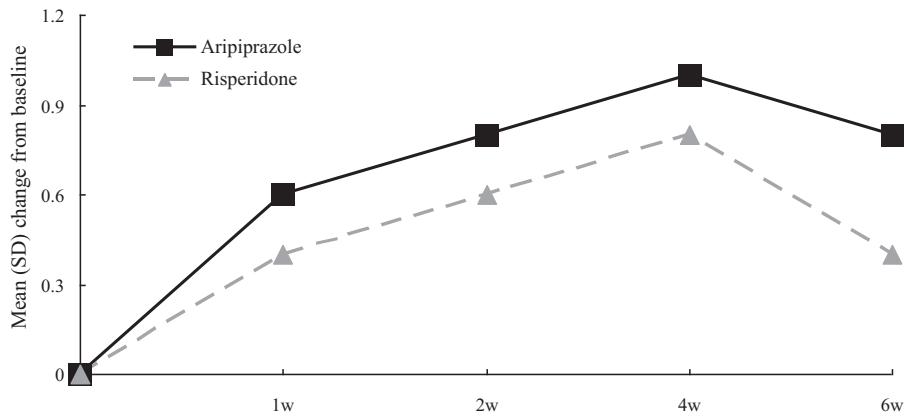


Fig. 3. Mean change from baseline of Simpson–Angus scores and Barnes Rating Scale scores over 6 weeks of the treatment with aripiprazole and risperidone. A: Simpson–Angus scores; B: Barnes Rating Scale scores. The data were expressed as mean \pm SD (Standard Deviation). No statistically significant differences were found between the two groups over 6 weeks. $p > 0.05$.

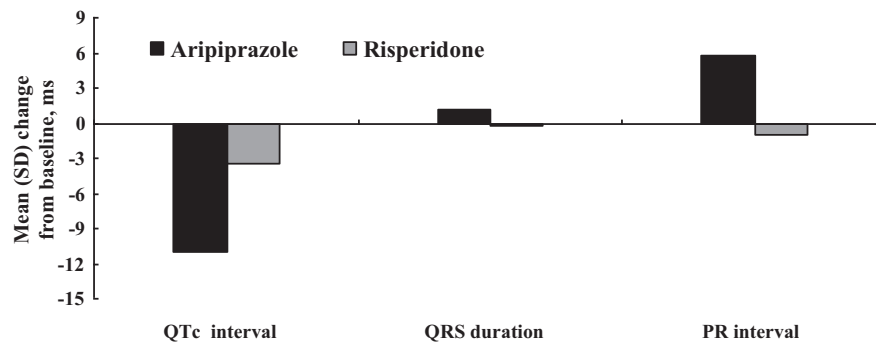


Fig. 4. Mean change of ECG parameters from baseline to last assessment. No statistically significant differences were found between the two groups over 6 weeks. $p > 0.05$.

(Khanna et al., 2014). So it is necessary to design a further study with a larger sample to demonstrate the conclusion.

The data in our study were similar to the findings from previously reported 6-week double-blind multicenter trials. McEvoy JP, Findling RL, and Kane JM have described the short-term efficacy of aripiprazole of 10 to 20 mg/day for adult subjects (McEvoy et al., 2007) and 10 mg/day and 30 mg/day for adolescents (Findling et al., 2008), and similar improvements to perphenazine were seen in treatment-resistant subjects who have failed to respond to olanzapine or risperidone (Kane et al., 2007). The efficacy of aripiprazole in this study was also consistent with the study reported by Chan et al. (2007). In that study, the efficacy and safety of 15 mg/day aripiprazole in Taiwanese subjects with an acute relapse of schizophrenia were investigated for 4 weeks. Our study further provided evidence that aripiprazole, a dopamine-serotonin system stabilizer, could induce clinically meaningful and sustained improvements in the symptoms of schizophrenia in Chinese subjects. The persistent effects of aripiprazole differs from other agents with dopamine D_2 partial agonist characteristics such as preclamol, which clinical utility had been limited due to the deficiency of sustained activity (Lahti et al., 1998). It has been suggested that one of the reasons might be the differences in the intrinsic activity of each agent at the D_2 receptors (Burriss et al., 2002).

The rates of discontinuation in both groups were very low and only one subject withdrew due to adverse events in our study. The result was similar to that of Findling's study (Findling et al., 2008), in which one subject in the aripiprazole group withdrew because of dystonia. However, the discontinuation rates were lower in this study than in the trials reported by Potkin SG et al. (2003) and Chan et al. (2007). In Chan's study, the discontinuation might be related to the treatment shift from another antipsychotic (Chan et al., 2007). If the subjects are treated by shifting from stronger D_2 antagonists to D_2 partial agonist, adverse effects related to dopamine receptors can occur. Other researchers have described the cases when this happens and proposed that it might be attributed to the impact of the partial dopamine agonist effect in patients with effects from up-regulated DA receptors in their previous treatment (Raja, 2007; Tadokoro et al., 2012). We don't know what medications patients received before aripiprazole and whether the patients previously on strong D_2 antagonists did not fare as well in terms of efficacy or side effects. The randomized double-blind design assured that patients be assigned to two groups impartially and that the exclusion criteria restricted some antipsychotics patients received before. These could relieve the influence of prior medication to some extent. In addition, the theory about patients previously on strong D_2 antagonists is in agreement with this study's results that risperidone tended to have more efficacy.

