Efficacy and Safety of Aripiprazole in the Acute Treatment of Schizophrenia in Chinese Patients With Risperidone as an Active Control: A Randomized Trial

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Objective: Asian populations may differ from other races in response to antipsychotics. Studies of aripiprazole in Asian populations are scarce. This study aimed to investigate the efficacy, safety, and tolerability of aripiprazole in Chinese patients with acute schizophrenia or schizoaffective disorder.

Method: This 4-week, double-blind, randomized, parallel study was conducted in 5 medical centers in Taiwan between March 2004 and January 2005. A total of 83 patients with a primary DSM-IV diagnosis of schizophrenia or schizoaffective disorder were randomly assigned (with a randomization ratio of 3:2) to 15 mg/day of aripiprazole (N = 49) or 6 mg/day of risperidone (N = 34). Efficacy measures included the Positive and Negative Syndrome Scale (PANSS) total, positive, and negative 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 assessed as measures of safety and tolerability.

Results: Both the aripiprazole and risperidone groups showed statistical improvement from baseline in PANSS total, PANSS positive, PANSS negative, and CGI-S scores at study endpoint (all $p < .001$). Significant improvement was noted in the first week of treatment for both treatment groups. There were no significant differences in efficacy measures between treatment groups. Aripiprazole showed significantly less EPS liability as assessed by the Simpson-Angus Scale ($p < .005$) and less serum prolactin level elevation ($p < .001$) than risperidone. Both groups showed mild weight gain. No patients showed clinically significant QTc interval prolongation in this study.

Conclusion: Compared with risperidone 6 mg/day, aripiprazole 15 mg/day has comparable efficacy and favorable safety and tolerability profiles in the short-term treatment of Chinese patients with acute schizophrenia. In this group of Chinese patients, the overall response to aripiprazole did not differ from that of white patients.

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Schizophrenia is a chronic and debilitating psychiatric illness and a major cause of disability. The condition affects approximately 0.3% to 0.4% of the Taiwan population and 1% of the general population worldwide.[1] Conventional antipsychotics, which are dopamine D_2 receptor antagonists, improve positive psychotic symptoms but not negative or cognitive symptoms.[2] Other problems related to conventional antipsychotics include induction of extrapyramidal symptoms (EPS) and hyperprolactinemia, which constitute a marked barrier to patient drug compliance. The development of atypical antipsychotics markedly improved the treatment of schizophrenia[3]; however, atypical antipsychotics still have side effects such as somnolence, obesity, hyperglycemia, hyperlipidemia, and QTc prolongation, which greatly influence prescribing habits and patient drug compliance.[4–6]

Therefore, the development of a dopamine partial agonist is a logical research direction in the quest for an "optimal" treatment for patients with schizophrenia. Under the dopamine hypothesis of schizophrenia, hyperdopaminergic activities in mesolimbic pathways and hypodopaminergic activities in mesocortical pathways

are proposed to contribute to the etiology of symptoms in schizophrenia. Dopamine partial agonists, which are thought to counterbalance dopamine transmission under both hyperdopaminergic and hypodopaminergic neurotransmitter environments, act as dopamine system stabilizers.[7] Aripiprazole is the first commercially available drug with dopamine partial agonist effects approved for the treatment of schizophrenia and bipolar disorder. In vitro experiments showed agonist effects to D_2 receptors, but with only about 30% intrinsic activity compared with that of endogenous dopamine. Thus, aripiprazole showed functional D_2 receptor antagonism effects in hyperdopaminergia and functional agonistic effect in hypodopaminergia states in animal studies.[8] Aripiprazole is also a 5-HT_{1A} partial agonist and 5-HT_{2A} antagonist in preclinical studies.[9] The 5-HT_{1A} partial agonist effect may improve anxiety and cognitive and depressive symptoms, while the 5-HT_{2A} antagonist effect is postulated to improve negative and cognitive symptoms and reduce EPS liability.[10,11]

To date, there have been no published reports of clinical studies of aripiprazole in Asian or Chinese populations. Therefore, we cannot be sure whether ethnic differences in this population affect the efficacy and safety of aripiprazole in patients with schizophrenia. There are studies showing different pharmacokinetic responses to antipsychotics between Chinese and white populations, and such differences might lead to different efficacy and safety concerns between ethnic groups.[12–14] The aim of this study was to investigate the efficacy and safety of 15 mg of aripiprazole in Taiwanese patients with acute relapse of schizophrenia. We chose risperidone 6 mg as an active comparator control.

METHOD

This study was conducted at 5 medical centers in Taiwan. It was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. The study protocol was approved by the Joint Institutional Review Board of Taiwan or independent ethics committees at each center. All patients gave informed written consent after the study procedure had been fully explained to them.

Inclusion and Exclusion Criteria

Men and nonpregnant, nonlactating women were eligible for enrollment in the study if they were aged 18 to 65 years, had a primary diagnosis of DSM-IV schizophrenia or schizoaffective disorder,[15] and were hospitalized due to an acute relapse. These patients had to have evidence of response to antipsychotic medication (i.e., had previously shown an improvement with an antipsychotic drug other than clozapine and had been an outpatient for at least one 3-month period during the past year) and a Positive and Negative Syndrome Scale (PANSS)[16] total score of at least 60 and a minimum score of 4 (moderate) on at least 2 of the 4 items of the PANSS positive subscale (hallucinatory behavior, delusions, conceptual disorganization, and suspiciousness). Patients taking a long-acting neuroleptic could be included if a time period of at least 1 treatment cycle plus 1 week had elapsed since their last injection. Study exclusion criteria included having a psychiatric disorder other than schizophrenia or schizoaffective disorder requiring pharmacotherapy, serious suicidal ideations, a first episode of schizophrenia or schizoaffective disorder, a clinically significant neurologic abnormality other than tardive dyskinesia or EPS, current diagnosis of psychoactive substance dependence or a history of drug or alcohol abuse within 1 month before the beginning of the study, any acute or unstable medical condition, or treatment with an investigational drug within 4 weeks before the start of placebo washout.

Study Design

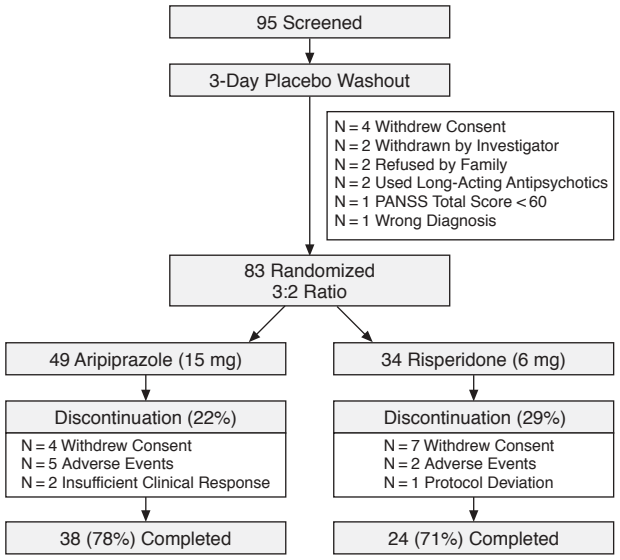
This was a randomized, 4-week, inpatient, double-blind, parallel-group study conducted at 5 medical centers in Taiwan between March 2004 and January 2005. Patients meeting all inclusion criteria and none of the exclusion criteria underwent a 3-day placebo washout period. Patients completing the washout period were evaluated for eligibility according to inclusion and exclusion criteria.

Patients were randomly assigned to receive either 15 mg/day of aripiprazole or 6 mg/day of risperidone for 4 weeks with a randomization ratio of 3:2 (aripiprazole: risperidone) using permuted block randomization stratified by center. The risperidone dosing regimen was selected on the basis of the drug's package insert and clinical practice at the time the study was initiated. Risperidone dosages were titrated upward (2 mg on day 1, 4 mg on day 2, and 6 mg/day for the remainder of the study) and administrated orally twice: once in the morning and once in the evening. Aripiprazole was given as a fixed full dose orally in the morning, with placebo given in the evening to maintain double blinding. All medications were identical in appearance. Dosages were fixed throughout the study and could not be increased for lack of efficacy or decreased for the occurrence of adverse events. Patients were hospitalized for the entire duration of the study.