Extrapyramidal side effects which have the potential to limit antipsychotic effectiveness are common in subjects receiving typical rather than atypical antipsychotics. In our study, the incidence of EPS-related AEs was similar for the two groups, and akathisia did not occur more frequently in the aripiprazole group. The EPS rate in this study was

close to that reported by Findling et al. (2008), and the incidence of akathisia was consistent with the data reported by Potkin et al. (2003). However, when compared with Chan's study, the percentage in the aripiprazole group was somewhat higher (Chan et al., 2007). This difference might not be clinically meaningful because both the aripiprazole dose and the sample size were different in the trials.

Weight gain associated with some antipsychotics could lead to an increase in the risk of cardiovascular disease and diabetes mellitus and to a decrease in compliance after long-term use (Kasper et al., 2003). In this 6-week study, both aripiprazole and risperidone treatments induced mild weight gain. However, aripiprazole was associated with significantly less change in weight and incidence of clinically significant weight gain when compared with risperidone. The results of this study are consistent with previous trials that have indicated a low risk of weight gain induced by aripiprazole in both short-term (Potkin et al., 2003; Chan et al., 2007) and long-term (Allison and Casey, 2001; Chrzanowski et al., 2006) studies. However, this study was only 6 weeks in duration. The long-term effects of aripiprazole on body weight in a Chinese population are unclear.

Hyperprolactinemia also has long been associated with antipsychotic treatment, and may induce symptoms such as anovulation, amenorrhea, decreased libido, orgasmic dysfunction, breast engorgement, galactorrhea, and hypoestrogenism/androgenism (Correll and Carlson, 2006). A lower rate of clinically significant elevations of serum prolactin levels was observed in the aripiprazole group throughout the trial compared with the risperidone group. This is consistent with the results reported in previous studies of schizophrenia (Inoue et al., 1996; Potkin et al., 2003; Chan et al., 2007). Because dopamine inhibits prolactin release, the low incidence of hyperprolactinemia with aripiprazole treatment would likely be due to the partial agonism at the D_2 receptor.

Prolongation of the QTc interval can be induced by some antipsychotics and raises a concern regarding torsade de pointes, a severe cardiac arrhythmia (Witchel et al., 2003). The impacts of aripiprazole treatment on ECG parameters, such as QTc intervals, were examined. There were no subjects with clinically significant prolongation of QTc interval in either the aripiprazole or risperidone group. Furthermore, aripiprazole treatment had no clinically significant effects on other ECG parameters such as QRS duration and PR interval. This suggests that aripiprazole has a low liability for arrhythmic potential in a Chinese population, similar to the observations in both short-term (Potkin et al., 2003; Chan et al., 2007) and long-term (Allison and Casey, 2001; Correll and Carlson, 2006) studies in non-Chinese populations. In addition, Aripiprazole dropped QTc more than risperidone. This is consistent with other comparisons of aripiprazole and risperidone (Chung and Chua, 2011).

The current study had some limitations. First of all, the study did not include a placebo control group because of ethical concerns. Potential placebo effects in a Chinese Han population or how efficacious aripiprazole and risperidone are compared with placebo is not clear. Secondly, the treatment duration (6 weeks) was short, and some

adverse events might not occur within that timeframe. It is known that some antipsychotics are associated with increased propensity for metabolic syndrome after long-term use. However, our study was a well-designed randomized controlled trial in the Chinese Han population, and the results could be a helpful reference for the treatment of schizophrenia in China.

Doses of aripiprazole and risperidone were flexible in this study by drug instruction. At the end of the second week, aripiprazole was titrated to 10–30 mg/day, and risperidone was titrated to 2–6 mg/day. In this study, the mean dose of aripiprazole was 23 ± 5 mg/day, and the mean dose of risperidone was 4.1 ± 0.8 . This is different from Chan's study in which patients were randomly assigned to 15 mg/day of aripiprazole or 6 mg/day of risperidone (Chan et al., 2007). A literature review reveals an effective dose range between 10 and 25 mg/day for aripiprazole in schizophrenia (Charpeaud et al., 2014). The therapeutic range of aripiprazole is wide. In clinical practice, antipsychotic dose may determine the efficacy and safety of treatment. The doses of this study could be used as references for clinicians.

In summary, results from the study demonstrated that aripiprazole is an effective and safe antipsychotic for Chinese Han subjects with schizophrenia. Aripiprazole provided a rapid and persistent effect in improving psychotic symptoms from the first week of therapy. Overall, the clinical efficacy and safety profile of aripiprazole appear to be similar in Chinese and Western populations.

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Contributors

Prof. Qingshan ZHENG from Shanghai Chinese Medicine University provided the help of data management. The authors acknowledge all the participants in this study.

Conflict of interest

Huafang LI, Jianfeng LUO, Chuanyue WANG, Shiping XIE, Xiufeng XU, Xiaoping WANG, Wenjuan YU and Niufan GU have disclosed that they have all worked as consultants for this study. They have disclosed that they have no relevant financial relationships.

Dr. Kane has been a consultant to and/or received honorarium for lectures from BMS, Forrest, Janssen, Lundbeck, Merck, Novartis, Otsuka, Roche, Sunovion.

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The study group is as follows: Huafang LI, Wenjuan YU, Niufan GU, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai; Jianfeng LUO, Department of Health Statistics and Social Medicine, School of Public Health, Fudan University, Shanghai; Chuanyue WANG, Beijing Anding Hospital, Beijing; Shiping XIE, Nanjing Brain Hospital, Nanjing; Xiufeng XU, First affiliated Hospital of Kunming Medical University, Kunming; Xiaoping WANG, First affiliated Hospital of Kunming Medical University, Kunming; John M. KANE, Zucker Hillside Hospital and The Hofstra North Shore-LIJ School of Medicine, Glen Oaks, NY.

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