Efficacy Assessments

Treatment efficacy was assessed using the PANSS and Clinical Global Impressions scale (CGI).[17] The PANSS evaluation included the total score (30 items), the positive subscale (7 items), and the negative subscale (7 items). The severity of each symptom on these subscales was rated on a 7-point scale. The CGI consisted of two 7-point subscales: -Severity of Illness (CGI-S) and -Improvement (CGI-I). For each patient, the same rater conducted the assessment throughout the study and was blinded to the

Figure 1. Summary of Participant Flow Among Chinese Patients With Schizophrenia Treated With Aripiprazole or Risperidone



Abbreviation: PANSS = Positive and Negative Syndrome Scale.

patient's treatment. Efficacy evaluations were performed at screening, at the end of the washout period (baseline), and at the end of each week during treatment (days 7, 14, 21, and 28). The primary efficacy parameter was the change from baseline in PANSS total score. Secondary efficacy parameters included the change from baseline in PANSS positive score, PANSS negative score, CGI-S score, and CGI-I score.

Safety Assessments

Adverse events were monitored at baseline and weekly thereafter by asking patients if they had experienced any problems or symptoms since the previous week. Investigators graded the intensity of events (mild, moderate, or severe) and assessed their likely relationship to the study medications. The status and intensity of previously reported events were also reevaluated at each weekly assessment.

The occurrence of parkinsonism, akathisia, and dyskinesia was evaluated using standardized EPS rating scales: the Simpson-Angus Scale (Simpson-Angus),[18] the Barnes Akathisia Rating Scale (BAS),[19] and the Abnormal Involuntary Movement Scale (AIMS),[20] respectively.

Vital signs (pulse and systolic and diastolic blood pressure) and body weight were measured at screening, at baseline, and on days 14 and 28 of the study. Serum prolactin level was measured at baseline and on days 14 and 28. Electrocardiographic (ECG) and hematologic parameters, serum chemical parameters, and urinalysis results were obtained at screening and on days 14 and 28.

Concomitant Medications

The use of psychotropic drugs other than those prescribed by the study protocol was prohibited during the study, with the exception of benzodiazepines for anxiety or insomnia. The use of intramuscular benzodiazepines was also permitted for emerging agitation, but only if deemed necessary by the investigator. Anticholinergic drugs for EPS were not permitted during the placebo washout period. If treatment for EPS during the double-blind period was judged necessary, patients were treated with an anticholinergic drug. The dose of anticholinergic drug could not exceed an equivalent of 6 mg/day of benztropine. All concomitant medications used during the study were recorded on the case report forms.

Statistical Procedures

The efficacy analyses were based on the intent-to-treat population defined as all randomized subjects. The last-observation-carried-forward dataset was used to estimate the missing data. Continuous efficacy data (e.g., change from baseline) were evaluated by analysis of covariance, adjusting for baseline values and the fixed factors treatment, center, and treatment-by-center interaction. The treatment-by-center interaction was tested at the .10 significance level and dropped from the model if it was not statistically significant. The hypothesis test was that the efficacy of aripiprazole was not inferior to risperidone, and 95% confidence intervals were examined. Categorical efficacy data (e.g., CGI-I scores) were analyzed using the Cochran-Mantel-Haenszel test with center control. For primary efficacy analyses, the hypothesis was 1-sided and evaluated at the .025 significance level. For other analyses, the test was 2-sided and evaluated at the .05 significance level. For safety parameters, mean change from baseline was evaluated by using 2-way analysis of variance with treatment, center, and treatment-by-center interaction.

RESULTS

Patient Disposition and Demographics

A total of 83 patients were randomly assigned to 2 treatment groups for 4 weeks (Figure 1): 15 mg/day of aripiprazole (N = 49) or 6 mg/day of risperidone (N = 34). Overall, 45 patients (54%) were men, and the mean age for patients in each treatment group was approximately 35 years. Of the total patient population, 80 (96%) were diagnosed with schizophrenia and 3 (4%) with schizoaffective disorder. Baseline demographic data were well matched between the 2 treatment groups (Table 1).

Of the 83 patients randomly assigned to treatment, all were included in the safety and efficacy analysis. In all, 62 patients (75%) completed the 4-week study period, and 21 (25%) discontinued treatment (Table 2). The main reasons for discontinuation were adverse events in the

Table 1. Baseline Demographic Characteristics and Clinical Correlates Among Patients With Schizophrenia Treated With Aripiprazole or Risperidone

Characteristic	Aripiprazole, 15 mg (N = 49)	Risperidone, 6 mg (N = 34)
Male/female, N	23/26	22/12
Age, mean ± SD, y	35.2 ± 10.9	35.1 ± 8.6
Body weight, mean ± SD, kg	64.1 ± 13.6	65.0 ± 15.5
Serum prolactin level, mean ± SD, ng/mL	22.7 ± 37.6	19.0 ± 15.2
No. of previous psychotic episodes, mean ± SD	3.1 ± 2.2	2.8 ± 1.9
PANSS score, mean ± SD		
Total	85.1 ± 15.7	84.6 ± 17.0
Positive	22.6 ± 4.6	20.0 ± 4.3
Negative	22.0 ± 6.3	21.3 ± 6.5
CGI-S score, mean ± SD	5.0 ± 0.7	5.1 ± 0.7

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, PANSS = Positive and Negative Syndrome Scale.

Table 2. Discontinuation Rates Among Patients With Schizophrenia Treated With Aripiprazole or Risperidone

Variable	Aripiprazole, 15 mg (N = 49)	Risperidone, 6 mg (N = 34)
Completed the study, N (%)	38 (78)	24 (71)
Discontinued the study, N (%)	11 (22)	10 (29)
Reasons for discontinuation, N (%)		
Adverse event	5 (10)	2 (6)
Insufficient clinical response	2 (4)	0 (0)
Withdrawal of consent[a]	4 (8)	7 (21)
Protocol deviation	0 (0)	1 (3)

[a]$p < .05$ between the 2 groups.

aripiprazole group (10%, N = 5) and consent withdrawal in the risperidone group (21%, N = 7). There was a statistically significant difference in withdrawal of consent between the 2 groups ($p < .05$).

Efficacy Data

Both the aripiprazole and risperidone groups showed significant improvement in primary and all secondary efficacy parameters compared with baseline (all p values < .001). The 2 treatments demonstrated rapid onset of efficacy with statistically significant effects evident from week 1 ($p < .001$ for primary efficacy parameter; $p < .007$ for all secondary efficacy parameters). There was no difference in improvement between the 2 groups (Table 3; Figures 2A–2C). Because a statistically significant treatment-by-center interaction in difference of PANSS positive score was observed at weeks 1 and 4 ($p = .003$ and $p = .073$, respectively), stratified analysis by treatment center was employed. The results did not show significant differences between treatment groups at each center.

In this study, we did not set a priori responder criteria. If we used a CGI-I score less than or equal to 2 or a greater than or equal to 30% decrease from baseline in PANSS total score as responder criteria, we found that the percentage of responders was 51% (25/49) for the aripiprazole group and 68% (23/34) for the risperidone group. Although the risperidone group had a higher percentage of responders, there was no statistically significant difference between the 2 groups ($p = .126$).

Table 3. Efficacy Data by Last Observation Carried Forward Among Patients With Schizophrenia Treated With Aripiprazole or Risperidone

Parameter	Aripiprazole, 15 mg (N = 49)	Risperidone, 6 mg (N = 34)	p Value[a]
PANSS score, mean ± SD[b]			
Total	–19.6 ± 18.1	–21.1 ± 17.1	.562
Positive	–5.8 ± 6.9	–8.1 ± 5.8	.252
Negative	–4.8 ± 5.1	–4.0 ± 5.7	.690
CGI-S score, mean ± SD[b]	–1.2 ± 1.1	–1.6 ± 1.0	.114
CGI-I score, mean ± SD	3.0 ± 1.5	2.6 ± 1.1	.154
Responder rate, %[c]	51	68	.126

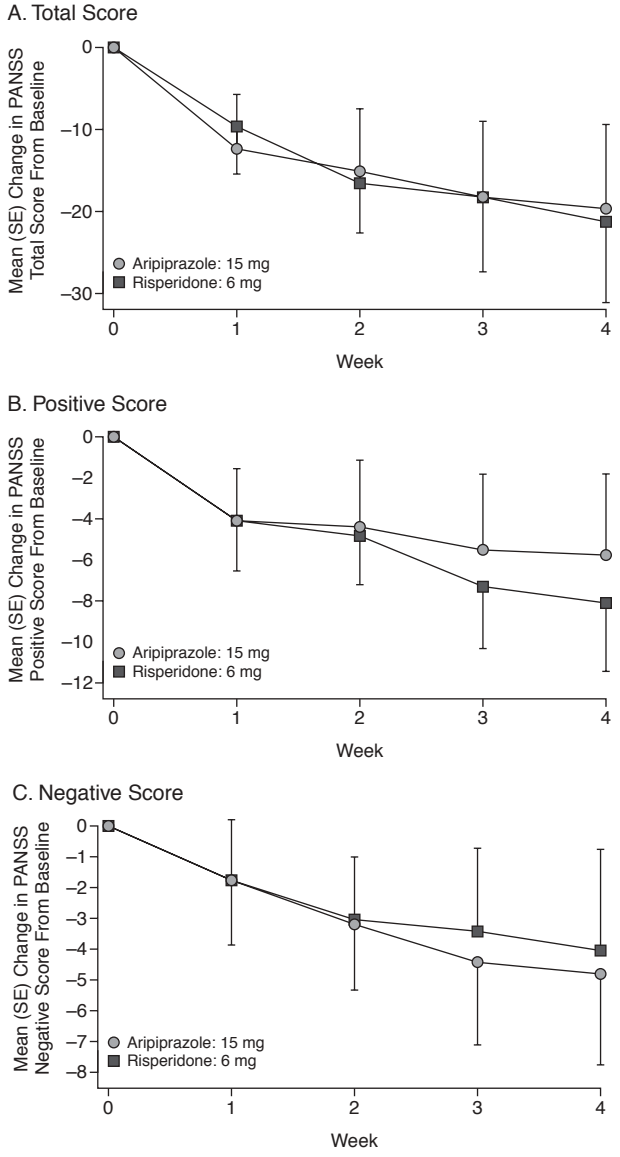
[a]Comparisons between the aripiprazole and risperidone groups.
[b]Values are given as the mean change from baseline.
[c]Patients with a score of 1 (very much improved) or 2 (much improved) on the CGI-I scale or patients with a ≥ 30% decrease from baseline in PANSS total score.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, PANSS = Positive and Negative Syndrome Scale.

Safety Data

Adverse events. All patients who received treatment were included in the safety evaluation (N = 83). The incidence of adverse events was similar in both treatment groups, with the majority of events of mild-to-moderate severity. Forty-one patients (84%) in the aripiprazole group and 27 patients (79%) in the risperidone group experienced at least 1 treatment-emergent adverse event, and there was no statistical difference between the 2 groups. Adverse events occurring at an incidence of 5% or more in any treatment group are shown in Table 4; there was no statistical difference between the 2 groups for any individual event. In the aripiprazole group, adverse events of insomnia, psychotic disorder, extrapyramidal disorder, vomiting, and constipation occurred most frequently (≥ 10%); in the risperidone group, extrapyramidal disorder, insomnia, akathisia, dizziness, and constipation were most frequently observed.

A total of 7 (8%) of 83 patients discontinued the trial because of adverse events: 5 patients (10%) in the aripiprazole group and 2 patients (6%) in the risperidone group. All adverse events leading to discontinuation in the aripiprazole group were because of "worsening of psychosis." Most discontinuations for this reason were during the second week of the study. One patient experienced a serious adverse event in the risperidone group. He presented with elevated glutamic oxaloacetic transaminase (186 U/L) and glutamic pyruvic transaminase (410 U/L) levels at the 2-week visit. This serious adverse event was considered unrelated to study medications after labora-

Figure 2. Mean Change From Baseline in Positive and Negative Syndrome Scale (PANSS) Scores Over 4 Weeks of Treatment With Aripiprazole 15 mg/day and Risperidone 6 mg/day[a]



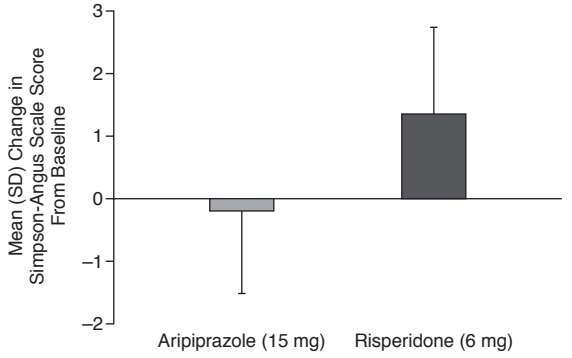
[a]All p > .05 between the 2 groups over 4 weeks.

Table 4. Incidence of Treatment-Emergent Adverse Events (≥ 5% incidence in any treatment group) Among Patients With Schizophrenia Treated With Aripiprazole or Risperidone[a]

Adverse Event	Aripiprazole, 15 mg (N = 49)	Risperidone, 6 mg (N = 34)
Gastrointestinal disorders, N (%)		
Abdominal pain	3 (6)	0 (0)
Abdominal pain, upper	4 (8)	1 (3)
Constipation	5 (10)	4 (12)
Diarrhea	4 (8)	1 (3)
Nausea	2 (4)	2 (6)
Toothache	3 (6)	3 (9)
Vomiting	5 (10)	1 (3)
Infections and infestations, N (%)		
Nasopharyngitis	3 (6)	0 (0)
Nervous system disorders, N (%)		
Akathisia	1 (2)	4 (12)
Dizziness	2 (4)	4 (12)
Extrapyramidal disorder	6 (12)	8 (24)
Headache	4 (8)	1 (3)
Psychiatric disorders, N (%)		
Agitation	4 (8)	0 (0)
Anxiety	1 (2)	2 (6)
Insomnia	13 (27)	7 (21)
Psychotic disorder	8 (16)	2 (6)

[a]All p values were > .05 in comparison between the 2 groups.

Figure 3. Mean Change From Baseline to Last Visit in Simpson-Angus Scale Scores (last observation carried forward)[a]



[a]Pairwise comparison, p < .005.

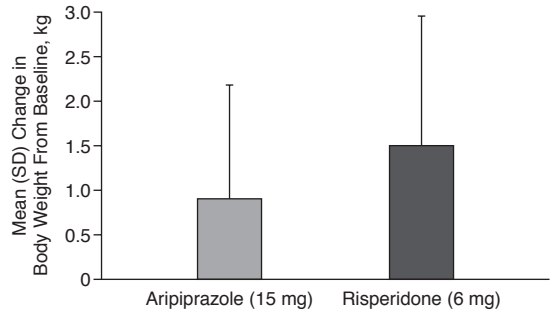
tory examinations showed evidence of reactivation of a previous hepatitis B viral infection.

Extrapyramidal symptoms. The overall incidence of EPS-related adverse events was lower in the aripiprazole group than in the risperidone group. Six patients (12%) in the aripiprazole group and 8 patients (24%) in the risperidone group had EPS; 1 (2%) of the aripiprazole patients and 4 (12%) of the risperidone patients reported akathisia. For relief of EPS, 12 patients (25%) in the aripiprazole group used anticholinergics as concomitant medications, in contrast to 14 (41%) in the risperidone group.

The mean ± SD change from baseline to endpoint in the Simpson-Angus score in the aripiprazole group was significantly better than that in the risperidone group (–0.2 ± 2.3 and 1.3 ± 2.4, respectively; p < .005; Figure 3). There were no significant differences between the aripiprazole and risperidone groups for the mean change in the BAS (0.1 ± 1.0 and 0.5 ± 1.4, respectively; p = .129) or AIMS (–0.4 ± 2.5 and 0.4 ± 1.7, respectively; p = .351) scores.

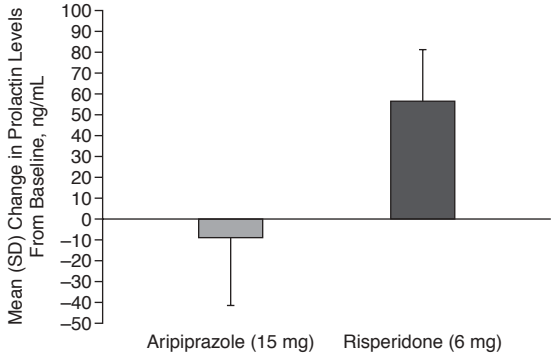
Body weight, glucose, and lipids. Both the aripiprazole and risperidone groups showed mild body weight gain during the 4-week study period with no statistical difference (mean ± SD = 0.9 ± 2.2 and 1.5 ± 2.5 kg, re-

Figure 4. Mean Change in Body Weight From Baseline to Last Visit (last observation carried forward)[a]



[a]Pairwise comparison, p > .05.

Figure 5. Mean Change in Serum Prolactin Levels From Baseline to Last Visit (last observation carried forward)[a]



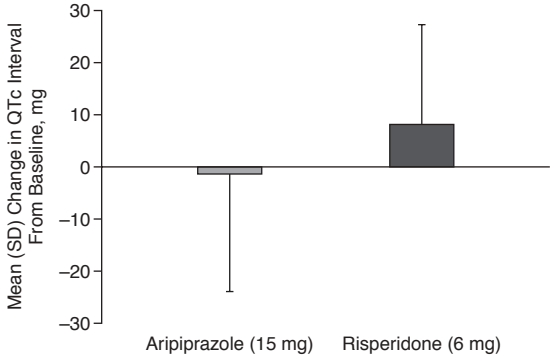
[a]Pairwise comparison, p < .001.

spectively; p = .502; Figure 4). The incidence of clinically significant weight gain (≥ 7% increase from baseline) was not statistically different between the groups (4% [2/49] and 12% [4/34], respectively; p = .221).

At endpoint, both the aripiprazole and risperidone groups showed mild fasting glucose changes (mean ± SD = 4.1 ± 32.0 and –2.7 ± 27.6 mg/dL, respectively; p = .444). Total cholesterol levels changed, but there was no significant difference between the 2 groups (mean ± SD = –3.1 ± 52.3 and 19.2 ± 27.9 mg/dL, respectively; p = .214).

Serum prolactin levels. At study endpoint, the serum prolactin level was lower than baseline in the aripiprazole group, but the risperidone group showed a significant increase. There were statistically significant differences in change between the aripiprazole and risperidone groups (mean ± SD = –9.0 ± 96.4 and 55.4 ± 42.3 mg/dL, respectively; p < .001; Figure 5). The percentage of patients who had an abnormal prolactin level (greater than 25 ng/mL) at endpoint was also significantly higher in the risperidone group (aripiprazole 5% [2/39], risperidone 93% [26/28]; p < .001).

Figure 6. Mean Change in QTc Interval From Baseline to Last Visit (last observation carried forward)[a]



[a]Pairwise comparison, p > .05.

QTc prolongation. No patients had clinically significant increases in QTc interval in either group. The QTc interval was calculated using Bazett's formula (QT/√RR). The mean change in QTc interval was –1 ± 39 ms in the aripiprazole group and 8 ± 34 ms in the risperidone group. This difference was not statistically or clinically significant (p = .619; Figure 6).

Vital signs and other laboratory evaluations. In general, changes in vital signs between treatment groups were unremarkable. There were no significant differences between treatment groups in other laboratory examinations with the exception of serum prolactin level. One patient in the risperidone group presented with clinically abnormal and severe liver function impairment and was subsequently discontinued from the study.

DISCUSSION

To the best of our knowledge, this study is the first randomized controlled trial to evaluate the efficacy and safety of aripiprazole in the treatment of Chinese patients with schizophrenia or schizoaffective disorder. The results of this study found that aripiprazole 15 mg/day was effective, safe, and well tolerated in the treatment of patients with acute relapse of schizophrenia or schizoaffective disorder. Aripiprazole 15 mg/day demonstrated similar efficacy to risperidone 6 mg/day, the active comparator, in the positive and negative symptoms of schizophrenia. Rapid onset of efficacy was noted in both the aripiprazole and risperidone groups. Both drugs produced statistically significant improvement as early as week 1 (PANSS total, PANSS positive, PANSS negative, and CGI-S scores). These significant improvements were sustained through the course of the 4-week study.

The efficacy data of this study were similar to that of previous studies. Aripiprazole 15 mg/day was as effective as haloperidol 10 mg/day in the treatment of patients with acute exacerbations of schizophrenia.[21] Higher doses of aripiprazole, 20 to 30 mg/day, also showed similar efficacy with haloperidol or risperidone in patients with acute relapse of schizophrenia.[21,22]

The persistent effect throughout the 4-week treatment period provided evidence that aripiprazole can produce clinically meaningful and sustained improvements in the symptoms of schizophrenia in Chinese populations, as has been shown in Western populations.[21,22] The sustained effects differed from other medications with dopamine D_2 partial agonist characteristics such as preclamol.[23] Although we do not know the exact mechanisms of this difference, differences in the intrinsic activity of each agent at the D_2 receptors might be 1 of several possible reasons.

Although the overall discontinuation rate was somewhat lower in the aripiprazole group, the discontinuation rate because of adverse events was slightly higher in the aripiprazole group. Among the aripiprazole patients, all of the adverse events that led to early termination were reported as "worsening of psychosis." In contrast, no discontinuation was due to the adverse effect of psychosis exacerbation in the risperidone group. This finding suggests that a small proportion of patients may suffer from worsening of psychosis during the initial phase of aripiprazole treatment after washout from another antipsychotic.[24] Among the 5 patients with adverse events in the aripiprazole group, 3 were shifted from haloperidol (10–15 mg/day), 1 from chlorpromazine (500 mg/day), and 1 from olanzapine (30 mg/day). This phenomenon is most likely related to D_2 receptor sensitivity in patients who have been treated with stronger D_2 antagonists prior to receiving a D_2 partial agonist. Gradual tapering of the previous antipsychotic after aripiprazole introduction may minimize this effect.

Aripiprazole was associated with lower incidence of EPS, fewer concomitant anticholinergic medications, and lower Simpson-Angus scores compared with risperidone. These results might reflect the lower propensity of aripiprazole at 15 mg/day than that of risperidone at 6 mg/day to produce EPS. In fact, the mean Simpson-Angus scores of the aripiprazole group did not increase at the end of the trial. Aripiprazole's dopamine partial agonistic effect may account for this result. The choice of 6 mg/day of risperidone was based on the prescribing information at the time of study initiation and local trial experiences in the acute treatment of schizophrenia.[25] While this dose maximized the opportunity to observe a treatment effect in risperidone-treated patients, the use of 6 mg/day may also highlight the tendency for risperidone to produce mild EPS. Of note, there may be a racial difference in EPS liability for risperidone, which may have led to more prominent risperidone-related EPS than previously reported in a similar study of Western populations.[22]

Hyperprolactinemia can lead to several medically important conditions such as amenorrhea, irregular menstrual cycles, sexual dysfunction, gynecomastia, and galactorrhea, and it can also limit patient drug compliance. The serum prolactin levels decreased in the aripiprazole group but markedly increased in the risperidone group over the course of treatment. The decrease of prolactin level in the aripiprazole group might be because of its D_2 partial agonistic effect.

QTc interval prolongation at ECG examination has been observed in some antipsychotics. Torsade de points, a severe cardiac arrhythmia, might appear if the QTc interval is greater than 500 ms.[26] There were no cases of clinically significant increase in QTc interval in either the aripiprazole or risperidone groups. This result supported the hypothesis that aripiprazole has a low risk of arrhythmic potential in Chinese populations.

Weight gain is also a potentially serious side effect associated with the use of some antipsychotics, leading to patient disturbance and compromised compliance. It is also known to be associated with increased propensity for metabolic syndrome after long-term use. In this short-term study, the aripiprazole and risperidone groups had mild and clinically insignificant weight gain. While this finding is comparable to previous studies[22] and consistent with our overall knowledge about aripiprazole, long-term studies of aripiprazole in the Chinese patient population are warranted.

Our study had some limitations. First, the study was not designed to have a placebo control group because of ethical concerns, so we do not know the potential placebo effect in this Chinese population or how well aripiprazole and risperidone act compared with placebo. The measurement of efficacy and safety and the characteristics of study participants might also be influenced by the inclusion of a placebo group. Second, the sample size was small, so the statistical power may be inadequate to detect differences between the treatment groups. However, our study is the first well-designed randomized controlled trial in Asian or Chinese populations. The results could have important implications for the treatment of schizophrenia in these populations.

In summary, we found that aripiprazole is an effective and safe antipsychotic agent in the treatment of Chinese patients with acute relapse of schizophrenia or schizoaffective disorder. Both aripiprazole and risperidone demonstrated a quick and sustained effect to improve psychotic symptoms from the first week of treatment, but aripiprazole 15 mg/day showed good tolerability with less EPS and hyperprolactinemia than risperidone 6 mg/day. The overall clinical response to aripiprazole in this group of Chinese patients was similar to that of white patients.

Drug names: aripiprazole (Abilify), benztropine (Cogentin and others), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

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